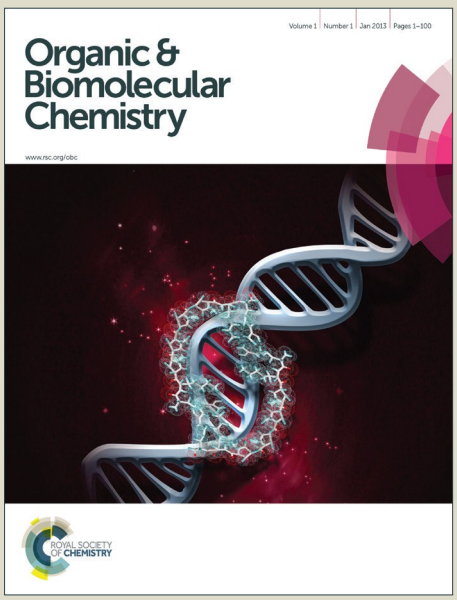
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Barata-Vallejo, S. M. Bonesi and A. POSTIGO, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB00763E.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB00763E

LATE STAGE TRIFLUOROMETHYLTHIOLATION STRATEGIES FOR ORGANIC COMPOUNDS

Sebastian Barata-Vallejo[a], Sergio Bonesi,*[b] Al Postigo*[a]

a.-Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires-CONICET-Junín 954 CP 1113-Buenos Aires-Argentina
b.-Departamento de Química Orgánica, CIHIDECAR-CONICET, Pabellón II, 3er piso, Ciudad Universitaria, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1428, Buenos Aires, Argentina

Abstract

Substitution by the CF_3S group allows for an increase in lipophilicity and electron-withdrawing properties along with an improvement in the bioavailability of medicinal targets; consequently, the late stage introduction of CF_3S moieties into medicinal scaffolds is a sought-after strategy in synthetic organic chemistry. Different newly-developed electrophilic and nucleophilic reagents are used to effect the trifluoromethylthiolation of (hetero)aromatic compounds, aliphatic compounds (alkyl, alkenyl, alkynyl substrates), the trifluoromethylthiolation at the α- and β-carbonyl positions, and heteroatoms (*N*- and *S*-). Such reactions can involve homolytic substitutions, or functional-group substitutions (*ipso*). Addition reactions of electrophilic reagents to double and triple bonds followed by ring-cyclizations will be shown to yield relevant CF_3S-substituted heteroaromatic compounds with relevant pharmacological action.

Index

View Article Online
DOI: 10.1039/C6OB00763E

1.-Introduction

Fluoroalkylthio group substitutions increase the lipophilic properties of medicinal targets and compounds in general as revealed by the Hansch constant (i.e.: 1.44 for CF_3S group, as being the highest Hansch constant).[1] Also, the strong electron-withdrawing properties of CF_3S has recently attracted the attention of medicinal chemists worldwide, and initiated an active area of research in this field. These sole features (electronegativity and lipophilicity) render CF_3S substitutions a sought-after strategy in drug design. Consequently, there have been recent reports on medicinal targets bearing the CF_3S group[2,3] which underscore the relevance of this substitution.

There are already several marketed drugs with distinct and potent pharmacological action that contain the CF_3S functionality. Figure 1 depicts relevant examples. Compound **1** *tifluorex* (a stimulant amphetamine derivative), has been employed for the treatment of nervous anorexia.[4a,b] Compound **2** has been employed as an antimalarial and anti-pneumonia agent.

View Article Online
DOI: 10.1039/C6OB00763E

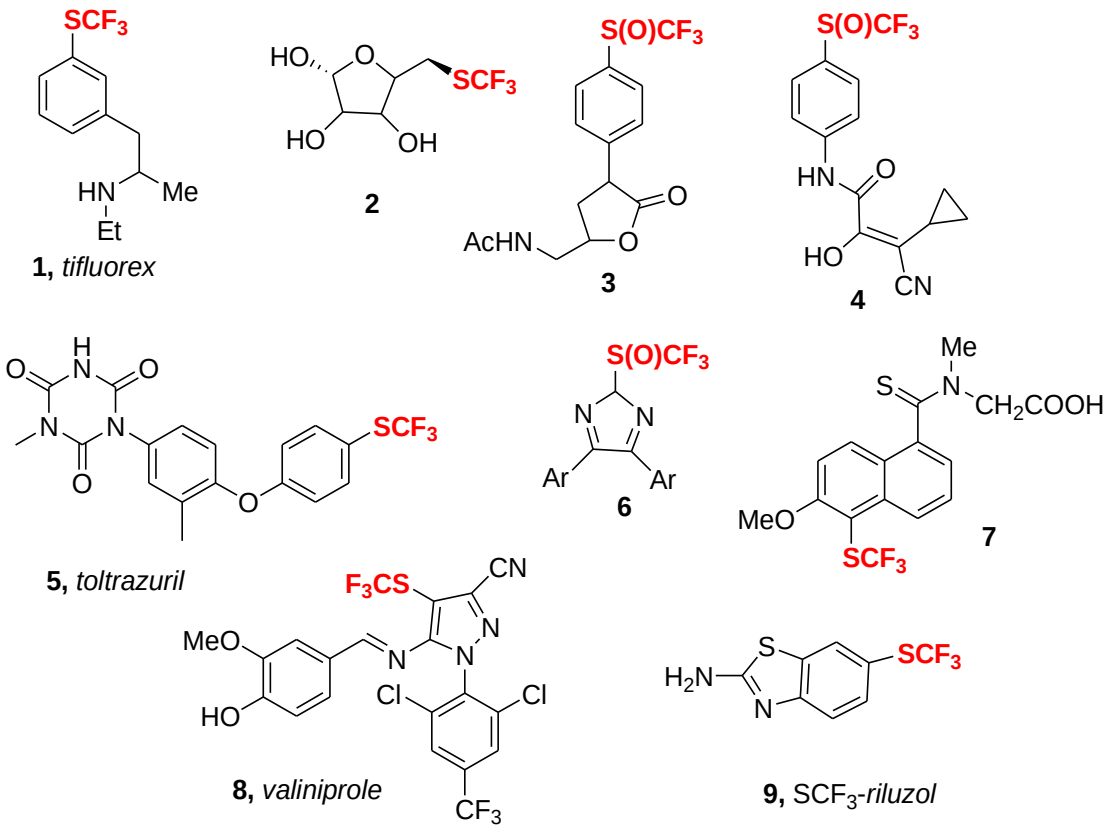


Figure 1. Medicinal compounds containing the CF_3S functionality

Compound **3** has shown antibacterial properties (Figure 1); **4** has antihypertensive and anti-arthritis potency, whereas compound **5** is the commercial *toltrazuril*, one of the few active drugs used as a coccidiostatic (antiprotozoal) agent.[4e] Compound **6** is an anti-inflammatory agent (Figure 1) and **7** is currently used for the treatment of diabetes mellitus. *Vaniliprole* **8** is an insecticide (acaricide) (Figure 1). The thio analogue of *riluzole* has been tested for its potential biological activities[4f] (**9**, Figure 1) in the lateral amyotrophic sclerosis.

This review article intends to present new synthetic methodologies for accomplishing late stage trifluoromethylthiolation reactions on molecules (drugs/pro-drugs) with pharmacological activity. It is not the aim of this review article to describe or enumerate CF_3S-containing drugs and their mechanism of action or their *de novo* synthesis

View Article Online
DOI: 10.1039/C6OB00763E

from commodity or readily prepared fluorothioalkyl building blocks. Fluorination, and fluoroalkylation strategies will not be considered in this review.

2.-Reagents Used to Introduce CF_3S Group in Medicinal Targets

Among the known electrophilic trifluoromethylthiolating reagents (Figure 2), 1-((trifluoromethyl)thio)pyrrolidine-2,5-dione **10** developed by Hass[5], 2-(trifluoromethyl)thio)-isoindoline-1,3-dione **11,** developed by Munavalli[6] and exploited by Rueping[7], trifluoromethanesulfenamide **12**[8], ((2-(2-iodophenyl)propan-2-yl)oxy)(trifluoromethyl)sulfane **13**, developed by Lu and Shen[9-11], reagent **14** developed by Shibata[12,13], ((2-(5-aryl-2-iodophenyl)propan-2-yl)oxy)(trifluoromethyl)sulfane **15**, developed by Buchwald[14], and *N*-(4-dimethyl-*N*-((trifluoromethyl)thio)benzenesulfonamide **16**, developed by Billard[15] are commercially available and/or recent CF_3S reagents employed for late-stage trifluoromethylthiolation reaction.

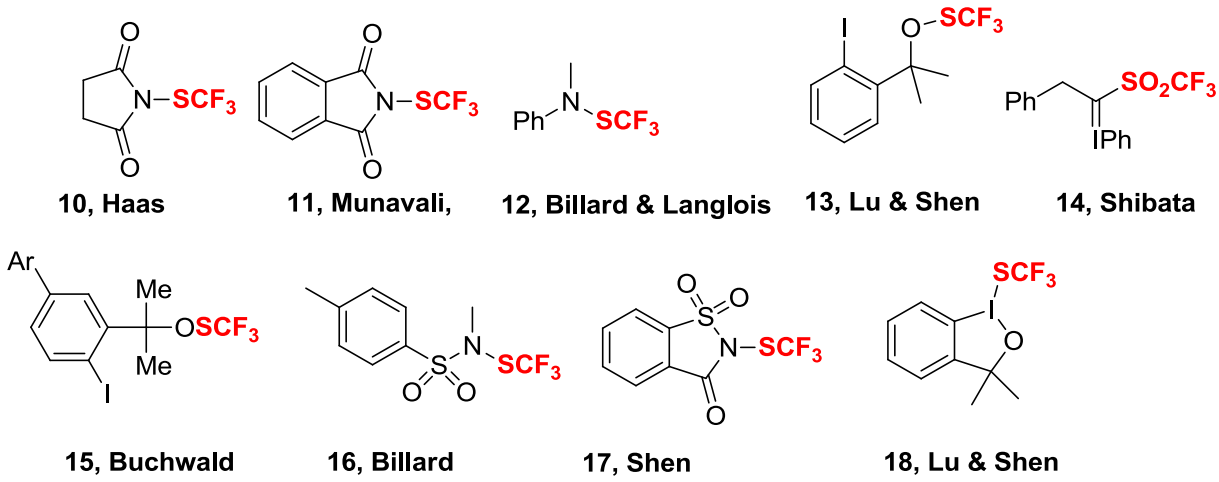


Figure 2. Electrophilic trifluoromethylthiolating reagents

Electrophilic reagents **17** and **18** (Figure 2)**,** have also been developed by Shen and co-workers and found recent applications.[9-11]

View Article Online
DOI: 10.1039/C6OB00763E

Recently, Cheng and co-workers[16] have come up with a quantitative scale for the electrophilic trifluoromethylthiolating ability of an array of electrophilic CF_3S reagents. They[16] concluded through calculations that the electrophilic transfer of a CF_3S group from reagent to substrate should not proceed via an S_N1-type process involving a free CF_3S^+ intermediate but rather via an S_N2-type mechanism. For the Billard and Langlois reagent **12** (Figure 2), the ability to transfer the electrophilic CF_3S group follows the increasing order shown in Figure 3.

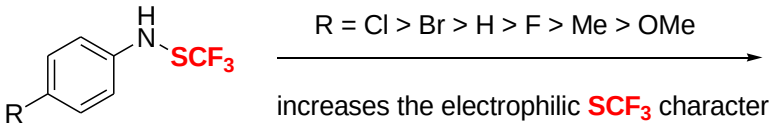


Figure 3. Calculated (6-311++G level) trend for the ability of transferring electrophilic reagents bearing CF_3S group

Among the nucleophilic trifluoromethylthiolating reagents, $AgSCF_3$[17,18], Me_4NSCF_3, $CuSCF_3$, $NaSO_2CF_3/(EtO)_2P(O)H$[19], and mixtures of S_8 and $TMSCF_3$,[20] are the most widespread and employed.More recent transition metal-SCF_3 reagents are used as straightforward reagents for the synthesis of trifluoromethylthiolated compounds, such as $(bpy)Cu(SCF_3)$.[21,22]

3.- Direct or Late-stage Trifluoromethylthiolation Methods for Aryl Moieties

3.1.- Conversion of C_{Ar}-X into C_{Ar}-SCF_3 Bonds (X = OT_f, N_2^+, $B(OH)_2$, Cl, Br, I)

Billard and co-workers have recently reviewed the direct synthetic strategies to introduce CF_3S group into organic substrates.[23] Long-established methods to achieve conversion of C_{Ar}-X into C_{Ar}-SCF_3 involved harsh reaction conditions, such as the use of toxic thiophosgene and a fluoride source [7] at very low temperatures. Improved and

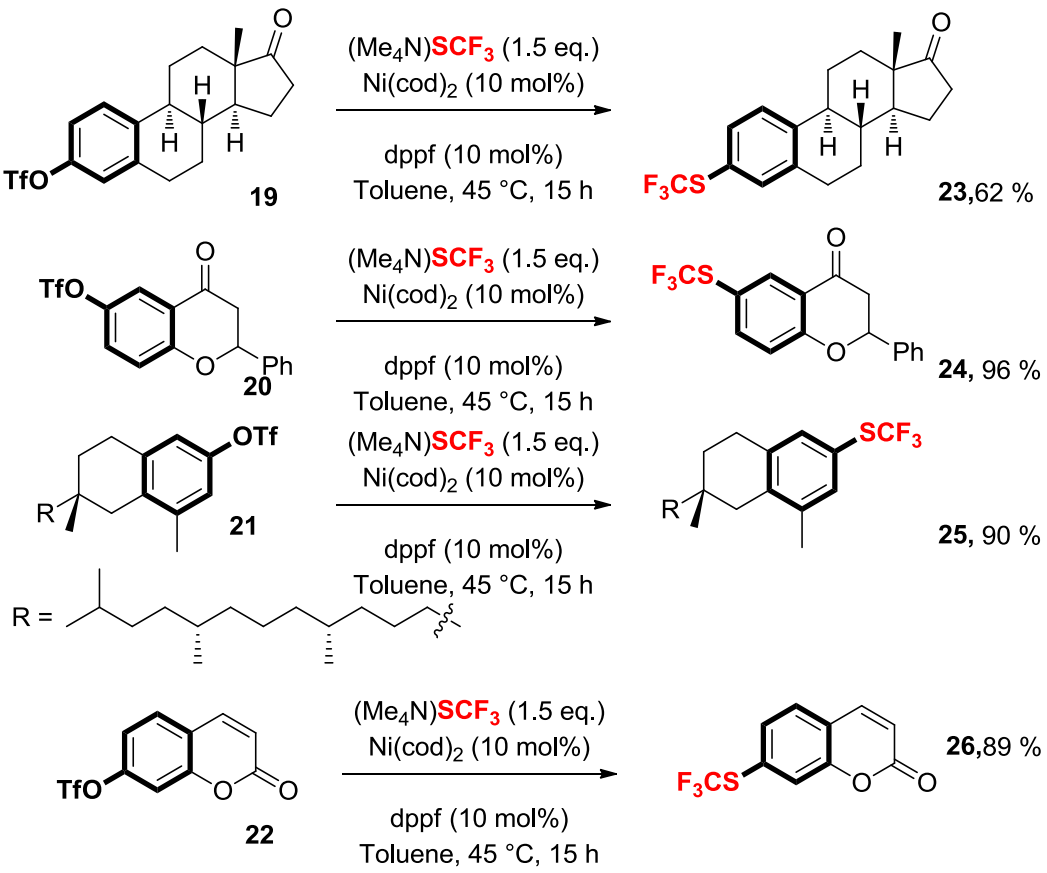
View Article Online
DOI: 10.1039/C6OB00763E

convenient methods for late-stage conversion of C_{Ar}-X into C_{Ar}-SCF_3 have recently attracted the attention of synthetic chemists.

Schoebeneck and co-workers have developed the first efficient protocol to trifluoromethylthiolate C_{sp2}-O bonds under nickel catalysis, giving the mild and operationally simple C-SCF_3 coupling of a range of aryl and vinyl triflates and aryl and vinyl nonaflates.[24] The mild reaction of aryl and vinyl triflates and nonaflates with $(Me_4N)SCF_3$ (1.5 eq.) involves the use of catalytic amounts of $Ni(cod)_2$ (10 mol %) and the phosphine ligand dppf (i.e.: 1,1'-bis(diphenylphosphino)ferrocene, 10 mol%), in toluene at 45 °C during 12 – 15 h. The reaction tolerates a wide range of electron-donor and electron-acceptor groups attached to the aryl moiety as well as conjugated vinyl derivatives. The desired trifluoromethylthiolate derivatives are obtained in good to excellent yields.

The triflate derivatives of *estrone* **19** (an estrogenic hormone), 6-hydroxy flavanone **20** (a plant secondary metabolite used *inter alia* as an antioxidant) and δ-tocopherol **21** (*vitamin E*) show an excellent functional group match, containing predominantly ketone and benzylic C-O bonds that are less reactive than C-OT_f and C-SCF_3. Also, 7-triflate coumarin **22** is suitable under this new methodology. The trifluoromethylthiolation reaction was successfully accomplished in 62 – 96 % yield (products **23-26**), highlighting the potential of this method for pharmaceutical application (Scheme 1).

View Article Online
DOI: 10.1039/C6OB00763E



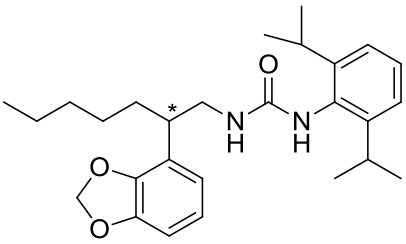
Scheme 1. Trifluoromethylthiolation of bioactive molecules

1,3-Benzodioxol-4-yl group is an interesting motif present in racemic *N*-2-(1,3-benzodioxol-4-yl)hepty-*N'*-2,6-diisopropylphenylurea which is a potent *ACAT-inhibitor* (*Acetyl Coenzyme A* acetyltransferase) and has a strong lowering effect on plasma cholesterol-level in hamster and rat models.[25] Also, its *ACAT*-catalyzed cholesterol esterification is higher than known inhibitors such as CL-283546.[26] Synthetic preparation of racemic inhibitor starts from 1,3-benzodioxyl derivatives as useful building-blocks. Introduction of CF_3S group in the early-stage of the synthesis warrants that the final drug shows enhanced lipophilicity.

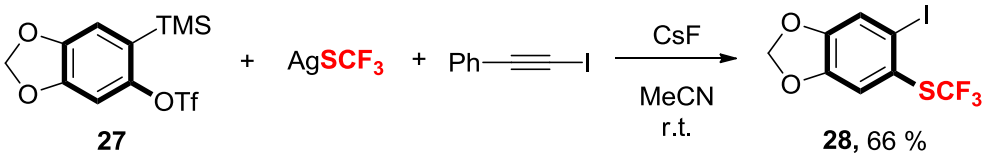
Silver-mediated trifluoromethylthiolation-iodination of arynes provides in a one-pot fashion CF_3S-containing useful building blocks.[27] This mild and convenient reaction involves the use of $AgSCF_3$ (3 equiv.) and 1-iodophenylacetylene (2 equiv.) that reacts with the aryne precursor in the presence of CsF (4 equiv.) in MeCN at room temperature. The

View Article Online
DOI: 10.1039/C6OB00763E

desired products are obtained in good yields and a wide variety of substituents are tolerated. Scheme 2 depicts the structure of the *ACAT inhibitor* and the trifluoromethylthiolation reaction of a benzodioxole core derivative **27**, affording 66% yield of the iodotrifluoromethylthio-substituted derivative **28**.



Racemic ACAT inhibitor

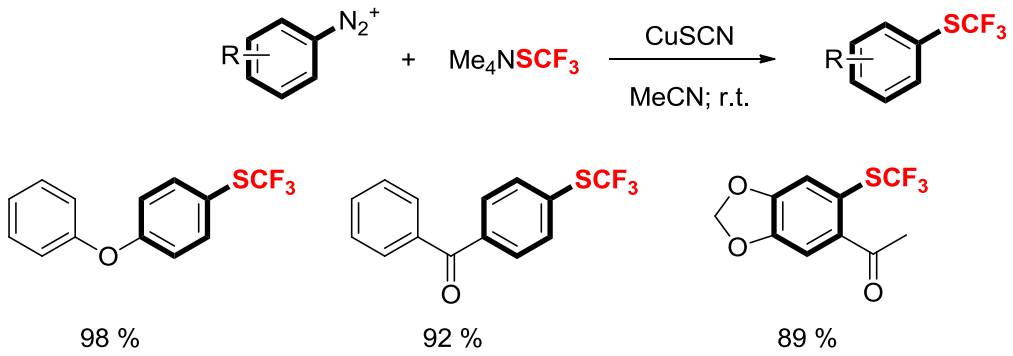


27 **28,** 66 %

Scheme 2. Trifluoromethylthiolation-iodination reaction of arynes

In 2016 Goossen and co-workers have reported an elegant and mild methodology to incorporate a CF_3S group to (hetero)aromatic diazonium salts that are building-blocks in the preparation of agrochemicals and pharmaceuticals.[28] Reaction of an aryl diazonium tetrafluoroborate (1.0 mmol) with Me_4NSCF_3 (1.8 mmol) in the presence of catalytic amounts of CuSCN (10 mol%) in MeCN for 1 h at room temperature furnished the desired trifluoromethylthiolated product in good to excellent yields (Scheme 3).

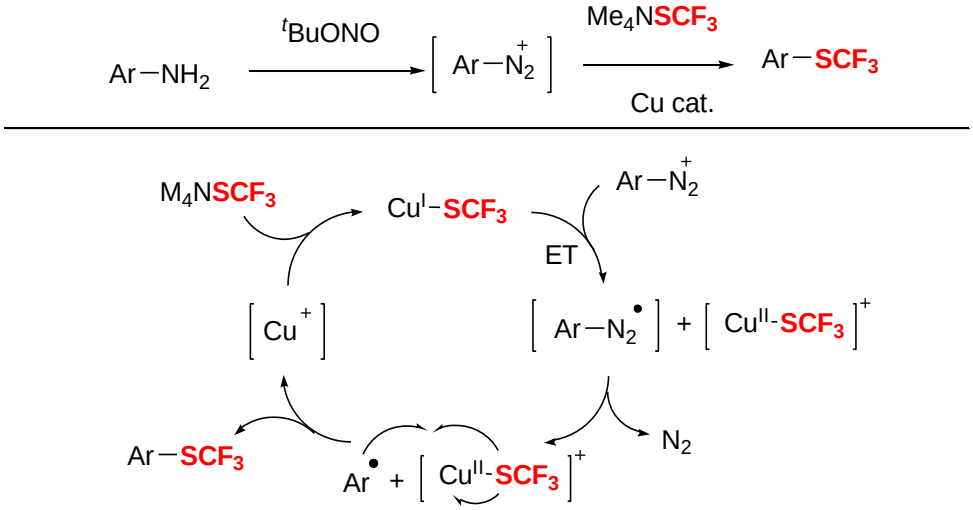
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 3. Scope of the Sandmeyer trifluoromethylthiolation reaction of aryl moieties

Alternatively, the same authors have proposed another methodology to produce aryl (and heteroaryl, *vide infra*) trifluoromethyl thioethers starting from aryldiazonium tetrafluoroborates.[29] The reaction takes place efficiently with Me_4NSCF_3 (2 equiv.) as the SCF_3 source in the presence of CuSCN (0.5 equiv) and Cs_2CO_3 (2 equiv.) in MeCN at room temperature for 12 h. However, this methodology affords the trifluoromethylthiolated products in modest to good yields.

The mechanism proposed for the transformation is depicted in Scheme 4.



29

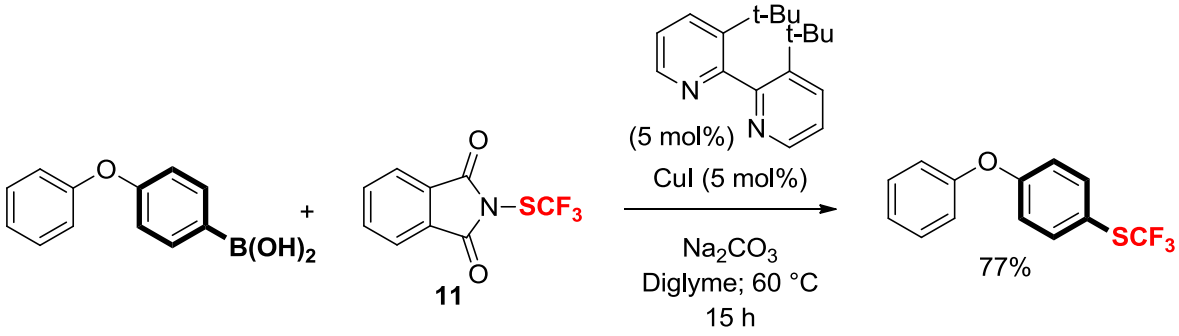
Scheme 4. Proposed reaction mechanism for the trifluoromethylthiolation of diazonium salts

View Article Online
DOI: 10.1039/C6OB00763E

According to the reaction mechanism proposed[28], an ET reaction takes place between the diazonium salt, Me_4NSCF_3 and the copper catalyst CuSCN (Scheme 4). The diazonium salt is reduced and the copper catalyst is oxidized. After loss of nitrogen, aryl radicals react with complex **29** (Scheme 4), affording substitution.

Aryl boronic acids have been reported to undergo a trifluoromethylthiolation reaction through a variety of trifluoromethylthiolating reagents: with $TMSCF_3$ and S_8[30a], with the use of Me_4NSCF_3 mediated by copper[30b], or the use of the Togni reagent **18** and $Cu(MeCN)_4PF_6$-bpy[31], or the use of $NaSO_2CF_3$ and S_8 in the presence of copper.[20] The trifluoromethylthiolation of aryl boronic acids has also been carried out in the presence of reagent **11**, CuI, a 2,2´-bipyridyl derivative as ligand, Na_2CO_3 as base in diglyme as solvent.[32-34] These transformations have been reviewed recently.[23]

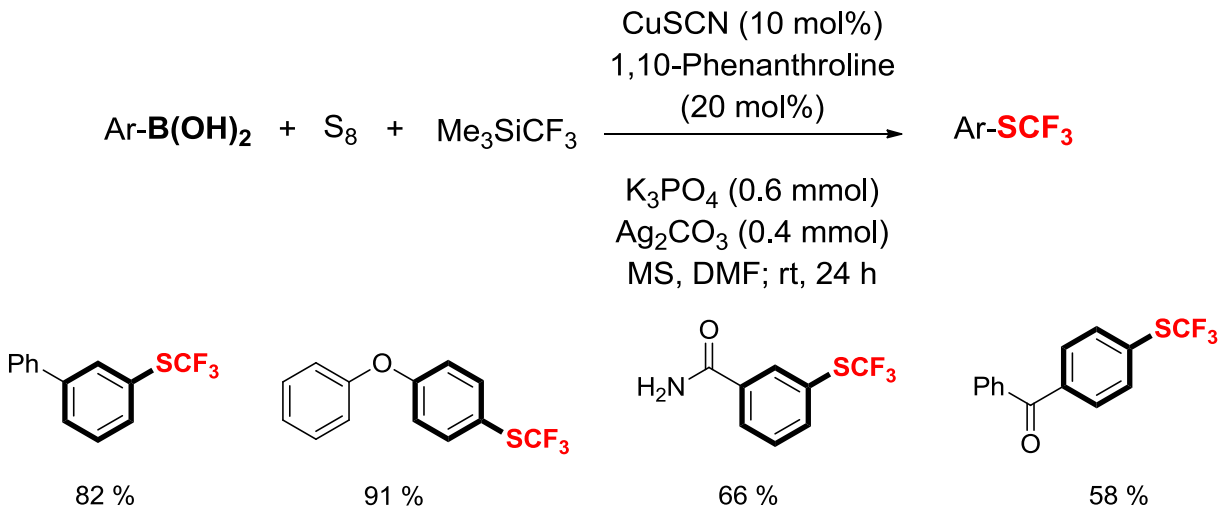
Shen and co-workers have developed a protocol that allows introduction of CF_3S group onto (hetero)aromatic compounds (see Scheme 5).[33] Reaction of arylboronic acids with *N*-(trifluoromethylthio)phthalimide **11** (0.75 mmol) in the presence of CuI (5 mol%) and *t*-Bubpy (5 mol%) and Na_2CO_3 (0.25 mmol) in diglyme at 60 °C for 15 h provides cleanly the desired products in good to excellent yields. This protocol applies satisfactorily with a wide variety of substituents and also with heterocyclic compounds such as thiophene and pyridine derivatives.



Scheme 5. Trifluoromethylthiolation reaction of (hetero)aryl boronic acids

View Article Online
DOI: 10.1039/C6OB00763E

Trifluoromethylthioarenes are interesting building blocks for the synthesis of trifluoromethyl aryl sulfoxides[35] and the trifluoromethanesulfinyl substituent is also present in the structure of the potent insecticide *Fipronil* (Figure 4).[36] Qing and co-workers have reported the copper-catalyzed oxidative trifluoromethylthiolation of aryl boronic acids with $TMSCF_3$ and elemental sulfur.[37] The reaction was conducted with the aryl boronic acid in DMF at room temperature. The oxidative trifluoromethylthiolation of aryl boronic acid (0.2 mmol) with S_8 (0.6 mmol) and $TMSCF_3$ (1.0 mmol) in the presence of CuSCN (0.02 mmol), 1,10-phenanthroline (0.04 mmol), K_3PO_4 (0.6 mmol), Ag_2CO_3 (0.4 mmol) and molecular sieves (4 Å) in DMF at room temperature for 24 h gives the desired products in good yields. This mild reaction conditions apply satisfactorily with aryl boronic acids bearing a range of different functional groups (Scheme 6).



Scheme 6. Trifluoromethylthiolation of aryl boronic acids

Aryl halides (predominantly bromides) undergo trifluoromethylthiolation substitution in the presence of $Na_2S_2O_3$, the Langlois reagent (i.e.: Me_3SiCF_3), $Cu(OT_f)$, phenanthroline, and K_3PO_4 as base in DMSO as solvent.[38,39]

A variety of biological-active compounds, employed as insecticides, contains in their molecules the motif phenoxyphenyloxy which are juvenile hormone analogs (JHAs) mimicking insecticide used for control of flies, beetles, midges and mosquitoes in public

View Article Online
DOI: 10.1039/C6OB00763E

health applications such as *Pyriproxyfen*, *Teflubenzuron* and *Fenoxycarb*[40] (Figure 4). Also, some of these insecticides are used in agriculture in some countries, e.g. the USA. For example, *Pyriproxyfen* is used against *Plutella Xylostella* (diamond black moth) because affects every life stage of the moth. Anchoring the CF_3S group to the aromatic moiety of insecticides is expected to increase their lipophilicity, in particular, for those insecticides that are used in public health applications.

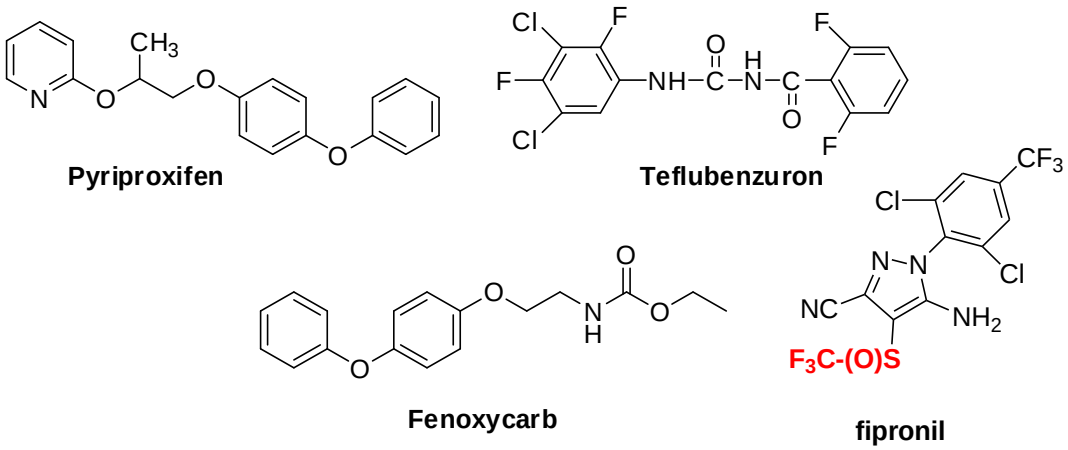
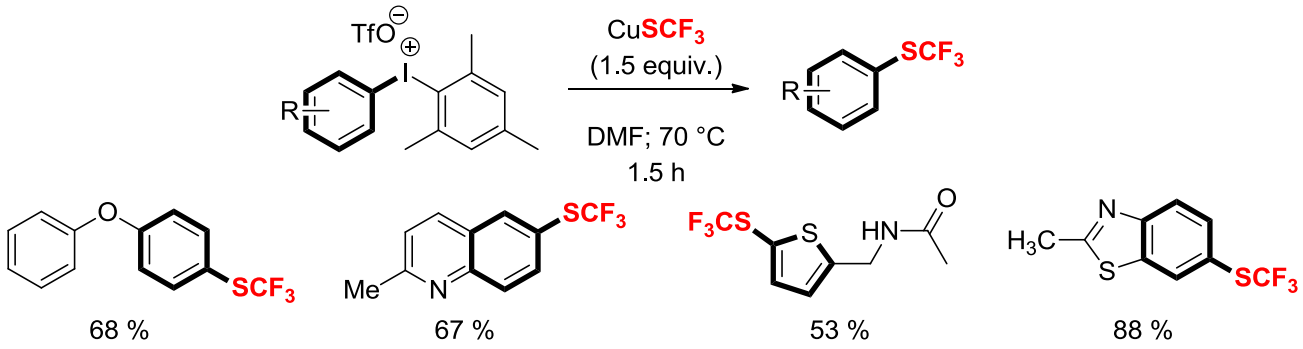


Figure 4. Structures of *Pyriproxyfen*, *Teflubenzuron* and *Fenoxycarb*

The synthesis of *tiflorex* (*flutiorex*, *vide supra* Figure 1)[4a,b] *N*-alkyl-4-(5*H*-dibenzo[*a*,*d*]-[7]annulen-5-ylidene)piperidines (being tested as dopamine antagonists,[4c,d] *toltrazuril*[4e] (Figure 1) and the thio analogue of *riluzole* (Figure 1)[4f], such aromatic derivatives containing one or more SCF_3 substituents can be prepared according to the mild and convenient strategy reported in 2016 by Rueping and co-workers.[41]

This interesting methodology[41] was applied to a series of unsymmetrical arylmesityliodonium salts where $CuSCF_3$ (1.5 equiv.) was the trifluoromethylthiolating source employed in DMF at 70 °C for 1.5 h. The reaction provided the desired products in good yields and with total regiocontrol. Scheme 7 shows the trifluoromethylthiolation reaction of unsymmetrical aryl(hetero)aryliodonium salts.

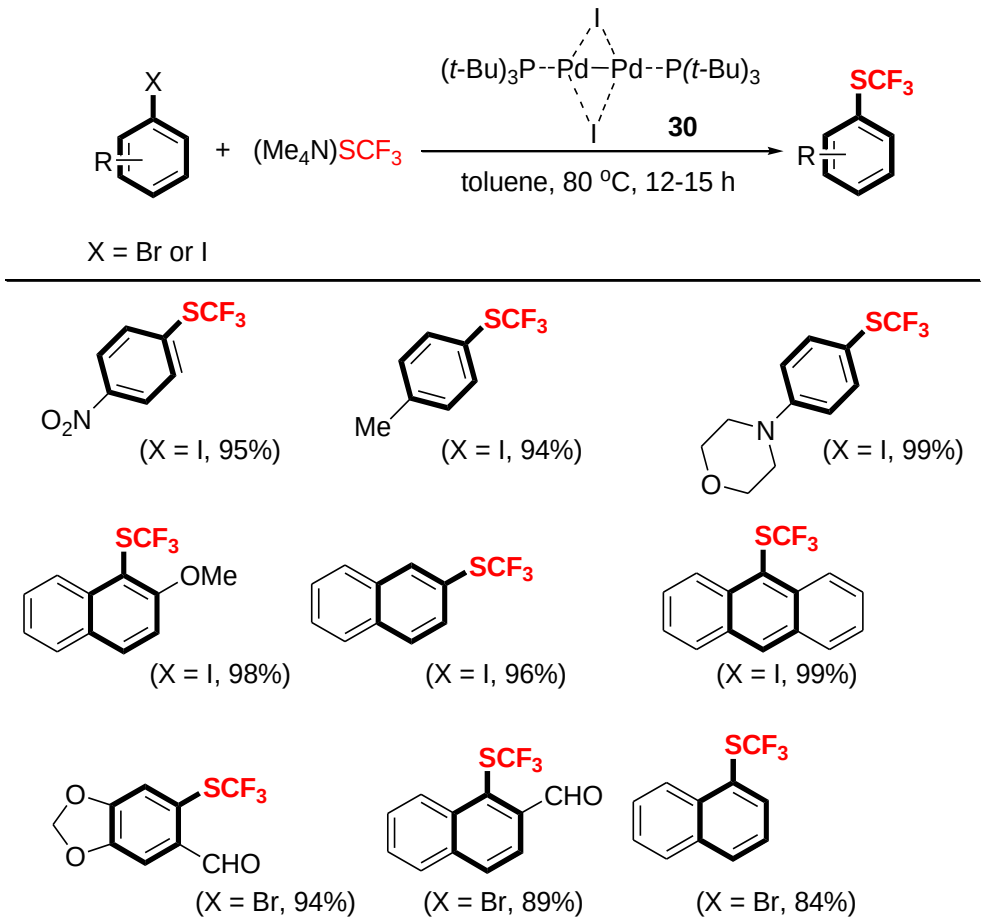
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 7. Trifluoromethylthiolation of unsymmetrical diaryldiodium salts

Schoenebeck and co-workers[42] have been able to synthesize an *in situ* CF_3S-bridged Pd^I dimer that is capable of trifluoromethylthiolate a variety of aryl iodides and bromides. The reaction of reagent **30** (Scheme 8) with the nucleophilic $(Me_4N)SCF_3$ reagent and a variety of aryl iodides and bromides in toluene as solvent are able to accomplish the trifluoromethylthiolation substitution of X (X = I, Br) for SCF_3 efficiently, as illustrated in Scheme 8.

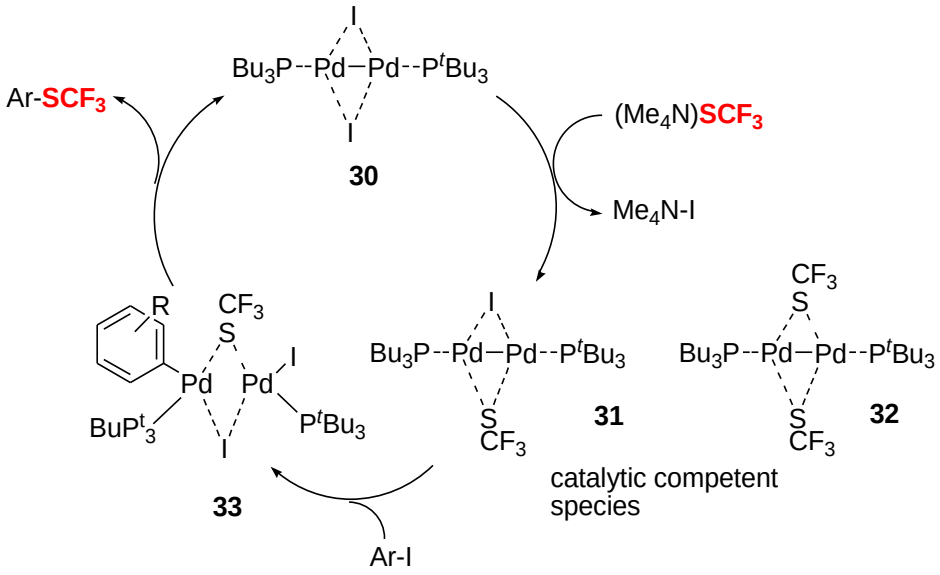
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 8. Selected examples for the trifluoromethylthiolation of aryl iodides and bromides

The proposed mechanism for the trifluoromethylthiolation of aryl iodides (and bromides) with di-palladium (I) catalyst is given in Scheme 9.

View Article Online
DOI: 10.1039/C6OB00763E

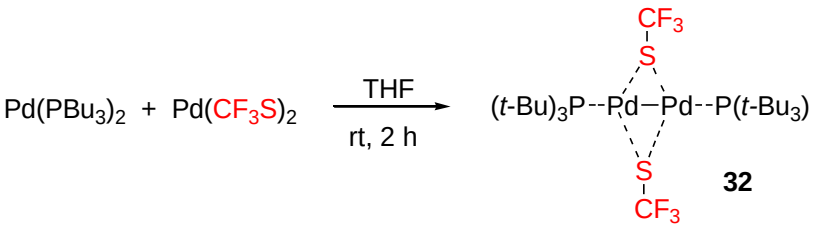


Scheme 9. Proposed catalytic trifluoromethylthiolation reaction of iodoarenes in the presence of $(Me_4N)SCF_3$ and di-Pd(I) catalyst

In the reaction mechanism shown in Scheme 9, the di-palladium (I) di-iodo catalyst **30** reacts with $(Me_4N)SCF_3$ (a good nucleophile capable of replacing an iodine atom for SCF_3 and stabilize the complex) to yield the catalytic competent species **31** or **32** (Scheme 9). One of these species (**31** or **32**) can react with Ar-I (or Ar-Br) to afford intermediate **33**, a Pd(II) species, which by ligand exchange and reduction affords the Ar-SCF_3 product and regenerates the di-iodo-di-palladium (I) catalyst **30** (Scheme 9).[42]

In order to test the mechanism, and the hypothesis that either **31** or **32** are intermediates in the trifluoromethylthiolation of aryl bromides (and aryl iodides), the authors[42] have been able to synthesize a CF_3S-bridged Pd^I dimer **32** (Scheme 10) that is capable of trifluoromethylthiolate a variety of aryl iodides and bromides.

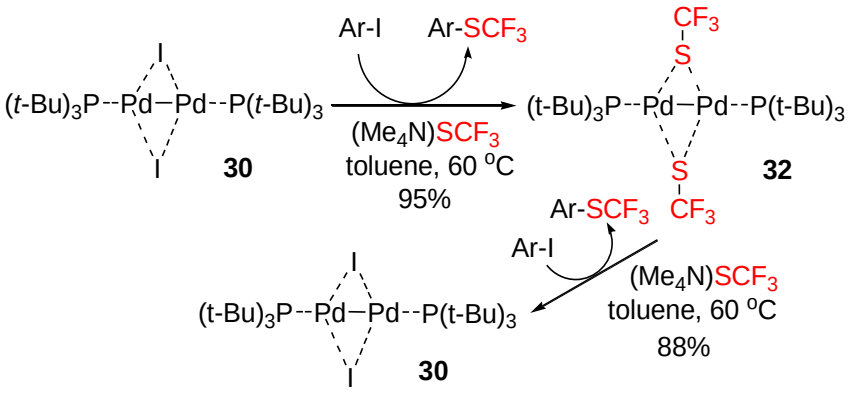
Reagent **32** is then synthesized *in situ*, from the diiodo Pd^I dipalladium catalyst, and used with the nucleophilic $(Me_4N)SCF_3$ reagent, according to Scheme 10.



View Article Online
DOI: 10.1039/C6OB00763E

Scheme 10. Synthesis of Pd^{I} dimer **32**

In this manner, reaction of reagent **30** with an aryl iodide and $(Me_4N)SCF_3$ (Scheme 11) affords 95% yield of Ar-SCF_3, and produces di-palladium (I) catalyst **32** (Scheme 11). In turn, the reaction of this di-palladium (I) (SCF_3) catalyst **32** (prepared by the independent route according to Scheme 10) with Ar-I in the presence of $(Me_4N)SCF_3$, affords 88% yield of Ar-SCF_3, regenerating catalyst **30** (Scheme 11). This methodology turned out to be quite convenient, since the re-generation of di-palladium (I) catalyst is attained with high efficiency.

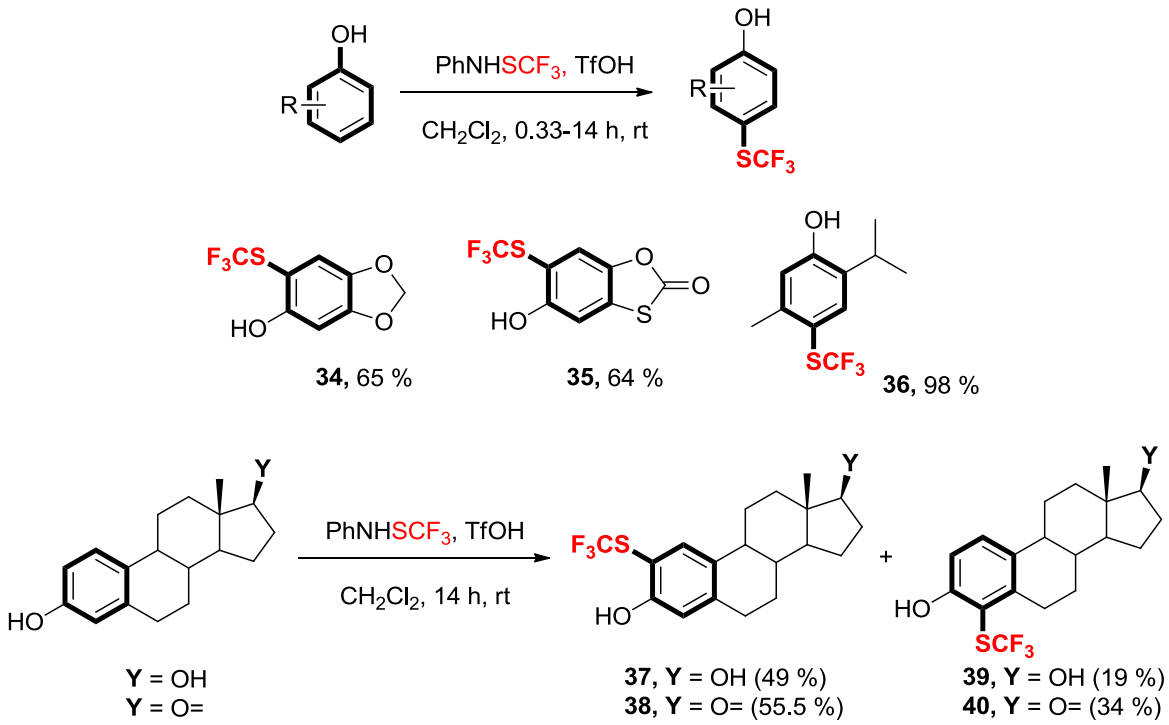


Scheme 11. Demonstration of recyclability of Pd(I)-dimer catalyst

3.2.-Conversion of C_{Ar}-H into C_{Ar}-SCF_3 Bonds

Jereb and Gosak have studied the metal-free acid-promoted electrophilic aromatic ring trifluoromethylthiolaton reaction of various substituted phenols using PhNHSCF$_3$, in the presence of 1.2 – 4 equiv. of T_fOH or $BF_3{\cdot}OEt_2$ as the acid promoters in CH_2Cl_2 at room temperature for 14 h.[43] The functionalization was highly selective and the products were obtained in good to excellent yields. Furthermore, the authors have tested this selective methodology with some biologically relevant molecules possessing a phenolic functionality (Scheme 12).

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 12. The reactivity of some biologically active phenols with $PhNHSCF_3$

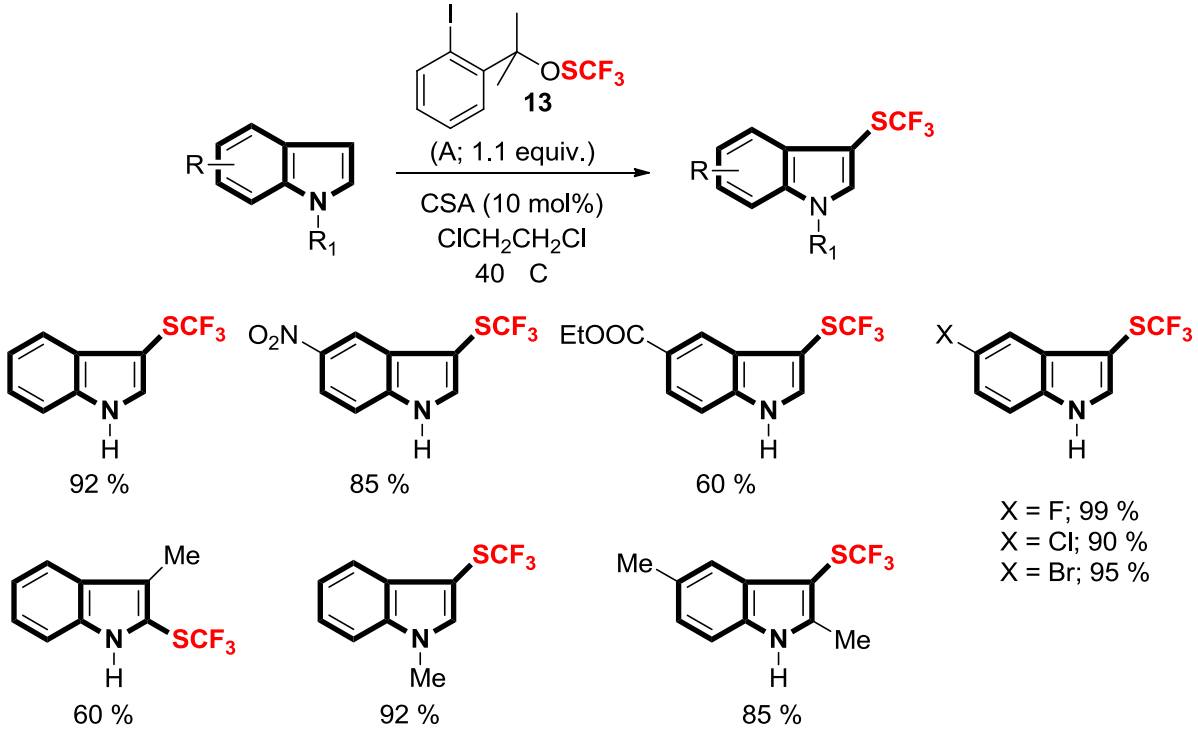
3,4-(Methylenedioxy)phenol as a highly reactive substance afforded selectively the corresponding 6-SCF_3 **34,** derivative as the sole product. 6-Hydroxy-1,3-benzoxathiol-2-one was successfully converted into its 5-SCF_3 derivative **35,** in spite of the acid-sensitive oxathiolone functional group, demonstrating that the acidic reaction system is also compatible with sensitive functionalities. *Thymol* (Scheme 12), a biologically active molecule, was also transformed to the desired product **36** in high yield (98 %). *Estrone* (Y = O, Scheme 12) and *estradiol* (Y = OH, Scheme 12) are important steroid hormones bearing a phenolic functionality and were regioselectively converted to the corresponding *o*-SCF_3 analogues **37** and **38**. However, the selectivity of trifluoromethylthiolation reaction was higher in the case of *estradiol*.

4.- Direct or Late-stage Trifluoromethylthiolation of Heterocycles

4.1.-Direct or Late-stage Trifluoromethylthiolation of Nitrogen-containing Heterocycles

View Article Online
DOI: 10.1039/C6OB00763E

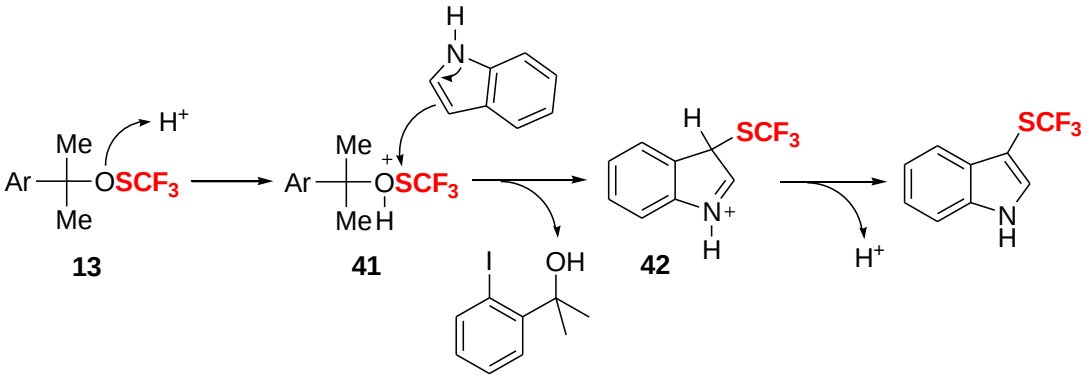
Development of new methods for functionalization of indole is of great current interest. Several groups have investigated the trifluoromethylthiolation of indole derivatives, as being this core a structural privileged motif in biological systems and biologically active natural products such as aminoacids and alkaloids. In this regard, Shen and co-workers have reported an efficient Brønsted acid-catalyzed electrophilic trifluoromethylthiolation of indoles under mild conditions.[9] Reaction of indoles with the trifluoromethylthiolation reagent **13** in the presence of camphorsulfonic acid (CSA, 10 mol%) proceeds efficiently in 1,2-dichloroethane at 40 °C for 24 – 48 h. The desired products are obtained in good to excellent yields(Scheme 13).



Scheme 13. Trifluoromethylthiolation reaction of indole derivatives

The proposed reaction mechanism for this transformation is depicted in Scheme 14.

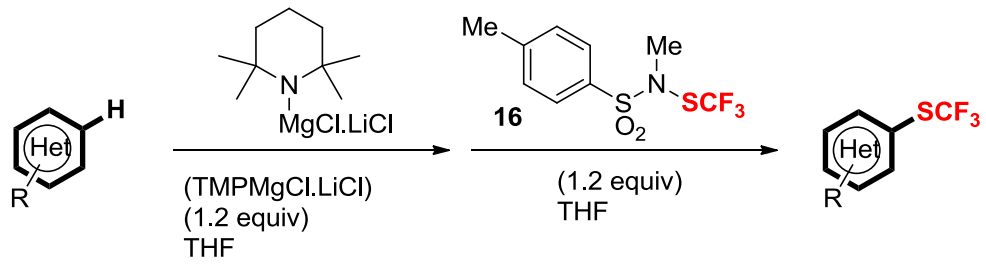
View Article Online
DOI: 10.1039/C6OB00763E

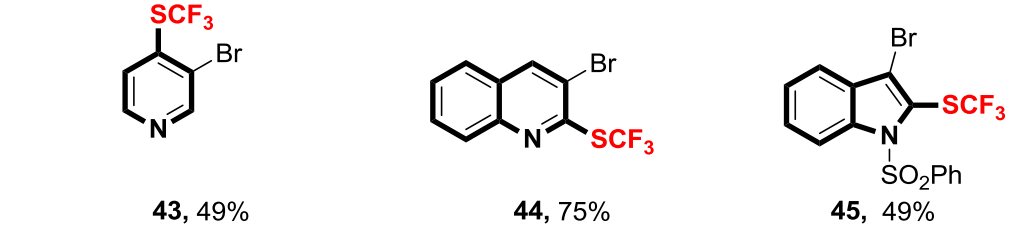


Scheme 14. Proposed reaction mechanism for the trifluoromethylthiolation of indoles

In the proposed reaction mechanism (Scheme 14) reagent **13** is protonated in the presence of camphor sulfonic acid (CSA) affording intermediate **41**. Upon electrophilic attack on indole, adduct **42** is formed, which on deprotonation affords product (Scheme 14).

Billard and co-workers have studied the trifluoromethylthiolation reaction of some heterocyclic compounds by using the second commercial generation of trifluoromethanesulfenamide reagent.[44] The reaction involves a two-step procedure: (1) selective deprotonation of the heteroarene with TMP-MgCl.LiCl (i.e.: *the Hauser base*, 2,2,6,6-tetramethylpiperidin-1-ide-MgCl-LiCl salt, 1.2 equiv.); (2) selective trifluoromethylthiolation of the formed anion with *N*-methyl-*N*-tosyl trifluoromethanesulfenamide **16** (1.2 equiv.). Interestingly, this method allows the synthesis of CF_3S-heterocycles bearing a bromine atom. Such compounds constitute valuable building-blocks for further synthesis of more elaborated molecules. Some selected trifluoromethylthiolated bromo heteroarenes are depicted in Scheme 15.





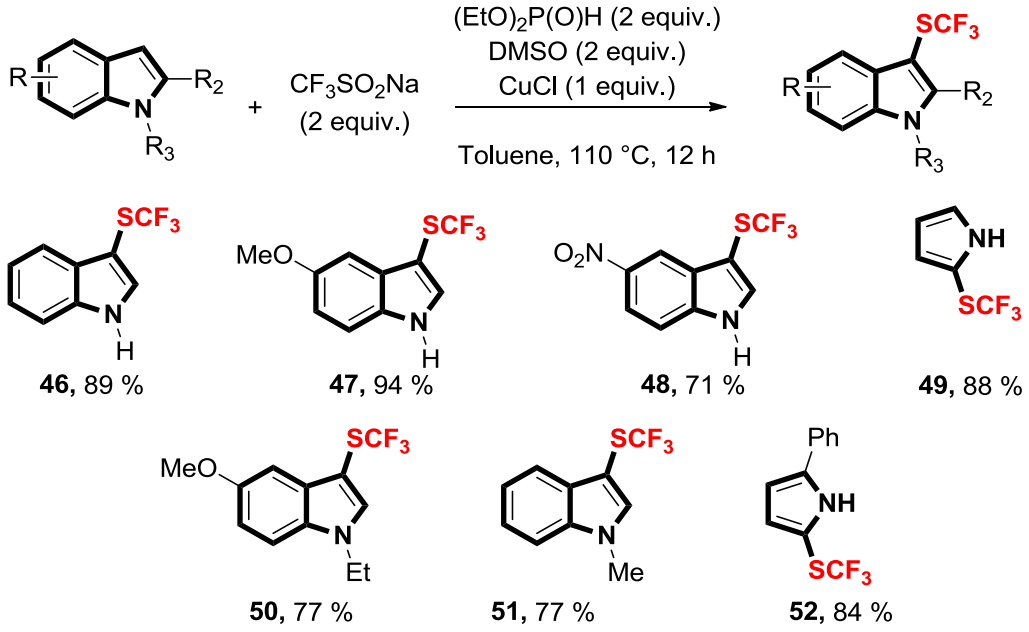
View Article Online
DOI: 10.1039/C6OB00763E

Scheme 15. Selective trifluoromethythiolation reaction of heteroarenes.

Thus, 3-bromopyridine, 3-bromoquinoline, and 3-bromo-1-phenylsulfonyl-1*H*-indole afford the corresponding CF_3S-substituted compounds vicinal to the bromine atom (**43-45**, Scheme 15).

Recently, Yi, Zhang and co-workers have reported the direct trifluoromethylthiolation of indoles and pyrroles, with sodium trifluoromethanesulfinate in the presence of CuCl.[45a] The optimized methodology involves the use of sodium trifluoromethanesulfinate[45b] ($NaSO_2CF_3$, 2.0 equiv.), $(EtO)_2P(O)H$ (2.0 equiv.), DMSO (3 equiv.), and CuCl (1 equiv.) in toluene at 110 °C for 12 h and provides the trifluoromethylthiolated indoles (**46-48, 50, 51** Scheme 16) and pyrrols (**49, 52**, Scheme 16) in good to excellent yields. In the case of indoles, a noticeable selectivity of the reaction is observed and trifluoromethylthiolation takes place on the *3*-position of indoles. This methodology tolerates a wide variety of functional groups. Enamines, important building blocks for a variety of biologically and synthetically interesting nitrogen-containing heterocycles,[46] are also used, enlarging the scope of this practical methodology. Some selected examples and the general reaction are shown in Scheme 16.

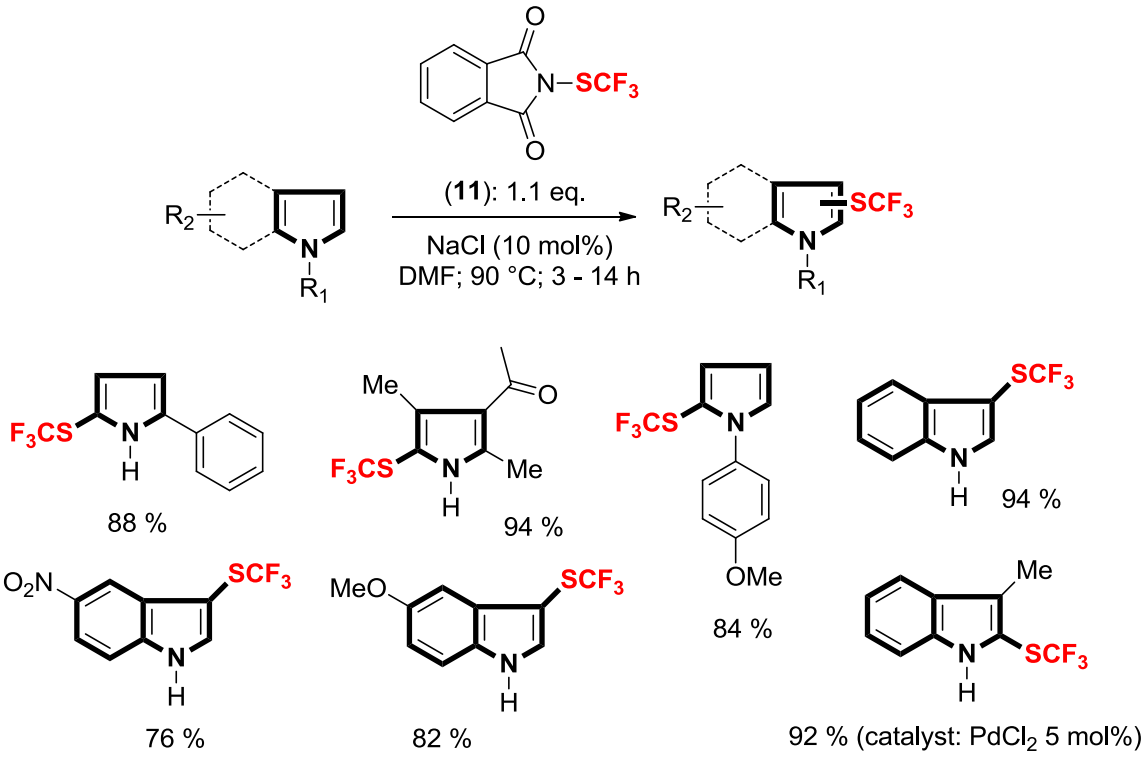
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 16. Trifluoromethylthiolation of indoles and pyrrols

A metal-free trifluoromethylthiolation methodology has been developed and applied satisfactorily to pyrroles, indoles and *N*-heteroarene derivatives.[47] *N*-trifluoromethylthiophthalimide (**11**, Scheme 17) was chosen as the electrophilic reagent[48] that easily delivers the trifluoromethylthio group onto heteroarenes. The reaction is straightforward.[49] Alkali chlorides and tetrabutylammonium chloride are the most active Lewis base catalysts to promote the activation of the electrophilic reagent **11**. Also, palladium(II) chloride and gold(III) chloride both display high catalytic activities. Scheme 17 shows some selected examples. This method is operationally simple, exhibits high functional group tolerance, and the *N*-heteroarenes do not require protecting groups.

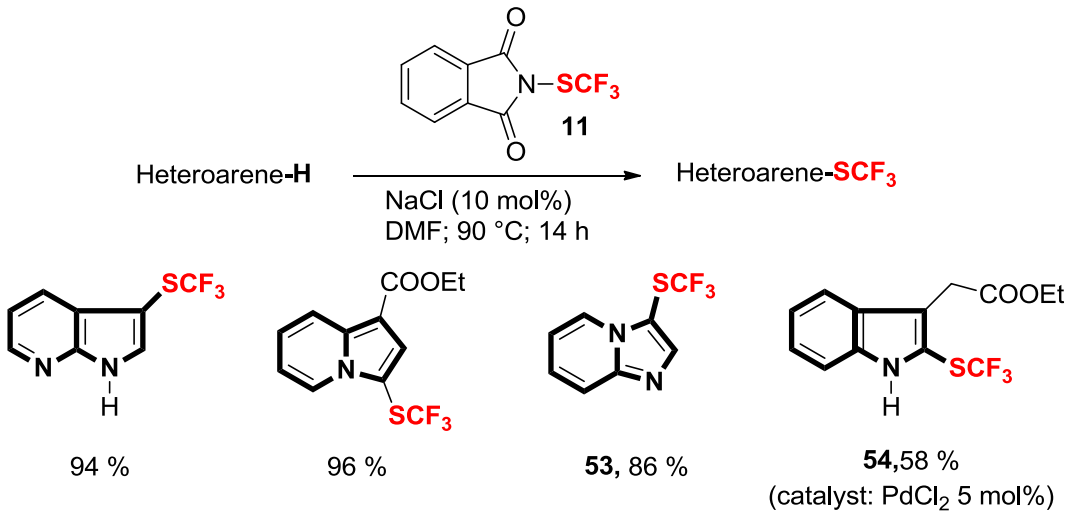
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 17. Trifluoromethylthiolation of indole and pyrrol derivatives

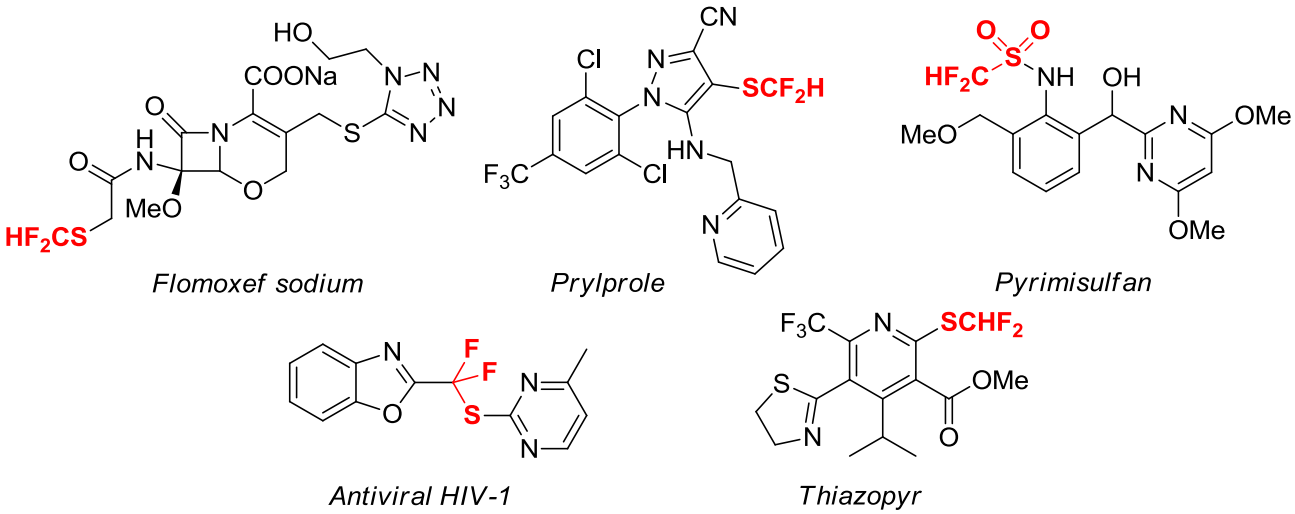
The trifluoromethylthiolation protocol was also performed on important classes of bioactive compounds such as 7-azaindole and an indolizine derivative[50] providing the desired products in excellent yields (see Scheme 18). Furthermore, this metal-free methodology was applied successfully on imidazo[1,2a]pyridine, which represents an important class of drugs acting as $GABA_A$ receptor agonists[51], rendering the product **53** in 86 % yield. The trifluoromethylthiolation reaction was carried out with ethyl-3-indole-acetate and the desired product **54** was obtained in 58 % yield using $PdCl_2$ as the catalyst instead of NaCl. This 3-substituted indole represents a derivative of indole-3-acetic acid (IAA), a naturally occurring phytohormone that, along with its derivatives, is used in the agrochemical field.[50]

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 18. Trifluoromethylthiolation of different important classes of bioactive compounds

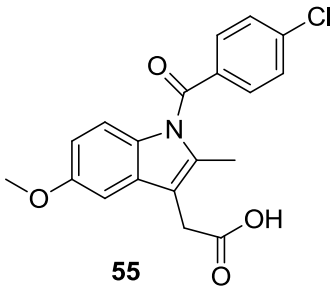
Difluoromethylthio group (−SCF_2H) which is generally considered as a highly lipophilic weak hydrogen bonding donor, is of great current interest.[52] Examples of drugs and agrochemicals bearing a difluoromethylthio unit include β-lactamase-resistant oxcephalosporin antibiotic *Flomoxef sodium*,[53] pesticide *Pyriprole*[54], broad-spectrum paddy herbicide *Pyrimisulfan*[55] and herbicide *Thiazopyr*.[56] These examples are shown in Figure 5.



View Article Online
DOI: 10.1039/C6OB00763E

Figure 5. Drugs and agrochemicals containing a difluoromethylthio group

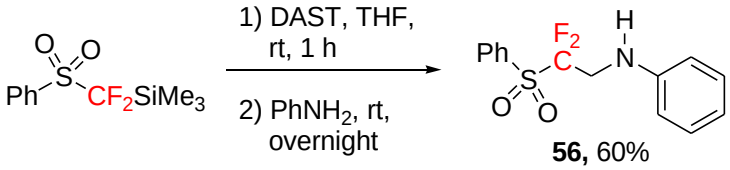
Therefore, selected methods for the late stage introduction of SCF_2H moiety is a subject of current interest. On the other hand, indole-3-acetic acids (IAAs) show widespread uses as agrochemicals, particularly as selective herbicides.[57] Substituted indole-3-acetic acids are also found as potent and selective CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) antagonists that possess good oral bioavailability.[58] The compounds may serve as novel starting points for the development of treatments of inflammatory diseases such as asthma, allergic rhinitis, and atopic dermatitis. For example, *Indomethacin* **55** (Figure 6) is a nonsteroidal anti-inflammatory drug (NSAID) that achieves analgesic and antipyretic activity through the inhibition of cylcooxygenases.



55

Figure 6. Structure of *indomethacin* **55**

Billard and co-workers[59] have recently informed a protocol for the introduction of difluoromethylthio moiety into indole-3-acetic acid derivatives. The authors[59] have developed a difluoromethylthiolation reagent that combines the lipophilic properties of CF_3S group (Hansch parameter π_R = 1.44) and the phenylsulfonyl group $PhSO_2$, characterized by the high electronic parameters (σ_m = 0.62, and σ_p =0.68) and low lipophilicity (π_R = 0.27). The synthesis of this reagent is depicted in Scheme 19.

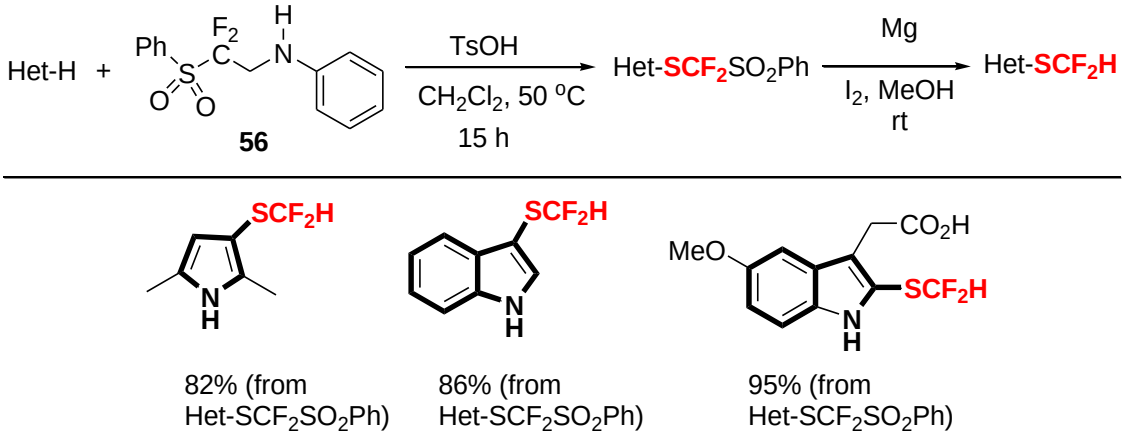


56, 60%

Scheme 19. Synthesis of (benzenesulfonyl)difluoromethanesulfenamide **56**

View Article Online
DOI: 10.1039/C6OB00763E

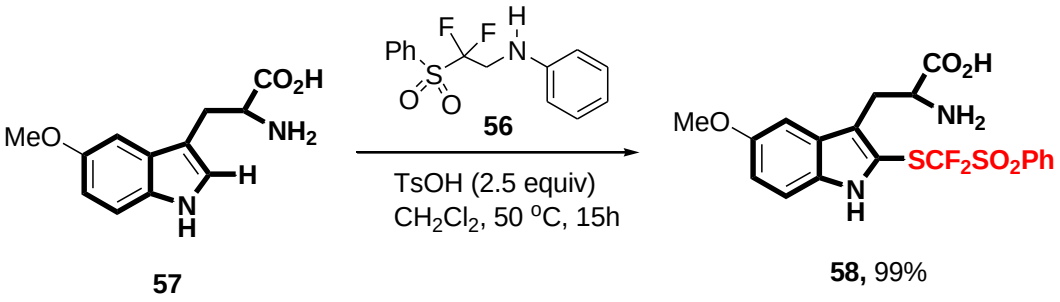
With reagent **56** in hand (Scheme 19), the authors proceeded to accomplish the difluoromethylthiophenylsulfonylation of (hetero)aromatic substrates[59] in the presence of *p*-toluensulfonic acid, TsOH, in CH_2Cl_2 as solvent at 50 ^oC. The difluoromethylthiophenylsulfonylated products can be reduced to the difluoromethylthiolated products in the presence of Mg. Some examples are depicted in Scheme 20 for the difluoromethylthiolation of one selected indole-3-acetic acid and pyrrols.



Scheme 20. Electrophilic difluoromethylthiophenylsulfonylation and ulterior reduction (Mg) towards the synthesis of difluoromethyl-substituted (hetero)aryl compounds, inter alia, 3-indole-acetic acid

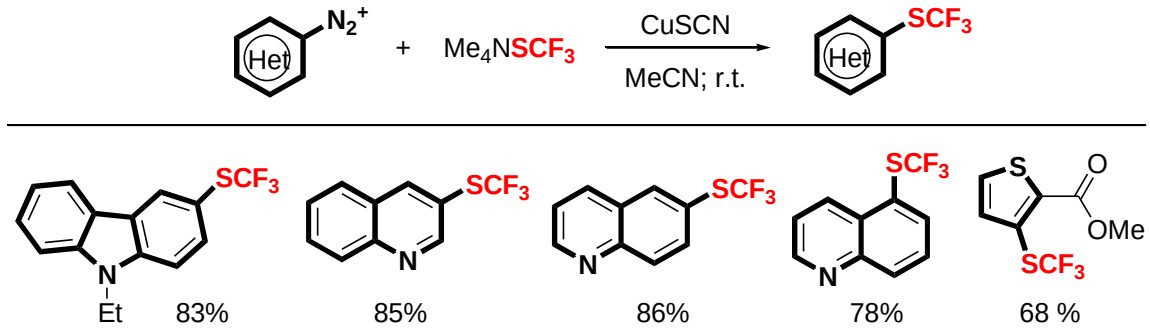
As observed with other electrophilic CF_3S reagents, the reactivity of CF_2HS is limited to electron-rich arenes. The authors observed that for less electron-rich (hetero)arenes, a stronger acid such as triflic acid is necessary to enhance the electrophilicity of **56.** An interesting observation, unprotected indoles and pyrrols can be difluoromethylthiophenylsulphonylated in high yields.[59] The reaction is also compatible with the presence of carboxylic acid moiety (Scheme 20), and free amino acid. An application to a biological relevant compound is the difluoromethylthiophenylsulfonylation of *tryptophane* **57**, which can be synthesized in good yields (**58**, Scheme 21).

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 21. Difluoromethylthiophenylsulfonylation of *tryptophane*

In 2016 Goossen and co-workers have reported the incorporation of a CF_3S group to heteroaromatic diazonium salts that are building-blocks in the preparation of agrochemicals and pharmaceuticals.[28] Reaction of an heteroaryl diazonium tetrafluoroborate (1.0 mmol) with Me_4NSCF_3 (1.8 mmol) in the presence of catalytic amounts of CuSCN (10 mol%) in MeCN for 1 h at room temperature gives the desired trifluoromethylthiolated product in good to excellent yields. Some representative examples are depicted in Scheme 22.



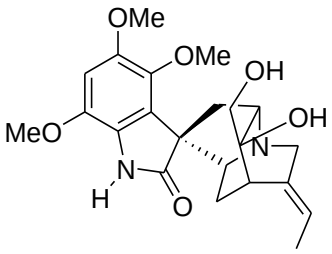
Scheme 22. Trifluoromethylthiolation of heterodiazonium salts

The mechanism for this transformation has been discussed in Scheme 4 (*vide supra*).

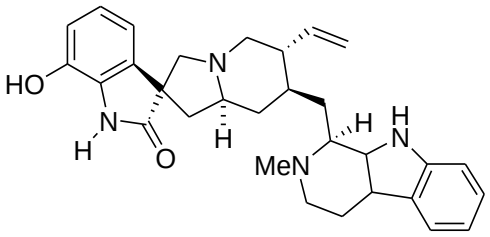
4.2.- Direct or Late-stage Trifluoromethylthiolation of Oxindole Derivatives

View Article Online
DOI: 10.1039/C6OB00763E

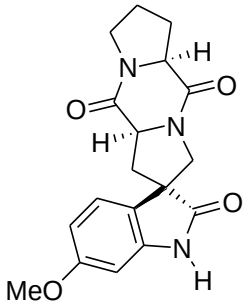
Oxindole is among one of the privileged structural motifs in biological systems and biologically active natural products.[60] *Chitosenine* **59** (Figure 7) exhibits short-live inhibitory activity of ganglionic transmission *in vivo* in rats and rabbits.[61] *Strychnofoline* **60** (Figure 7) inhibits mitosis in a number of cell lines including mouse melanoma B16, Ehrlich, and Hepatom HW165.[62] The *spirotryprostatins A* (**61**) and *B* (**62**) (Figure 7) were isolated from the fermentation broth of *Aspergillus fumigatus* and have been shown to completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mg.mL^{-1}.[63] The oxindole derivatives with biological properties are shown in Figure 7.



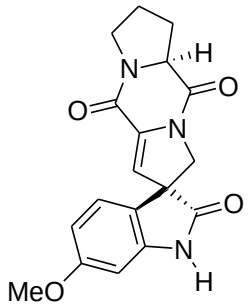
59,*Chitosenine*



60, *Strychnofoline*



61, *Spirotryprostatin A*



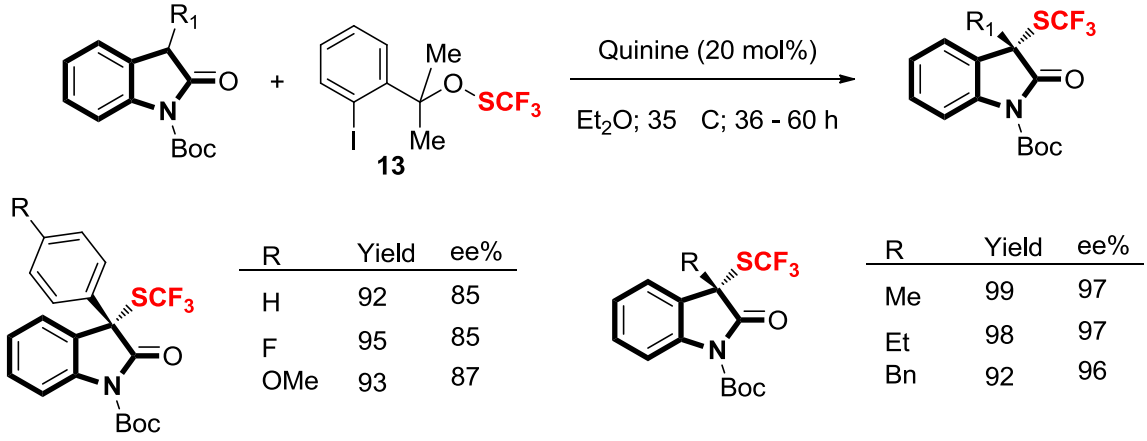
62, *Spirotryprostatin B*

Figure 7. Oxindole derivatives with pharmacological activity

Recently, Lu, Shen and co-workers have reported a cinchona alkaloid-catalyzed enantioselective trifluoromethylthiolation of 3-aryl and 3-alkyloxindoles.[64] The reaction is carried out with 3-alkyl and 3-aryloxindoles and trifluoromethylthioperoxide **13** as the CF_3S reagent in the presence of quinine (20 mol%) in diethylether at 35 °C for 36 – 60 h. The trifluoromethylthiolated products from 3-alkyloxindoles were obtained in excellent enantiomeric excess and yield, however, the enantiomeric excess diminishes significantly

View Article Online
DOI: 10.1039/C6OB00763E

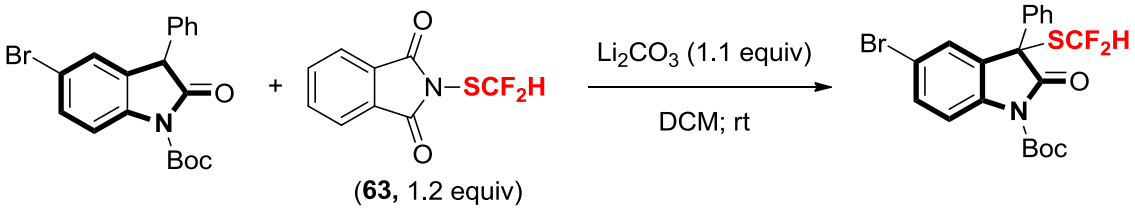
when 3-aryloxindoles are used (see Scheme 23). The absolute *S* configuration of the stereogenic center was determined by X-ray crystallographic analysis.



Scheme 23. Enantioselective trifluoromethylthiolation of 3-aklyl and 3-aryloxindoles

Rueping and co-workers have also reported an organocatalytic enantioselective trifluoromethylthiolation of oxindoles with *N*-(trifluoromethyl)thiophthalimide **11** as the CF_3S source.[65] The reaction was carried out in the presence of $(DHQD)_2Pyr$ **(**i.e.: hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether**)** as the chiral organocatalyst in Et_2O at – 10 °C and the optically active products with a quaternary stereogenic center bearing a CF_3S-group were obtained in good yields and with good to excellent enantioselectivities. The absolute *S* configuration of the stereogenic centre for all the products obtained was assigned by crystallographic analysis.

Shen and co-workers[66] have accomplished the direct difluoromethylthiolation of oxindole derivatives in the presence of *N*-difluoromethylthiophthalimide **63**, a shelf-stable electrophilic reagent, under mild conditions, in 70% yield, according to Scheme 24.

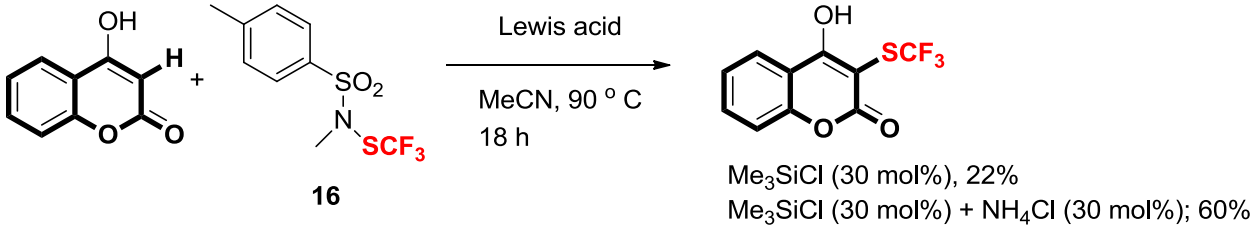


Scheme 24. Difluoromethylthiolation of oxindole derivative

View Article Online
DOI: 10.1039/C6OB00763E

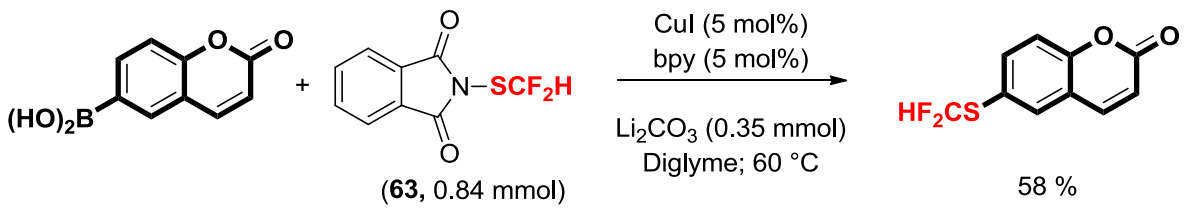
4.3.- Direct or Late-stage Trifluoromethylthiolation of Coumarin and Quinone Derivatives

Schoebeneck and co-workers have been able to trifluoromethylthiolate hydroxycoumarins.[24] In the case of 4-hydroxycoumarin, only low yield of product was observed, whatever the amount of Me_3SiCl. Because of Me_3SiCl is quenched by the hydroxyl group disfavoring the efficient activation of **16**, addition of catalytic amounts of NH_4Cl precludes the OH-$ClSiMe_3$ interaction. In this way, a good yield of trifluoromethylthiolation is observed (Scheme 25).



Scheme 25. Trifluoromethylthiolation of coumarin

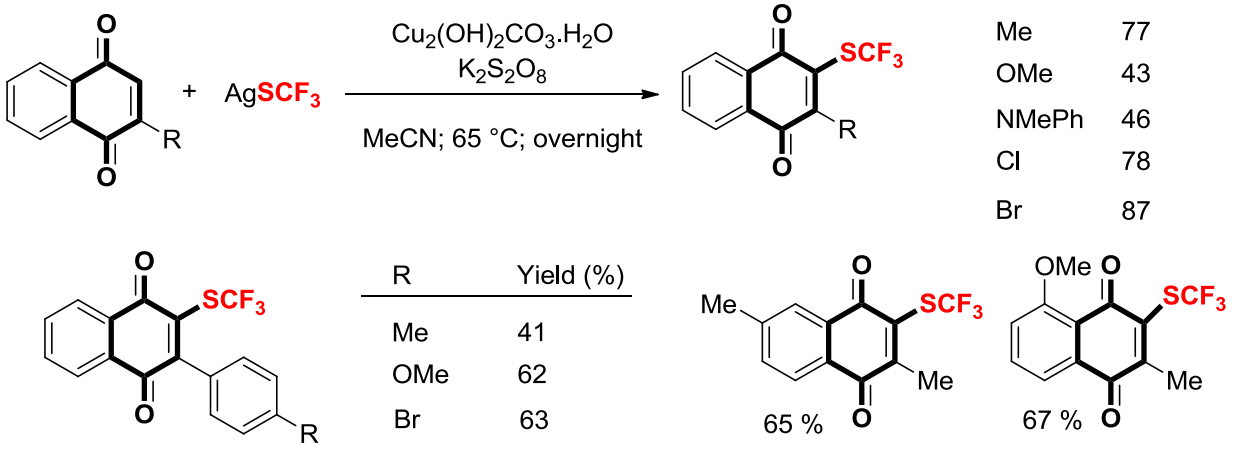
Shen and co-workers[66] have accomplished the difluoromethylthiolation of boronic acid derivatives from coumarin cores with *N*-difluoromethylthiophthalimide **63** (structure in Scheme 26) in the presence of CuI (5 mol%), bpy (5 mol%) and Li_2CO_3 in diglyme at 60 °C from their corresponding boryl acids in good yields (See Scheme 26). Thus, the copper-catalyzed method for the formation of difluoromethylthiolated arenes provides a complementary method for the introduction of the difluoromethylthio group into the medicinally important arene subunit.



View Article Online
DOI: 10.1039/C6OB00763E

Scheme 26. Difluoromethylthiolation of coumarin

Quinone motifs are prevalent in a number of naturally occurring biologically active compounds.[67] Many natural or synthetic quinones exhibit a wide range of pharmacological properties.[68] Recently, Qing and co-workers have developed a novel copper-mediated oxidative trifluoromethylthiolation of quinones.[69] The optimized protocol for this reaction involves the use of $AgSCF_3$ (0.6 mmol) as the CF_3S source, $Cu_2(OH)_2CO_3.H_2O$ (0.3 mmol) as the base and $K_2S_2O_8$ (0.6 mmol) as the oxidant, in MeCN at 65 °C under Ar atmosphere. The desired products are obtained in moderate to good isolated yields. Common functional groups including ethers, amines, and esters are well tolerated in this transformation. Notably, substrates bearing chloro- and bromo- substituents are compatible with the reaction conditions, thus providing opportunities for additional transformations. Some selected examples of the trifluoromethylthiolation reaction are depicted in Scheme 27.



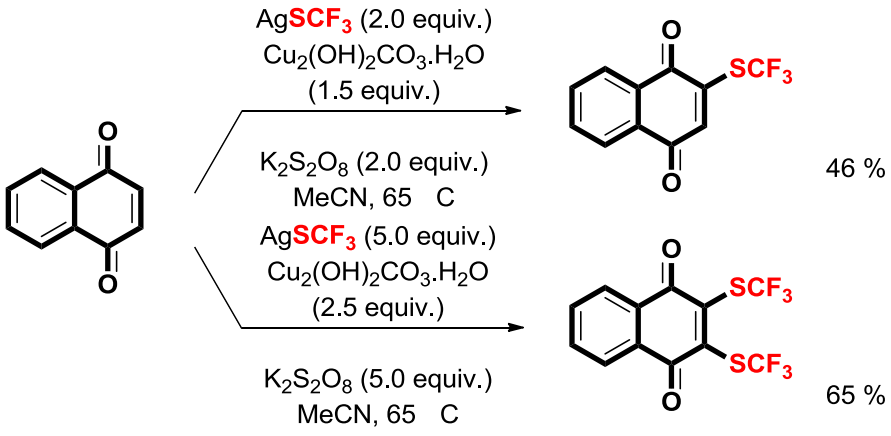
R	Yield (%)
Me	77
OMe	43
NMePh	46
Cl	78
Br	87

R	Yield (%)
Me	41
OMe	62
Br	63

Scheme 27. Copper-mediated oxidative trifluoromethylthiolation of quinones

View Article Online
DOI: 10.1039/C6OB00763E

In the case of quinones bearing electron-donating groups, however, excess amounts of $AgSCF_3$, base and oxidant were necessary to achieve high yields of substitution. Noteworthy, selective mono- and bistrifluoromethylthiolation was accomplished by controlling the amounts of reagents. Naphthoquinone, a model substrate, was subjected to react with 2 equiv. of $AgSCF_3$ and $K_2S_2O_8$ providing the mono-SCF_3 derivative in only 46 % yield; however part of naphthoquinone was not fully consumed. On the other hand, using 5 equiv. of $AgSCF_3$ and $K_2S_2O_8$, the starting material was totally consumed to give the bistrifluoromethylthiolated product in 65 % yield (see Scheme 28).



Scheme 28. Selective trifluoromethylthiolation of naphthoquinone

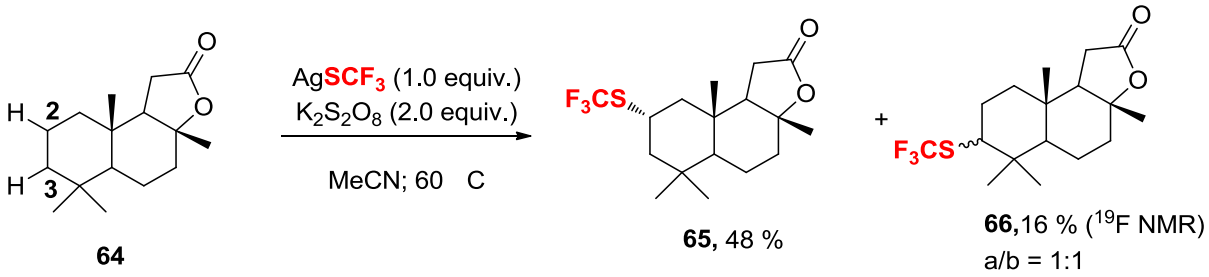
5.-Trifluoromethylthiolation of Aliphatic C Atoms

5.1.- sp^3 Carbon Atoms

Chen, Liu and co-workers have developed a direct trifluoromethylthiolation reaction of unactivated C(sp^3)-H bond of a wide variety of saturated hydrocarbons with $AgSCF_3$ (1 equiv.) in the presence of $K_2S_2O_8$ (2 equiv.) as the oxidant in MeCN at 60 °C.[70] The potential of this reaction in the late-stage synthetic planning of (+)-*sclareolide* **64** (Scheme 29), a terpenoid natural product with antifungal and cytotoxic properties, is shown in Scheme 29. Although the terpenoid contains 16 aliphatic C(sp^3)-H bonds, the C-2-

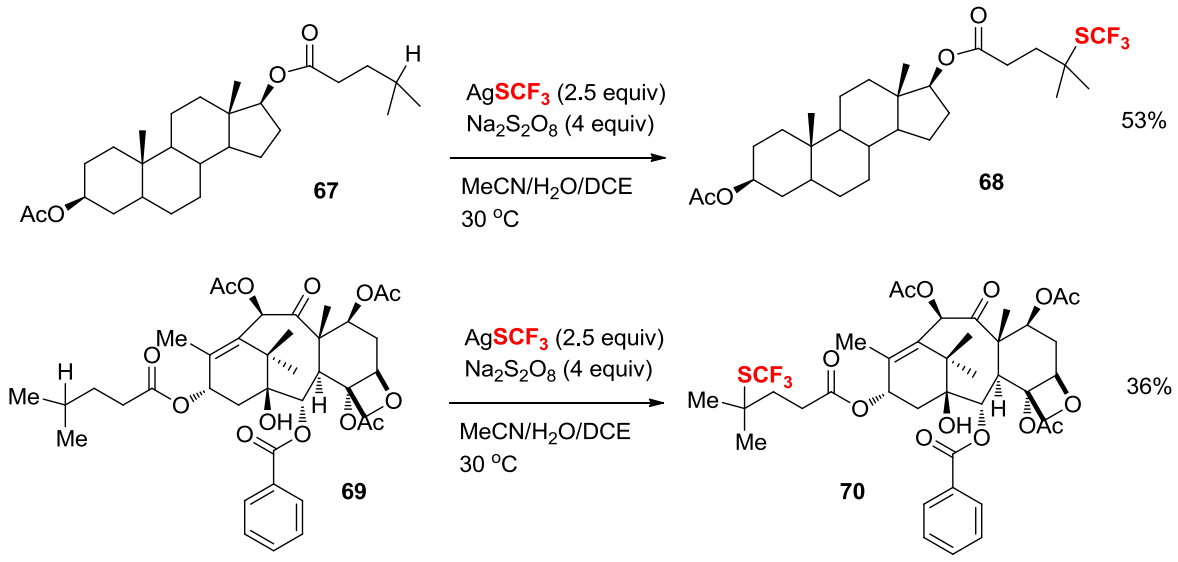
View Article Online
DOI: 10.1039/C6OB00763E

equatorial trifluoromethylthiolated product **65** is isolated as the major product in 48 % yield with minor amounts of product **66** as a 1:1 molar ratio of diasteromers α and β.



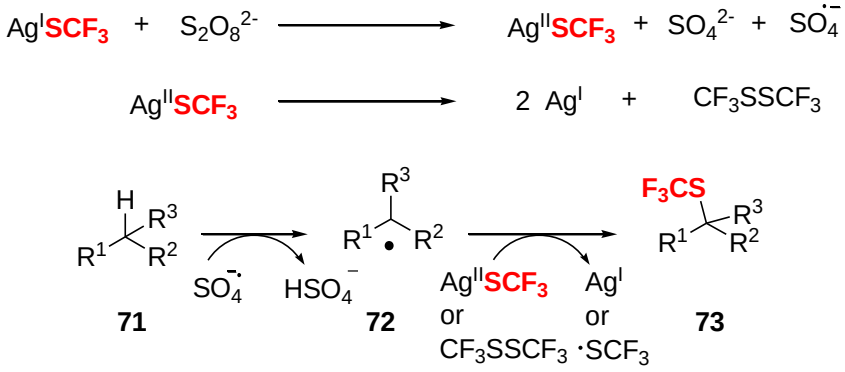
Scheme 29. Direct trifluoromethylthiolation reaction of (+)-*sclareolide* with $K_2S_2O_8$ and $AgSCF_3$

5α-Androstane-3β,17β-diol **67** (Scheme30) afforded the trifluoromethylthiolated product **68** in 53% yield (Scheme30). A derivative of the anticancer drug *taxol* **69** provided the corresponding trifluoromethylthiolated product **70** in 36% yield (Scheme30). Trifluoromethylthiolation occurred selectively at the methine position on the side chain owing to steric hindrance and the deactivation of the available tertiary C-H bonds on the rings of these substrates (**67**, **69**), Scheme30.[18]



View Article Online
DOI: 10.1039/C6OB00763E

Scheme30. Trifluoromethylthiolation of 5α-androstane-3β,17β-diol **67** and anticancer drug taxol **69**

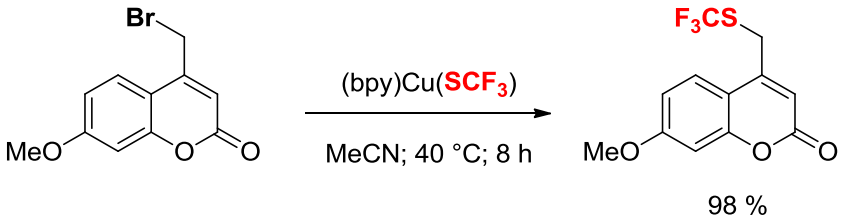


Scheme31. Proposed reaction mechanism for the trifluoromethylthiolation

The trifluoromethylthiolation does not take place at either of the two ring methine positions because of steric impediment; instead, selective trifluoromethylthiolation is observed at the C2 methine position, which is less sterically demanding.[18]

The mechanism for the transformation is depicted in Scheme31.[18] It is known[71] that peroxydisulfate anion disproportionate into sulfate dianion and sulfate radical anion in the presence of silver(I) salts. The authors[18] hypothesized that carbon radical **72** is formed by oxidation with a sulfate radical anion. Ag^{II}SCF$_3$ or CF$_3$SSCF$_3$, which may be formed from Ag^{II}SCF$_3$ through electron transfer,[72] can then react with the generated carbon radical **72** to provide the desired trifluoromethylthiolated product **73**.[73]

Jiang, Wang and co-workers have studied the nucleophilic trifluoromethylthiolation reaction of benzyl bromides using (bpy)Cu(SCF$_3$) (0.25 mmol) that provide the desired benzyl trifluoromethylsulfides in good to excellent yields.[74] Noteworthy, the authors have applied this methodology to the trifluoromethylthiolation of 4-bromomethyl-7-methoxycoumarin, a biologically active molecule, and the 4-trifluoroethylthio-7-methoxycoumarin is obtained in 98 % yield (Scheme32).

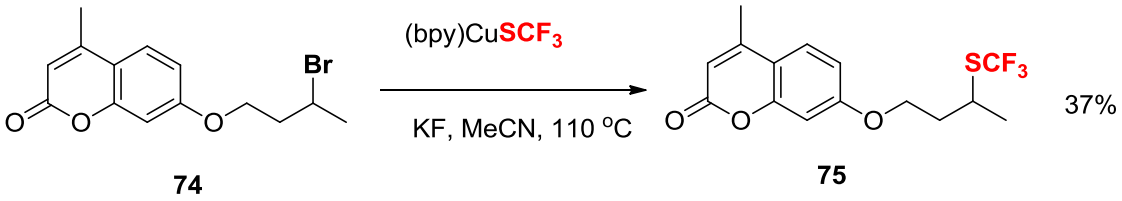


View Article Online
DOI: 10.1039/C6OB00763E

Scheme32. Trifluoromethylthiolation of 4-bromomethyl-7-methoxy coumarin

Alkylation of 4-methyl-7-hydroxycoumarin with alkyl halides provides 7-alkyloxy coumarin derivatives that are useful components in sun-screen with topical application in human skin.[75,76] Enhanced lipophilicity of these coumarin derivatives can be achieved by introduction of the CF_3S group to the aliphatic pendant chain.

Weng and co-workers[77] have accomplished the trifluoromethylthiolation of alkyl bromides of relevant biological substrates, employing (bpy)Cu(SCF_3), KF, in MeCN as solvent, as depicted in Scheme33. Treatment of 7-(3-bromobutyryloxy)-4-methyl coumarin **74** with (bpy)CuSCF_3 in the presence of KF (2 equiv.) in MeCN at 110 °C for 15 h gives the expected SCF_3-derivative in modest yield[75,76] (Scheme33).

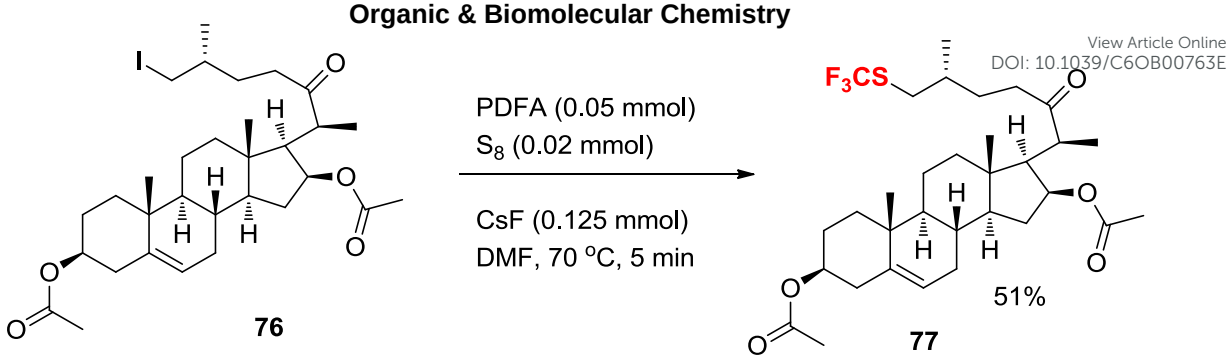


Scheme33. Trifluoromethylthiolation of 7-(3-bromobutoxy)-4-methyl-2*H*-chromen-2-one

The authors[77] concluded by a series of experiments that there are no radicals involved in the reaction by attempting to react bromomethyl cyclopropyl with (bpy)Cu(SCF_3), KF, in MeCN as solvent, at 110 °C, as no ring opening product from the cyclopropyl moiety was observed.

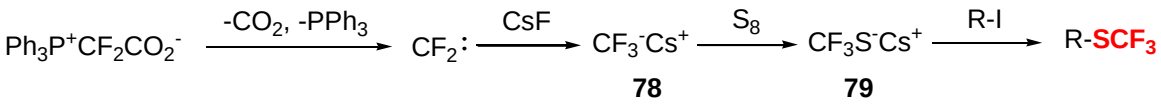
Xiao, Liang and collaborators[78] have attempted the trifluoromethylthiolation substitution of iodides utilizing difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA) as an efficient difluorocarbene reagent which can produce difluorocarbene in situ after decarboxylation of the phosphonium ylide $Ph_3P^+CF_2$[79] under neutral conditions without the addition of any other additive or base. The addition of S_8, CsF as additives in DMF as solvent at 70 °C are the optimized reaction conditions. They[78] applied the strategy to pharmacologically active compounds such as iodosteroid **76** as shown in Scheme34, affording 51% yield of **77** with no evidence of epimerization.

View Article Online
DOI: 10.1039/C6OB00763E



Scheme34. Trifluoromethylthiolation of iodosteroid **76**

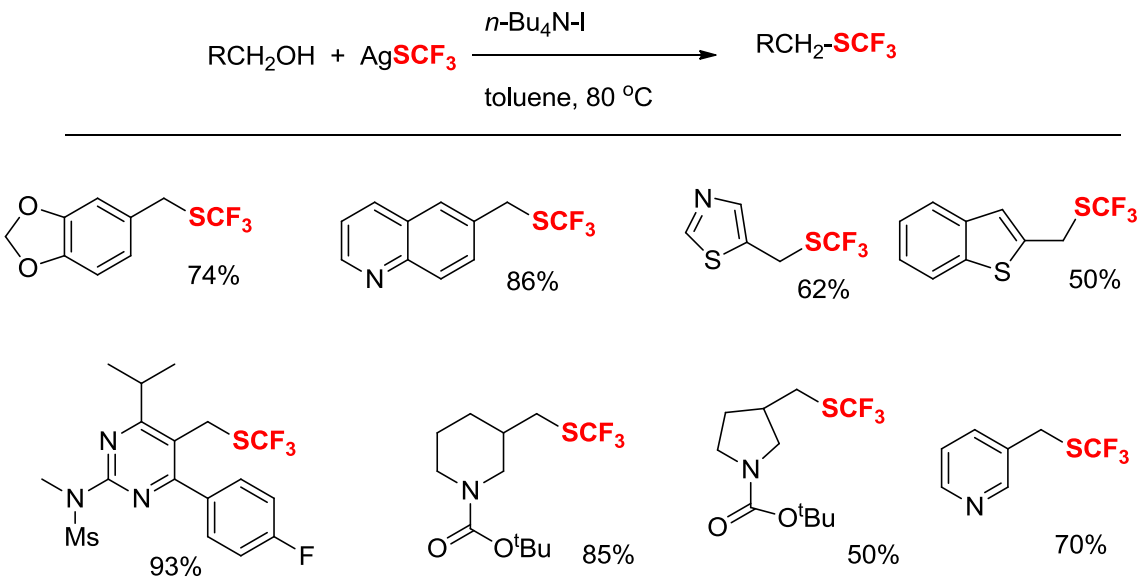
The authors[78] proposed the reaction mechanism illustrated in Scheme35. The reaction may proceed through decarboxylation of PDFA, which releases PPh_3 and generates difluorocarbene in situ. Difluorocarbene is readily trapped by CsF to produce the trifluoromethyl anion **78**, followed by the formation of the trifluoromethylthio anion **79** in the presence of elemental sulfur. The nucleophilic substitution between **79** and an alkyl electrophile furnishes the final product. The final step for the reaction between **79** and the electrophile should proceed by direct nucleophilic substitution without the occurrence of quaternization of PPh_3 (Scheme35).



Scheme35. Proposed reaction mechanism for the trifluoromethylthiolation of alkyl iodides

Qing and co-workers[80] have investigated the dehydroxytrifluoromethylthiolation reaction of alcohols. The authors found that the optimal reaction conditions involve the use of $AgSCF_3$, toluene as solvent, *n*-Bu_4NI as activator, at 80 °C. The authors apply the optimized reaction conditions to a series of primary alcohols, and the scope of the reaction is summarized in Scheme 36.

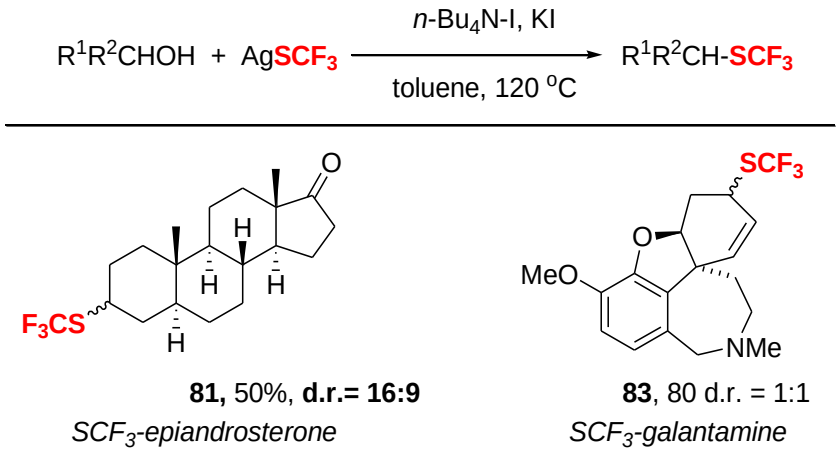
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 36. Scope of the trifluoromethylthiolation of primary alcohols

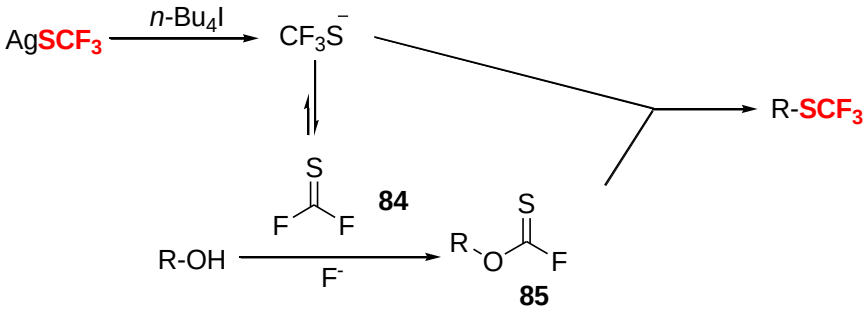
The authors[80] have also applied the strategy to compounds of medicinal interest. When *epiandrosterone* (**80**), a steroid hormone with weak androgenic activity, is submitted to the optimal reaction conditions the desired product **81** is obtained in 50% yield with 16:9 diastereoselectivity (Scheme 37). The reaction of *galantamine* (**82**), a drug used to treat Alzheimer´s disease and dementia, proceeds well and affords the trifluoromethylthiolated product **83** in 80% yield with 1:1 diastereoselectivity (Scheme 37). The above results show that this protocol might be applicable to late-stage dehydroxytrifluoromethylthiolation of some medicinally relevant compounds.

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 37. Synthesis of CF_3S-*epiandrosterone* and CF_3S-*galantamine*

The proposed reaction mechanism is illustrated in Scheme 38. The activation of $AgSCF_3$ (with *n*-Bu_4N-I) affords the more active trifluoromethanethiolate, which subsequently decomposes into carbonothioic difluoride **84** and fluoride anion. Then the alcohol reacts with in situ generated carbonothioic difluoride **84** to produce the carbonofluoridothioate intermediate **85**, which subsequently undergoes nucleophilic substitution by trifluoromethanethiolate to provide the trifluoromethylthiolated compound (Scheme 38).



Scheme 38. Proposed reaction mechanism for the trifluoromethylthiolation of alcohols

Allylic trifluoromethylthioethers are of particular significance due to a high hydrophobicity which makes them attractive for their potential applications in agrochemicals and pharmaceuticals. In fact, allylic trifluoromethylthioethers are highly versatile synthons in the preparation of biologically active compounds. Hang, Weng and co-workers have developed an expeditious synthetic protocol for the preparation of allylic

View Article Online
DOI: 10.1039/C6OB00763E

and propargylic trifluoromethyl thioethers with broad substrate scope by using air- and moisture-stable copper reagents.[81] This reaction provides the formation of a new C_{sp3}-SCF_3 bond from commercially available allyl halides. The methodology involves the use of CF_3SiMe_3 (3 equiv.) and S_8 (3 equiv.) in the presence of catalytic amounts of CuI (20 mol%) and of ligand bpy (20 mol%), KF (3 equiv.), a 18-crown-6 ether (2 equiv) in dioxane at 50 °C under N_2 during 16 h. In general, the desired products are obtained in moderate to good yields. In the case of propargyl chlorides, the catalytic amounts of Cu and the ligand are raised to 50 mol% and the optimal solvent is DMF. The products are formed in good yields.

Alkyl trifluoromethyl sulfides have been involved in numerous synthetic applications, mainly devoted to the synthesis of bioactive molecules. Examples include trifluoromethylthioacetic acid and its derivatives, which serve as useful intermediates in the synthesis of the cephalosporin antibiotic *cefazaflur* **86**[82] (Figure 8). Cephalosporin belongs to the β-lactam antibiotics and shows outstanding antibacterial properties *in vitro* and *in vivo*. In particular, one derivative, 7-trifluoromethylthioacetamido-3-(1-methyl-l*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (SK&F 59962, *cefazaflur* **86**), was found to have outstanding antibacterial activity *in vitro* and *in vivo.* Noteworthy, the presence of a trifluoromethylthioacetamido group attached to the cephalosporanic acids and cephalosporins also have *in vitro* activity essentially equal to that of the unfluorinated analog *cephalotin* **87** *(cefalotin).* Figure 8 shows representative structures of some *cephalosporin* derivatives.

View Article Online
DOI: 10.1039/C6OB00763E

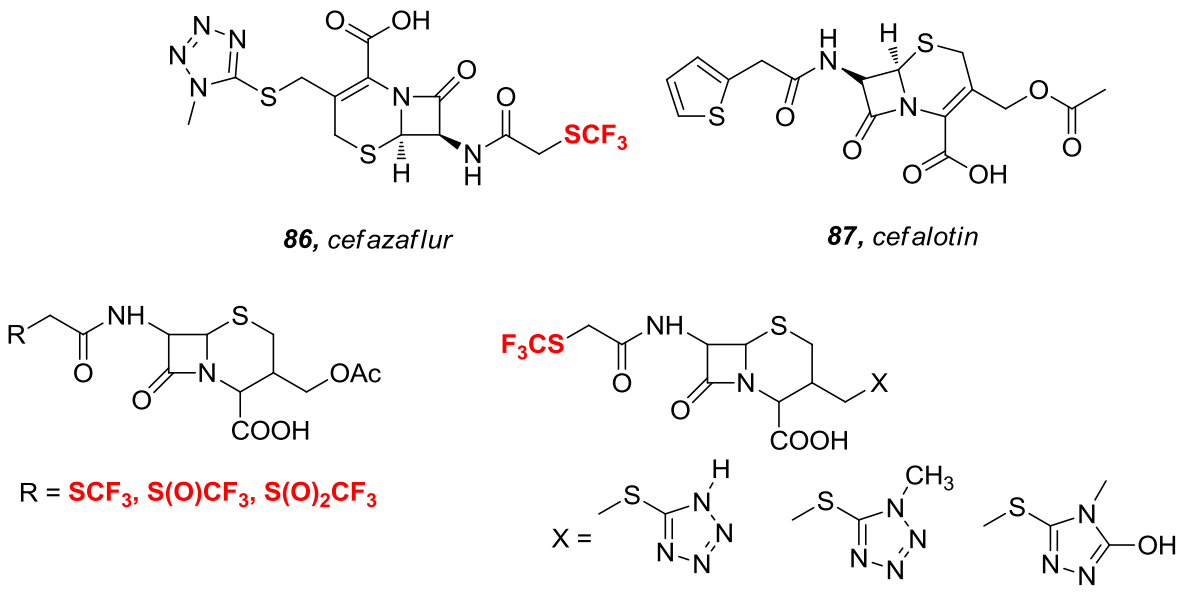
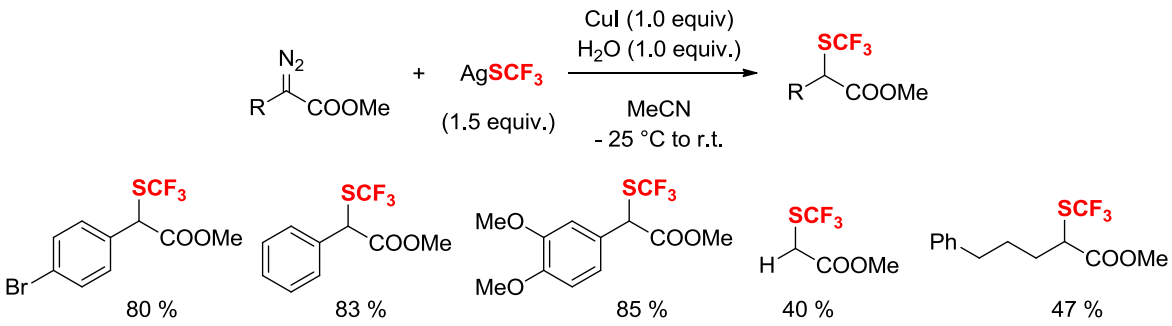


Figure 8. Representative structures of some *cephalosporin* derivatives

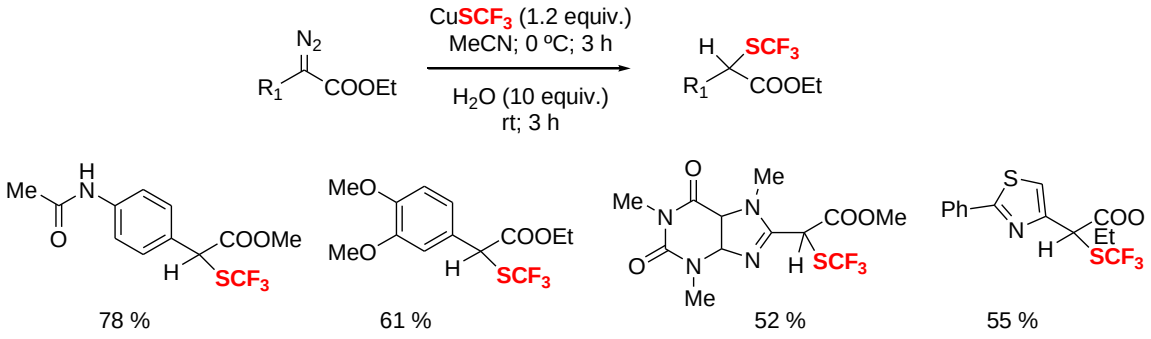
A synthetic strategy for the preparation of cephalosporin derivatives implies the condensation of trifluoromethylthioacetic acids and their derivatives with the amino group of the β-lactam moiety. Wang and co-workers have developed an efficient method to introduce the trifluoromethylthio group through the Cu(I)-promoted reaction of α-diazoarylacetates in the presence of nucleophilic $AgSCF_3$ as a trifluoromethythiolation reagent.[83] Various α-diazo arylacetates were smoothly converted under mild conditions to form the $C(sp^3)$–SCF_3 bond providing the expected products in good yields. The optimal protocol involves the reaction of methyl α-diazoarylacetate (1 equiv.) with $AgSCF_3$ (1.5 equiv.) in the presence of 1.0 equivalent of CuI and H_2O, respectively, in MeCN. Generally, this protocol applies satisfactorily with a series of α-diazoarylacetates bearing either electron-donating or electron-withdrawing groups. Some selected examples of the trifluoromethylthiolation reaction are shown in Scheme 39.

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 39. Trifluoromethythiolation of some methyl α-diazoarylacetates

Rueping and co-workers have developed a practical protocol for hydrotrifluoromethylthiolation of α-diazo esters in combination with a nucleophilic SCF_3 source that provides access to valuable trifluoromethylthiolated compounds.[84] The methodology involves the use of $CuSCF_3$ (1.2 equiv.) in the presence of H_2O as an additive in MeCN as solvent at 0 °C to room temperature for 6 h. Noteworthy, the additive was added to the reaction mixture after 3 h of reaction time. The desired products are obtained in good yields and the method is applicable in the presence of a wide range of functional groups (Scheme 40).

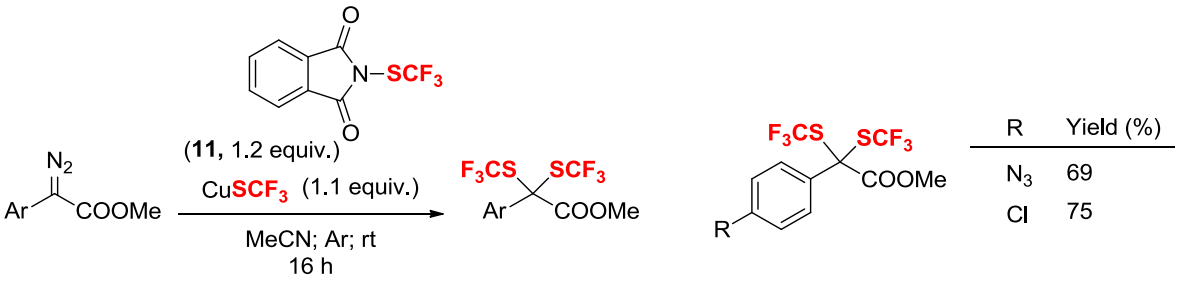


Scheme 40. Scope of the reaction using different aryldiazoacetic esters

The authors have also studied the full potential of diazo compounds and addition of an electrophilic CF_3S source to the reaction mixture in the absence of water that provided the formation of dithiolated products in good yield. *N*-Trifluoromethylthiophthalimide **11** was selected as the electrophilic CF_3S source. The method involves mixing of diazo ester

View Article Online
DOI: 10.1039/C6OB00763E

with **11** (1.2 equiv) in dry MeCN and, after 2 minutes, $CuSCF_3$ (1.1 equiv.) was added. Then, the yellow solution was stirred for 16 h at room temperature (Scheme 41). The dithiolated products were characterized by ^{19}F NMR.

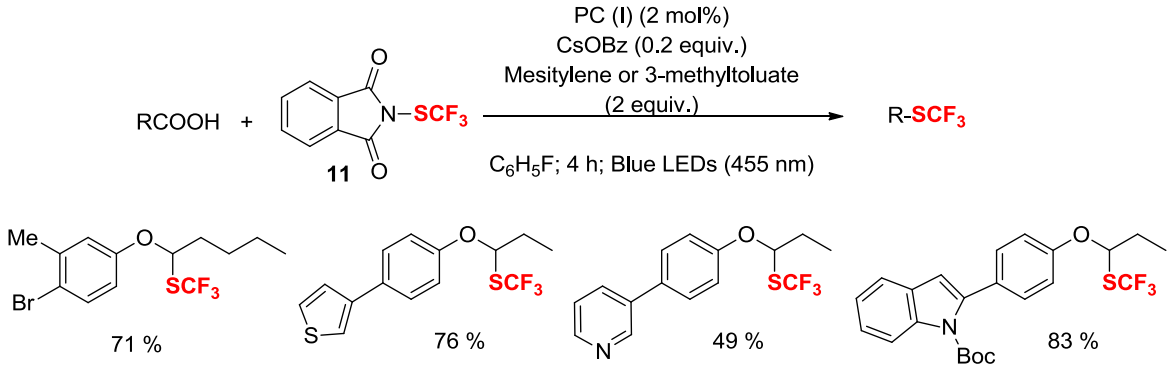


Scheme 41. Double trifluoromethythiolation of α-diazo esters

Incorporation of the SCF_3 group is known to increase a molecule's lipophilicity and metabolic stability.[85] In addition, the CF_2HS group has recently been found to be a highly lipophilic hydrogen bond donor, and is a potential lipophilic OH or NH surrogate.[86] Therefore, the development of mild and straightforward methodologies, capable of tolerating a wide range of functional groups, for the incorporation of SCF_2X (where X = H or F) moieties would be highly desirable. Furthermore, incorporation of CF_3S can be done selectively on alkyl-pendant chains instead of aryl moieties (*vide supra*). Alkyl carboxylic acids are desirable starting materials for the synthesis of valuable biologically compounds. In addition, their decarboxylation, which yields the traceless by-product CO_2, is an excellent method for accessing alkyl radicals, which can be readily functionalized. Glorius and co-workers have reported in 2016 an interesting methodology involving a visible light-promoted decarboxylative di- and trifluoromethylthiolation of alkyl carboxylic acids.[87] Reaction of the alkyl carboxylic acid with **11** (2 equiv.) in the presence of cesium benzoate (0.2 equiv) and the photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (i.e.: [4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate, PC (I), 2 mol%) in fluorobenzene as solvent under irradiation with blue LEDs (λ_{max}=455 nm). Addition of a sacrificial hydrogen atom donor, mesitylene or 3-methyltoluate (2 equiv.) is also required. The desired products are formed in good yields and a variety of different substituents are also tolerated. Some selected examples are depicted in Scheme 42. The metal-free trifluoromethylthiolation

View Article Online
DOI: 10.1039/C6OB00763E

reaction of carboxylic acids was also achieved employing the strongly oxidizing organic dye 9-mesityl-10-methylacridinium perchlorate (PC (II), 5 mol%- photocatalyst II).



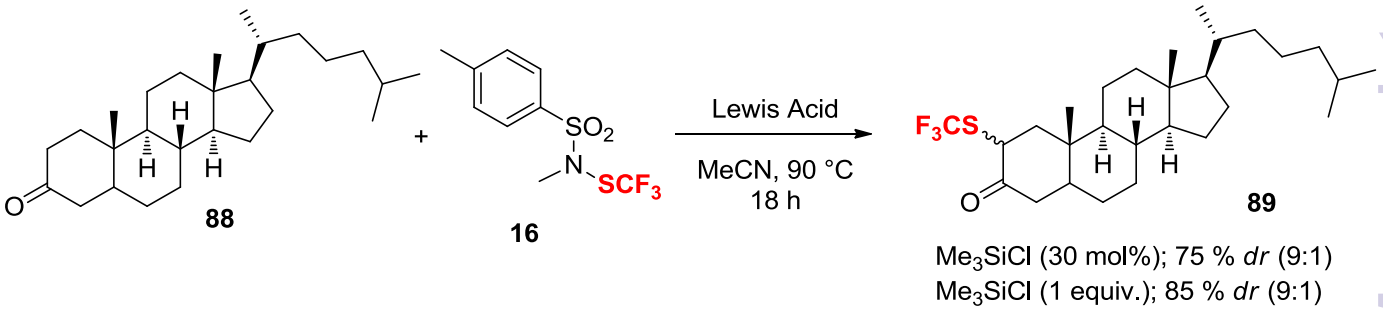
Scheme 42. Trifluoromethylthiolation reaction of alkyl carboxylic acids

Shen and co-workers reported the silver(I)-catalyzed decarboxylative trifluoromethylthiolation of alkyl carboxylic acids using $AgNO_3$ (30 mol%) and $K_2S_2O_8$ (1 equiv.) as oxidant.[88] While Shen's method was effective for the synthesis of secondary and tertiary alkyl products, it was found to be inefficient for the preparation of primary alkyl-SCF_3 species.

5.1.2-Trifluoromethylthiolation at the α- and β-positions of carbonyl compounds

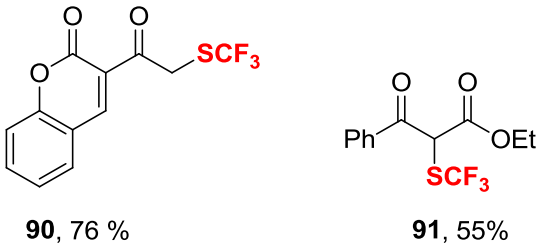
Billard and co-workers have studied the α-trifluoromethylthiolation of ketones and aldehydes with *N*-trifluoromethylthiosulfonamide (**16**) in catalytic soft acidic conditions to provide selectively the mono-trifluoromethylthiolated products in good to excellent yields.[89] The optimal conditions of the reaction involve the use of Me_3SiCl (30 mol%) as the Lewis acid catalyst and dry MeCN as the solvent. The reaction proceeds efficiently at 90 °C. The methodology is also useful for carbonyl compounds that are biologically active such as the one depicted in Scheme 43. Treatment of *cholestanone* **88** with **16** in the presence of catalytic amounts of Me_3SiCl gives the α-trifluoromethylthiolate derivatives **89** in 75 % yield with a diastereoselective ratio of 9:1. However, when Me_3SiCl is rose to 1.0 equiv. the yield is enhanced to 85 % with the same *dr*.

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 43. α-Trifluoromethylthiolation of a biologically active ketone *cholestanone*

Other biological interesting carbonyl compounds can be trifluoromethylthiolated in the presence of reagent **16** and Me_3SiCl, as illustrated in Figure 9. Acetate is one of the most fundamental building blocks in nature and organic synthesis, from which numerous natural products and medicinally important compounds, such as polyketides and statins are formed. Therefore, the incorporation of a CF_3S functionality into such a building block is of current interest. The trifluoromethylthiolation of ethyl-3-oxo-3-phenylpropanoate, affords product **91** in 55% yield.



90, 76 % **91**, 55%

Figure 9. Trifluoromethylthiolation employing reagent **16** and Me_3SiCl as Lewis acid

Tetralones bearing different oxygen functional groups on the aromatic ring are important intermediates for the synthesis of a wide variety of compounds, many of which are useful as chemotherapeutic agents.[90] For example, tetralones are building-blocks in the preparation of 3,4-dihydronaphthalene systems, bearing an aryl substituent at the 1-position, which show inhibition of tubulin assembly. Compounds such as *E*-2-benzylidene-1-indanones, -tetralones and –benzosuberones show *in vitro* antitumor activity. Furthermore, among them, *E*-2-(4'-methoxybenzylidene)-1-benzosuberone (Figure 10) shows the most outstanding *in vitro* antitumor (cytotoxic) activities.[91] β-Lactam fused

View Article Online
DOI: 10.1039/C6OB00763E

spiroisoxazolidine tetralones, which is an example of chiral tetralones, showed higher inhibition activity against *P. vulgaris* than the standard drug tetracycline but equally activity against *P. mirabilis* which are human pathogen bacteria.[92] Racemic and chiral 2-(4-pyridilmethyl)-1-tetralones were found to show inhibition of human placental aromatase.[93] On the other hand, 1-tetralone-derived β-ketoesters bearing stereogenic centers are valuable building blocks in the synthesis of *hamigeran* A (Figure 10) and the precursor of antibiotic *daunomycin* (Figure 10).[94]

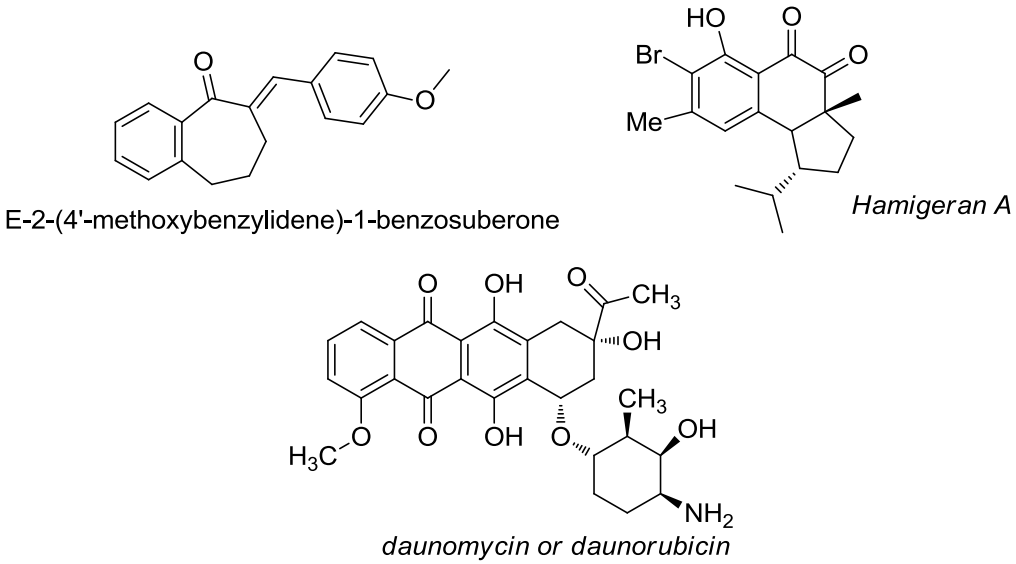


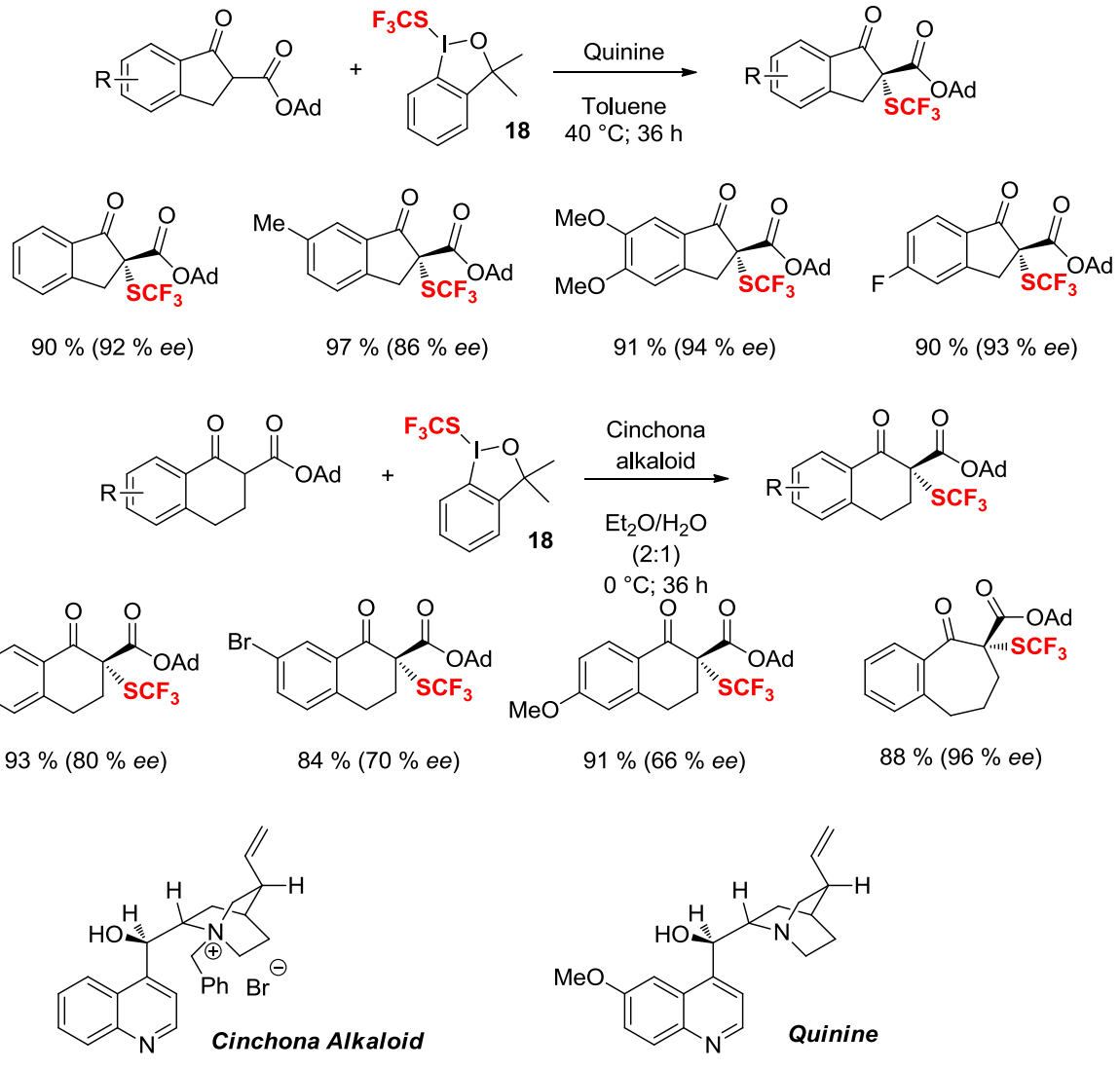
Figure 10. Structures of *Hamigeran A* and *daunomycin*

Enantioselective incorporation of CF_3S group in indanone, tetralone and suberone derivatives may have beneficial effects on the pharmacokinetics of those drugs that contain such motifs. Shen and co-workers have reported the enantioselective electrophilic trifluoromethylthiolation of β-keto esters using an electrophilic trifluoromethylthiolated hypervalent iodine reagent **18**, which is stable in the most common solvents even at 80 °C, and in the presence of quinine as the chiral catalyst that induced excellent enantioselectivity.[95]

The trifluoromethylthiolation reaction of indanone-derived β-keto esters (0.20 mmol) with the hypervalent iodine reagent **18** (0.024 mmol) in the presence of quinine (20 mol%) in toluene at 40 °C during 36 h provides the desired products in high yields and excellent enantioselectivities (86 – 94 % *ee*), regardless of the nature and position of the

View Article Online
DOI: 10.1039/C6OB00763E

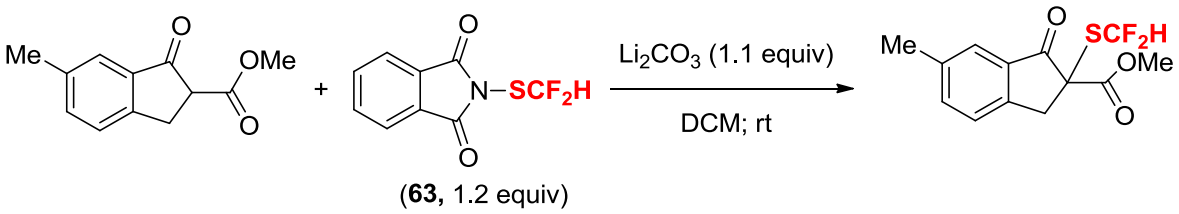
substituents on the β-ketoester derivatives (see Scheme 44). Interestingly, when more-enolizable tetralone- or 1-benzosuberone-derived β-ketoesters were subjected to the optimized reaction conditions, less than 5% of the β-ketoesters were converted to the corresponding trifluoromethylthiolated compounds after 36 h at 40 °C. However, the reactions of these substrates mediated by *cinchona* alkaloid-based chiral phase-transfer catalysts (PTC) gave the desired products in high yields and good enantioselectivities and with total consumption of the starting material. The reaction conditions involve the use of *cinchona* alkaloid (20 mol%), K_2CO_3 (0.4 mmol) in EtOH/H_2O (1:2) at 0 °C for 36 h. Some selected examples are depicted in Scheme 44.



View Article Online
DOI: 10.1039/C6OB00763E

Scheme 44. Some selected examples of the trifluoromethylthiolation reaction of β-ketoester derivatives.

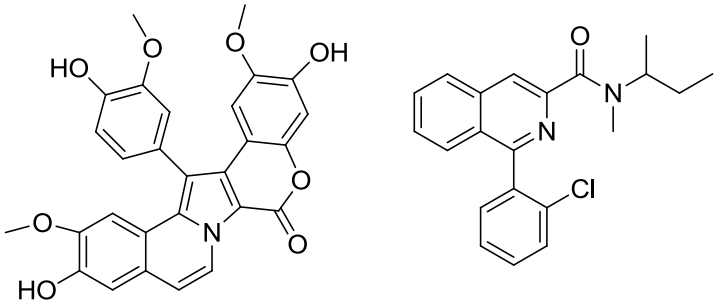
Shen and co-workers[66] have been able to introduce a CF_2HS group into soft nucleophiles such as β-ketoesters. The reaction of such nucleophiles with *N*-difluoromethylthiophthalimide **63** provides the CF_2HS-substituted β-ketoesters in good yields. Thus, various β-ketoesters derived from indanone or tetralone react with the difluoromethylthio reagent **63** in CH_2Cl_2 smoothly at room temperature to afford the desired difluoromethylthiolated products in good to excellent yields when K_2CO_3 was used as the base (see Scheme 45).



Scheme 45. Difluoromethylthiolation of tetralone derivative

5.2.-sp^2 Carbon Atoms

Isoquinoline is a privileged scaffold present in a broad range of natural products and pharmaceuticals. Drug molecules bearing the isoquinoline core often show remarkable biological activities.[96] For example, *PK11195* (Figure 11), an antagonist derived from isoquinoline, is active against *Plasmodium falciparum* inhibiting the parasite growth *in vitro*. Also, the potent activity of *PK11195* was effective against *toxoplasma gondii*. *Lamellarin* (Figure 11) derivatives have the isoquinoline core and are found to inhibit topoisomerase I (Top I).

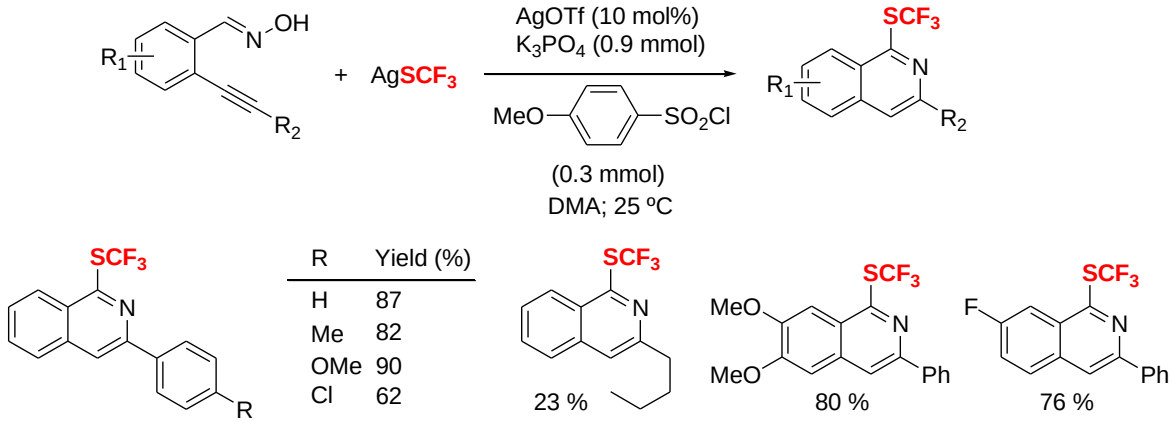


lamellarin D *PK-11195*

View Article Online
DOI: 10.1039/C6OB00763E

Figure 11. Structure of *Lamellarin D* and *PK-11195*

Among the *N*-heterocycles, fluorinated isoquinolines have served as building blocks for the design and synthesis of biologically active compounds, including antiproliferative drugs, myosin inhibitors, and agents for reducing intraocular pressure.[97] Introduction of a CF_3S group in building-blocks of small molecules with biological activity containing the isoquinoline core has flourished as a result of the attractive intrinsic properties of the CF_3S group such as the high lipophilicity and electronegativity. Ding, Wu and co-workers have successfully developed a method that provides the preparation of 1-[(trifluoromethyl)thio] isoquinolines using $AgSCF_3$ as the trifluoromethylthiolating reagent.[98] The protocol involves the use of 2-alkynylbenzaldoxime (0.2 mmol) and $AgSCF_3$ (0.3 mmol) in the presence of $AgOT_f$ (10 mol%) as the catalyst, a base such as K_3PO_4 (0.9 mmol) and *p*-methoxybenzensulfonyl chloride (0.3 mmol) as the activator in dimethylacetamide as solvent at 25 °C. The reaction tolerates a wide range of substituents in both the alkynyl and phenyl moieties furnishing the desired 1-[(trifluoromethyl)thio] isoquinoline derivatives in good to excellent yields. The general reaction and some selected examples are depicted in Scheme 46.



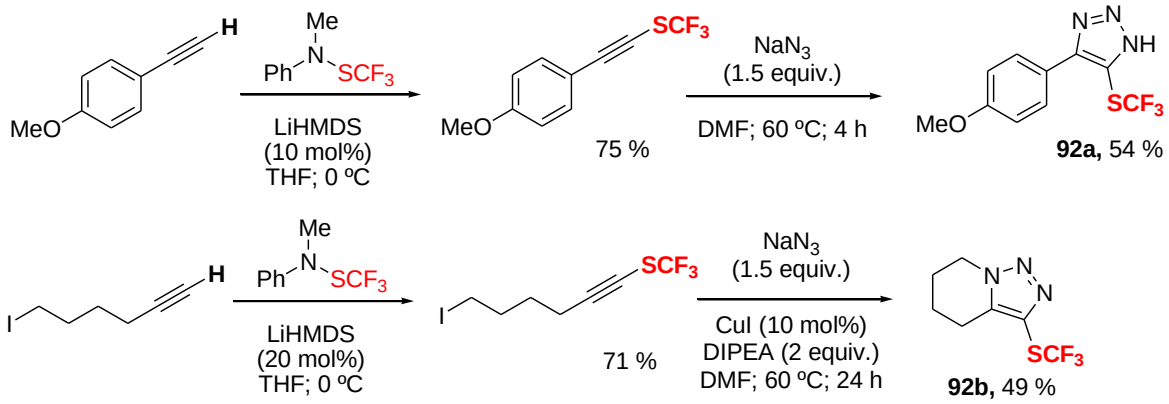
Scheme 46. Trifluoromethylthiolation of 2-alkynylbenzaldoxime.

5.3.-sp Carbon Atoms

Among all the efficient methods of trifluoromethylthiolation, the construction of C_{sp}-SCF_3 bond, has, to date, been rarely described[99] despite the fact that alkynes constitute

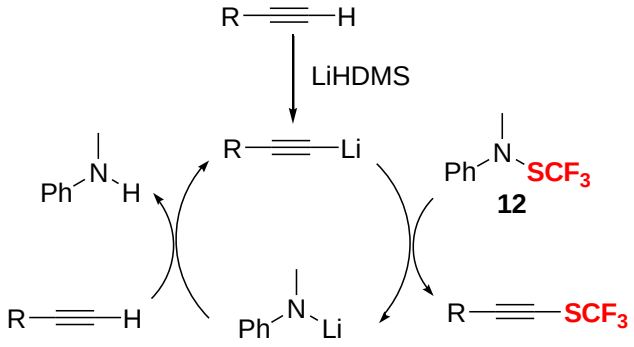
View Article Online
DOI: 10.1039/C6OB00763E

very valuable building blocks for the synthesis of various molecules, in particular, in medicinal chemistry.[100,7] Billard and co-workers have developed a novel methodology that allows preparing easily and in only 1 min of reaction time a set of trifluoromethylthio alkynyl derivatives.[101] Reaction of terminal aryl alkynes with *N*-methyl-*N*-phenyl trifluoromethanesulfenamide **12** in the presence of base (10 mol%) such as *n*-BuLi or LiHMDS in THF at 0 °C during 1 min afforded the desired product in good yields. A wide range of functional groups is compatible with the reaction conditions, even ones which are base-sensitive. Aromatic and aliphatic alkynes afford similar results. Scheme 47 illustrates the high potential of the CF_3S products as interesting building-blocks in the preparation of heterocyclic and bicyclic cores that are present in biologically active compounds. These two examples (**92a** and **92b**, Scheme 47) gave rise to satisfactory, but not optimized yields of triazoles.



Scheme 47. [3+2] Cycloaddition with trifluoromethylthioalkynes

The mechanism of the reaction is depicted in Scheme 48.



View Article Online
DOI: 10.1039/C6OB00763E

Scheme 48. Proposed reaction mechanism for the trifluoromethylthiolation of terminal alkynes

In the proposed reaction mechanism (Scheme 48) the lithiated terminal alkyne reacts with **12** to afford the substituted terminal CF_3S adduct. This method could be employed for the preparation of CF_3S-substituted triazoles of medicinal importance, such as those depicted in Figure 12. The triazoles in clinical use, *terconazole* **93,** *fluconazole* **94,** *cyproconazole* **95**, and *triazolam* **96** (Figure 12) are the most representative candidates for late stage trifluoromethylthiolation reaction.[102]

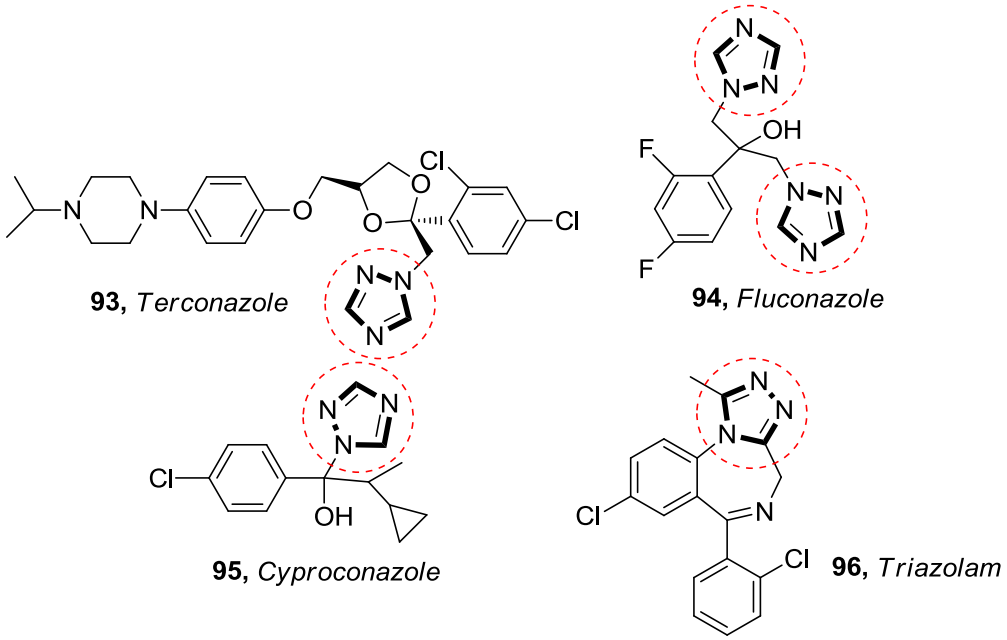
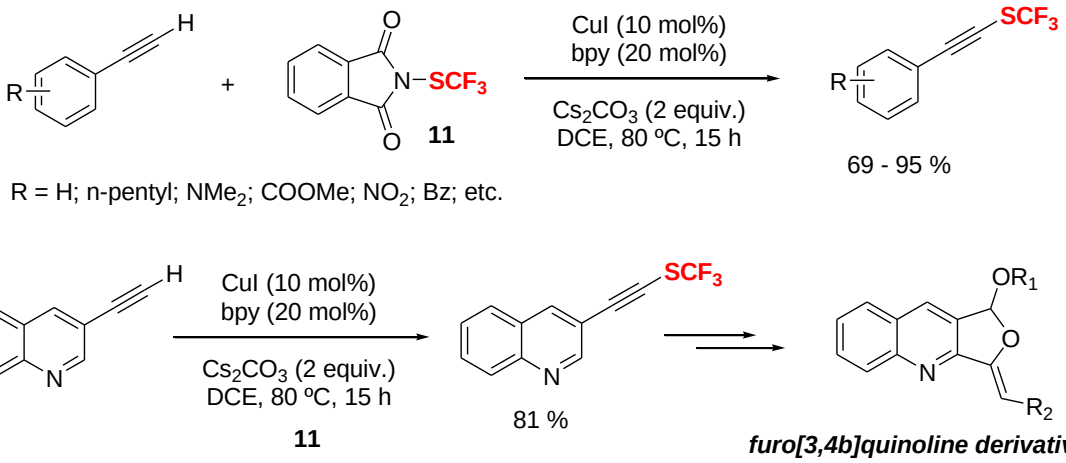


Figure 12. Triazoles already in clinical use

Rueping and co-workers have reported the catalytic trifluoromethylthiolation of alkynes employing electrophilic shelf-stable *N*-(trifluoromethylthio)phthalimide **11**.[103] The protocol of the trifluoromethylthiolation reaction of terminal alkynes involves the use of the electrophilic CF_3S reagent (1.2 equiv.) in the presence of CuI (10 mol%) and bpy (20 mol%) and Cs_2CO_3 (2 equiv.) in dichloroethane at 80 °C for 15 h (see Scheme 49). The desired products are obtained in good yields and a wide tolerance of electron donor and

View Article Online
DOI: 10.1039/C6OB00763E

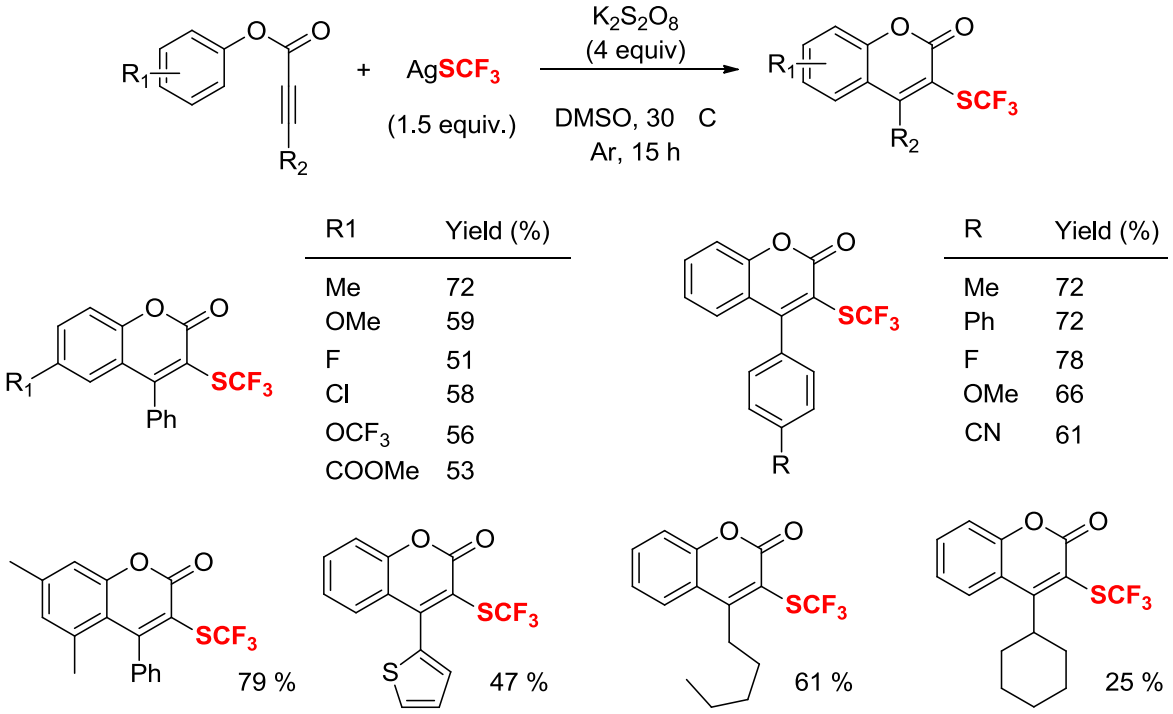
electron withdrawing substituents is observed. This method is interesting because offers the opportunity for further modifications. For example, quinoline is a structural motif present in furo[2,3*b*]quinolines and furo[3,4*b*]quinolines that show biological activity.[104] Thus, reaction of quinoline carbaldehydes *ortho*-substituted by alkynyl moieties under base catalysis provide a wide variety of furo[3,4*b*]quinoline derivatives. These pharmacophores are useful antihypertensive agents and exhibit antimicrobial activity against a number of microorganisms, such as bacteria, fungi, mycobacteria and protozoa.[105] Further, chemical modification of these heterocyclic compounds yields spiroketal and heterospirocyclic structures under [3+2] and [4+2] cycloaddition reactions and are of interest for their biological relevance, since a number of them can be found in natural products.



Scheme 49. Trifluoromethylthiolation of terminal alkynes and pharmacophore target structure

Recently, Wang and co-workers have developed a mild and convenient oxidative radical cyclization of aryl alkynoate esters using $AgSCF_3$ as the CF_3S-radical source for the synthesis of 3-trifluoromethylthiolated coumarins.[106,107] The reaction requires the use of $K_2S_2O_8$ (4.0 equiv.) as an oxidant and takes place efficiently in DMSO at 30 °C under argon atmosphere for 15 h. The use of other oxidants such as Oxone (potassium peroxymonosulfate), $Cu(OAc)_2.H_2O$ or PhI(OAc) did not furnish the coumarin products. This protocol is characterized by readily available starting esters, wide functional group tolerance and general good yields of the desired products observed. Some selected examples of the application of this methodology are depicted in Scheme 50.

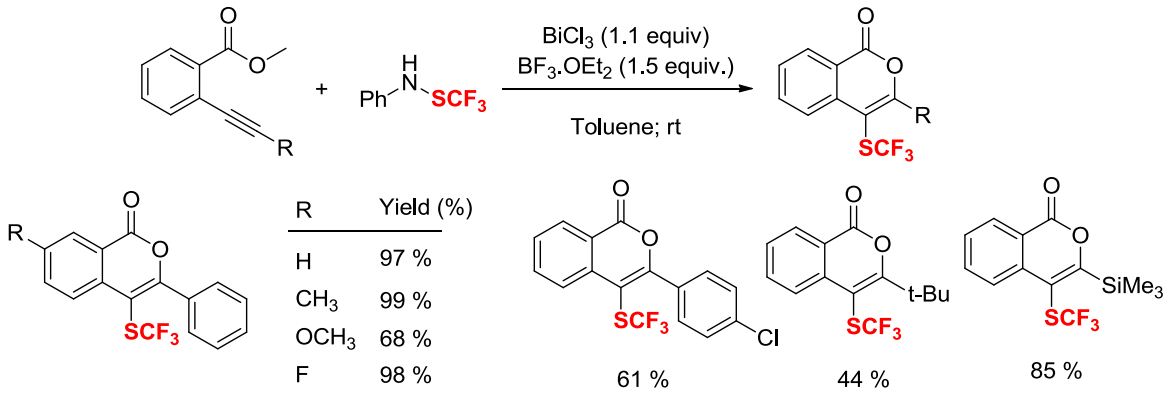
View Article Online
DOI: 10.1039/C6OB00763E



Scheme 50. Trifluoromethylthiolation of aryl alkynoate esters

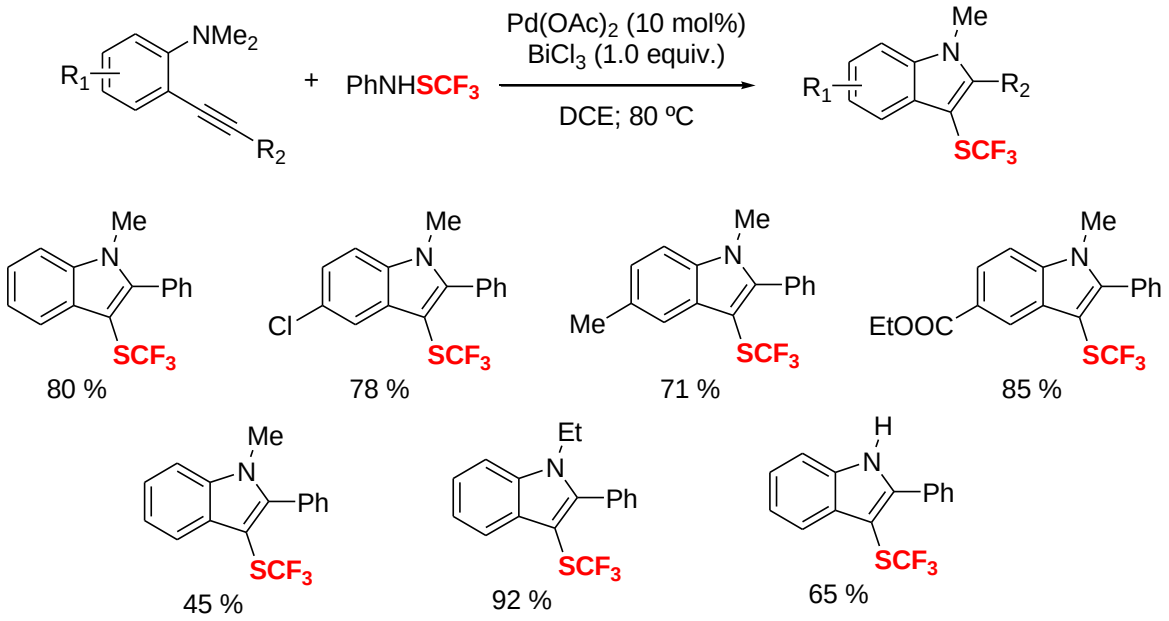
Isocoumarine and its derivatives can be found in many natural products and pharmaceuticals that show a wide range of physiological and biological activities, such as antibacterial, anti-inflammatory, and anticancer activities, or as protease inhibitors or weedkillers.[108] However, the direct synthesis of trifluoromethylthiolated isocoumarins had not been reported. Ding, Li and co-workers have developed a novel one-pot trifluoromethylthiolation/cyclization protocol for the synthesis of 4-[(trifluoromethyl)thio]-(1*H*)isochromen-1-one derivatives through reaction of 2-(2-alkynyl)-benzoates with trifluoromethanesulfanylamide as the CF_3S reagent under mild conditions.[109] The reaction was performed in the presence of both $BiCl_3$ (1.1 equiv.) and $BF_3.OEt_2$ (1.5 equiv.) in toluene at room temperature. The products were obtained in good to excellent yields and a wide variety of functional groups were tolerated under the optimized conditions. Selected examples of trifluoromethylthiolated isocoumarin derivatives are depicted in Scheme 51.

View Article Online
DOI: 10.1039/C6OB00763E



Scheme 51. Synthesis of some selected 4-[(trifluoromethyl)thio]-1*H*isochromen-1-one derivatives

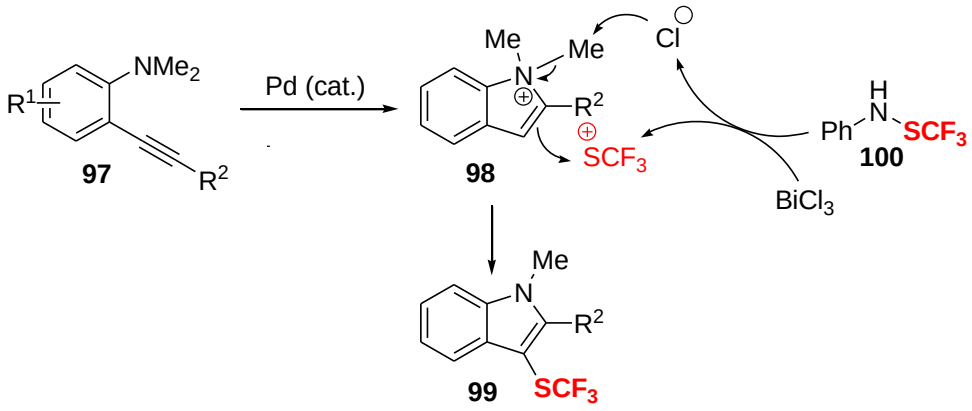
Wu and co-workers have studied the palladium(II)-catalyzed reaction of 2-alkynylaniline derivatives with trifluoromethanesulfanyl amides in the presence of $BiCl_3$, as a Lewis acid additive, providing indole derivatives in good yields.[110,111] The reaction was carried out with catalytic amounts of $Pd(OAc)_2$ (10 mol%) in the presence of $BiCl_3$ (1.0 equiv) in DCE at 80 °C and a good tolerance of a wide electron-withdrawing and electron-donor groups was observed. The scope of the reaction and some examples are depicted in Scheme 52.



Scheme 52. Synthesis of 3-((trifluoromethyl)thio)indoles

View Article Online
DOI: 10.1039/C6OB00763E

The proposed reaction mechanism for this transformation is illustrated in Scheme 53.

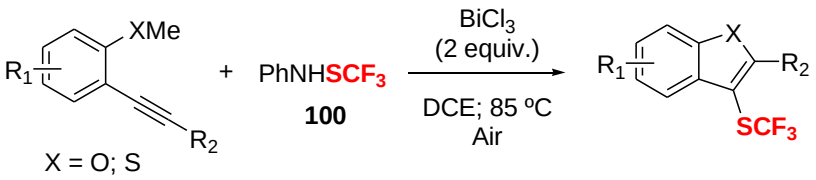


Scheme 53. Proposed reaction mechanism for the trifluoromethylthiolation of alkynes

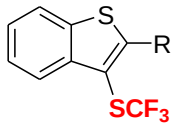
An intramolecular cyclization of *N*,*N*-dimethyl-2-alkynylaniline **97** will produce intermediate **98** (Scheme 53). Subsequently, the methyl group of intermediate **98** is removed by attack of the chloride from bismuth(III) chloride. In the meantime, the trifluoromethanesulfanyl cation (CF_3S^+) is formed via an activation of trifluoromethanesulfanylamide **100** by bismuth(III) chloride, which reacts with the *in situ* generated indole to produce the 3-((trifluoromethyl)thio)indole **99.**[111]

Benzofuran and benzothiophene are ubiquitous structural motifs found in a large number of biologically important natural products and pharmaceuticals (*vide supra*). Molecules with these core structures usually have a broad range of biological activities.[112] Wu and co-workers have reported the reaction of trifluoromethanesulfanylamide **100** with 1-methoxy-2-alkynylbenzenes or methyl(2-alkynylphenyl)sulfanes promoted by $BiCl_3$ which proceeded smoothly with broad functional group tolerance providing the desired heterocyclic compounds in good yields.[113] The optimized reaction conditions involve the use of $BiCl_3$ (2 equiv.) in DCE at 85 °C under air atmosphere and some selected examples are shown in Scheme 54.

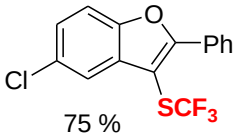
View Article Online
DOI: 10.1039/C6OB00763E

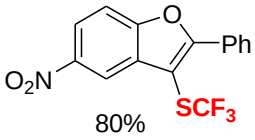


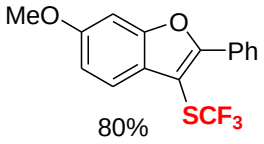
R	Yield (%)
Ph	88
4-MeOC$_6$H$_4$	88
4-ClC$_6$H$_4$	80
Cyclopropyl	77
t-Bu	74



R	Yield (%)
Ph	58
4-MeOC$_6$H$_4$	68
4-ClC$_6$H$_4$	66
Cyclopropyl	78
t-Bu	71

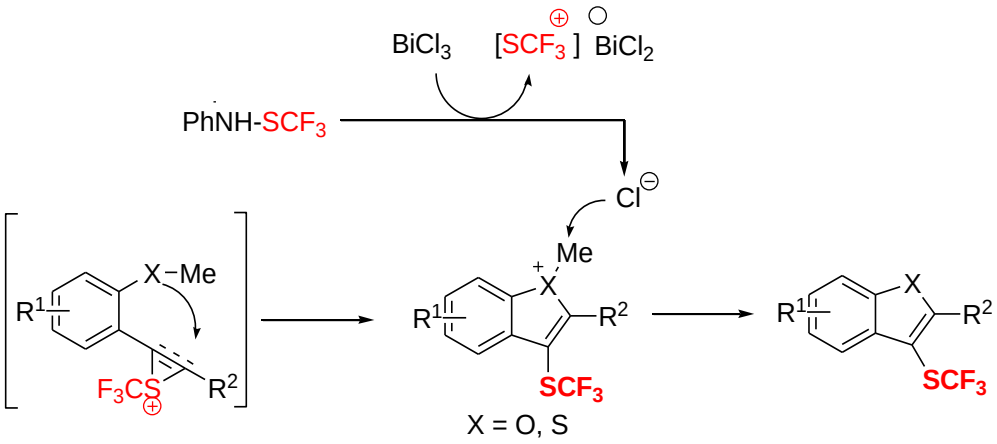






Scheme 54. Synthesis of 3-trifluormethylthiobenzofuran and benzothiophene derivatives

The authors[113] proposed the mechanism shown in Scheme 55.



Scheme 55. Proposed mechanism for the trifluoromethylthiolation of benzofurans and benzothiophenes

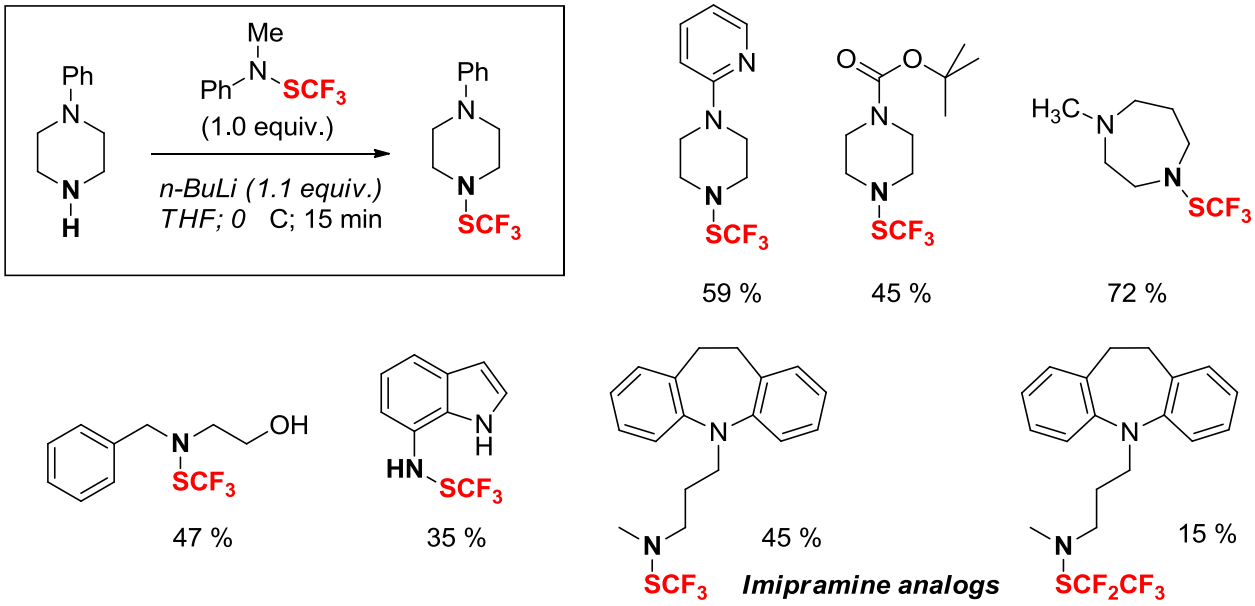
The mechanism is in agreement with that proposed by Wu and co-workers[111] in Scheme 53 for the case of indoles.

6.-Trifluoromethylthiolation of Heteroatoms

View Article Online
DOI: 10.1039/C6OB00763E

6.1.-*N* Atoms

Billard and co-workers have developed an interesting trifluoromethylthiolation reaction with *N*-methyl-*N*-phenyl trifluoromethanesulfenamide **12** that involves a transamination with secondary amines providing a new CF_3S-N bond.[114] The optimization of the reaction was performed with phenylpiperazine, a secondary amine, and reaction of this amine with **12** (1.0 equiv.) in the presence of *n*-BuLi (1.1 equiv.) in THF at 0 °C for 15 minutes afforded the expected CF_3S-N product in 86 % yield (Scheme 56). The reaction gives, in general, good yields with secondary amines. Also, primary amines such as aniline, affords the desired product in 68 % yield. Imines as well as amino alcohols and bis-amines were also trifluoromethylthiolated, with the most nucleophilic atom as the target, affording the desired products in good yields.

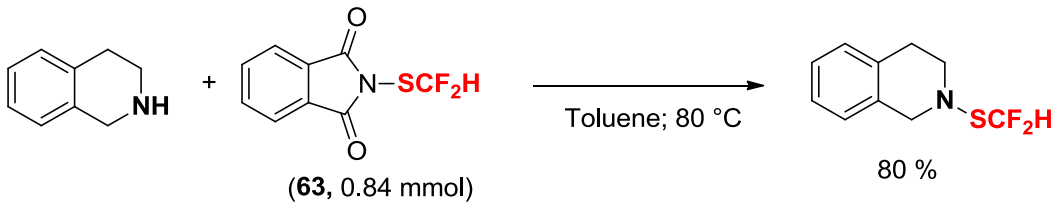


Scheme 56. Transamination of *N*-methyl-*N*-phenyl trifluoromethanesulfenamide with amines

This new method was applied to synthesize a trifluoromethylthio analog of the well-known tricyclic antidepressant *imipramine* (Scheme 56). The product was obtained in 45 % isolated yield. [114]

View Article Online
DOI: 10.1039/C6OB00763E

Shen and co-workers[66] have developed a protocol for the difluoromethylthiolation of secondary amines employing *N*-difluoromethylthiophthalimide **63** that takes place efficiently without the addition of any catalyst in toluene at 80 °C for 16 – 24 h. Notably, 1,2,3,4-tetrahydroisoquinoline provided the desired product in 80 % yield (see Scheme 57).



Scheme 57. Difluoromethylthiolation of a secondary amine

Compounds based on the 1,2,3,4-tetrahydroisoquinoline (THIQ) nucleus have been found to be some of the most potent inhibitors of human PNMT (hPNMT, human phenylethanolamine *N*-methyltransferase) yet reported.[115] The addition of hydrophilic or lipophilic electron-withdrawing substituents to the 7-position of THIQs leads to enhanced hPNMT inhibitory potency. However, THIQs bearing lipophilic 7-substituents are less selective than THIQs bearing hydrophilic 7-substituents due to significant affinity for the α_2-adrenoceptor.

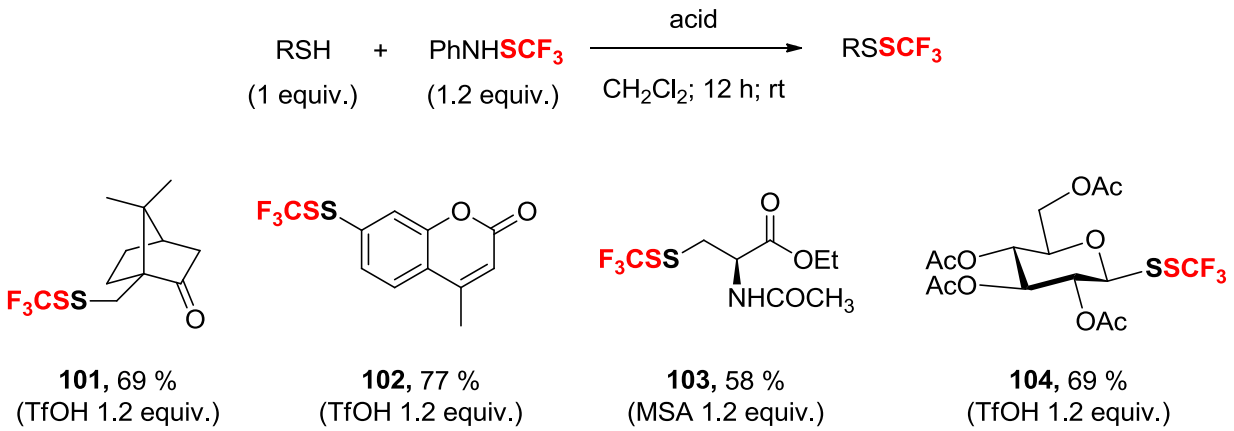
6.2.-S Atoms

Recently, Jereb and co-workers have studied the highly selective acid-promoted trifluoromethylthiolation reaction of thiols to the corresponding trifluoromethyl disulfides.[116] $PhNHSCF_3$ **100** is an easy-to-handle electrophilic CF_3S reagent that was developed by Billard, Langlois and co-workers.[117] This reagent promotes the trifluoromethylthiolation of a wide variety of aryl, benzyl and alkyl thiols in the presence of trifluoromethanesulfonic acid (1.2 equiv.) or methanesulfonic acid (1.3 equiv.) depending on both the nucleophilicity of the thiols and the strength of the promoter. The optimal solvent is dichloromethane and the reaction proceeds efficiently at room temperature during 12 h. Generally, the trifluoromethyl disulfides are obtained in good-to-excellent yields.

This methodology was also carried out with structurally diverse, acid-sensitive and biologically important thiols shown in Scheme 58. It is known that the camphor skeleton

View Article Online
DOI: 10.1039/C6OB00763E

could undergo an acid-catalyzed rearrangement; however, (-)-7,7-dimethyl-1-(mercaptomethyl)bicyclo[2.2.1]heptan-2-one yielded the expected trifluoromethyl disulfide **101** in 69 % isolated yield in the presence of T_fOH, and no rearrangement was noted. Also, 7-mercapto coumarin was converted to the corresponding trifluoromethyl disulfide **102** in the presence of T_fOH regardless of the presence of the acid-labile lactone group. The protected cysteine derivative and 1-thioglucose derivative, both biologically relevant thiols, were subjected to the trifluoromethylthiolation reaction. The functionalization of cysteine derivative proceeded completely in the presence of 1.2 equiv. of methanesulfonic acid rendering 58 % yield of the desired disulfide **103**. The reaction of 1-thioglucose in the presence of 1.2 equiv. of methanesulfonic acid took place smoothly, however, epimerization was observed in the ^1H NMR spectrum of the mixture. Interestingly, when 1.2 equiv. of T_fOH was used no epimerization took place and a single stereoisomer **104** was furnished in 69 % yield.



Scheme 58. Functionalization of the acid-sensitive and biologically important thiols

7.-Future Perspective and Conclusions

View Article Online
DOI: 10.1039/C6OB00763E

Trifluoromethylthiolation strategies for organic compounds are expanding and growing at almost the same pace as fluorination methods. Thus, this parallel growth dictates the trends in one and the other area of research.

Although there are some examples of regioselective and enantioselective trifluoromethylthiolations (for example Scheme 44), there are still a lot of challenges in this field, and further research is required. Homolytic substitution reactions of less electron rich nuclei such as pyridine derivatives with the SCF_3 group, should be further studied, in order to provide better substitution yields in electron-deficient systems, probably through radical reactions. In general, the (hetero)aromatic homolytic substitutions with the SCF_3 group lack in regioselectivity, and this point should be given special attention to. For instance, attempts could be made at employing anchimeric assisting groups which could enable *ortho*-substitution in (hetero)aromatic compounds, thus achieving good *ortho*-regioselective substitutions.

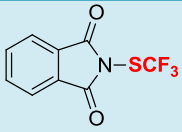
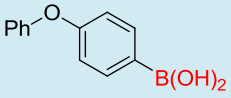
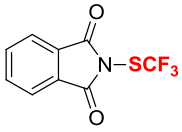
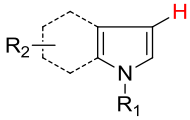
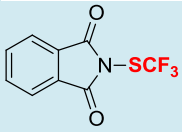
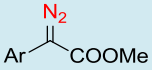
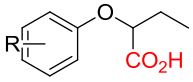
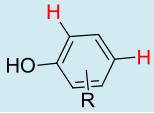
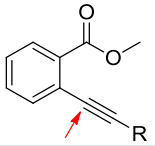
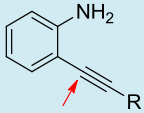
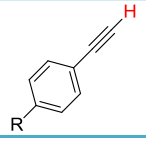
Attempts at the fluoroalkylthiolation of allylic and bis-allylic positions of organic compounds without the intermediacy of transition metals should be considered, in the context of the relevance that these functionalities have in unsaturated fatty acids. Other areas which should be devoted attention to are: (i) the trifluoromethylthiolation of sugars and nucleobase derivatives (ii) improved photocatalytic methods that allow for chain reactions capable of generating SCF_3 radicals that effect substitution and addition reactions efficiently and (iii) conversion /substitution of functional groups such as aliphatic OH, and its derivatives into SCF_3 functionality.

Table 1 summarizes the different applications of both electrophilic and nucleophilic reagents for the trifluoromethylthiolation of different families of organic compounds. In red

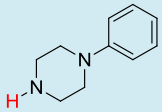
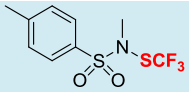
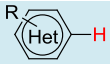
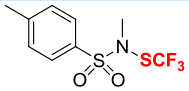
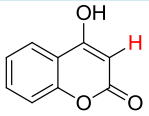
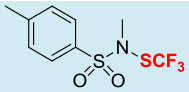
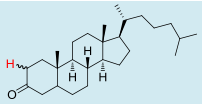
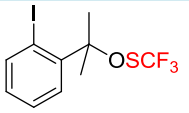
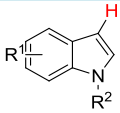
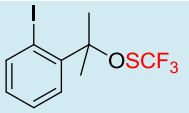
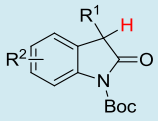
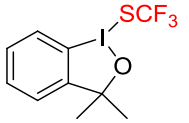
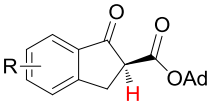
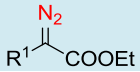
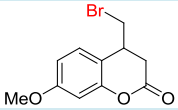
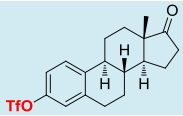
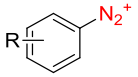
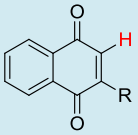
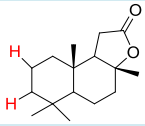
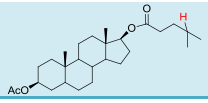
View Article Online
DOI: 10.1039/C6OB00763E

is the atom or group to be substituted by the CF_3S group, or position of addition of the CF_3S moiety. As opposed to the reactions illustrated in the text above, Table 1 classifies the transformations according to trifluoromethylthiolating reagent for a quick reference guide to reagent applications.

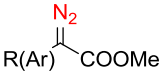
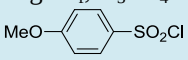
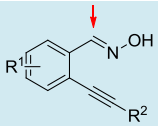
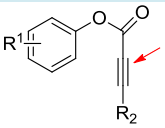
Table 1. Different fluorination strategies most commonly employed for medicinal targets. In red is the group/atom to be replaced by the CF_3S group or site of addition of the CF_3S moiety

CF_3S reagent	Organic family	Additive	Conditions	Substrate	Ref.
 **11**	(hetero)aryl boronic acids	*t*-Bu(bpy), CuI Na_2CO_3	Diglyme, 60 °C		33
 **11**	indoles, pyrroles, azaindoles	NaCl	DMF, 90 °C		47, 50
 **11**	α-diazoesters	$CuSCF_3$	MeCN, RT		84
 **11**	alkyl carboxylic acids	CsOBz, mesitylene or 3-methyltoluate-blue LED (455 nm)	C_6H_5F		87
PhNHSCF$_3$, **100**	Phenols	T_fOH	CH_2Cl_2, RT		43
PhNHSCF$_3$, **100**	internal alkynes-(i.e.:2-(2-alkynyl)-benzoates	$BiCl_3$, $BF_3.OEt_2$	Toluene, RT		109
PhNHSCF$_3$, **100**	internal alkynes-(i.e.:2-(2-alkynyl)-anilines	$BiCl_3$, $Pd(OAc)_2$	DCE, 80 °C		111
PhNMeSCF$_3$, **12**	terminal alkynes	LiHMDS, -78 °C	THF, 0 °C		99,100,101,105

View Article Online
DOI: 10.1039/C6OB00763E

$PhNMeSCF_3$, **12**	nitrogen atoms in piperidines	*n*-BuLi	THF, 0 °C		114
$PhNMeSCF_3$, **12**	sulfur atoms in thiols	-	CH_2Cl_2, RT	RSH	116,117
 **16**	heteroaromatic compounds	TMPMgCl.LiCl	THF		44
 **16**	coumarins	Me_3SiCl	MeCN, 90 °C		24,89
 **16**	α-carbonyl positions	Me_3SiCl	MeCN, 90 °C		89
 **13**	indole derivatives	CSA	$ClCH_2CH_2Cl$, 40 °C		9
 **13**	oxindole derivative	quinine	$C_2H_5OC_2H_5$, 35 °C		64
 **18**	indanone-derived β-keto esters	quinine	Toluene, 40 °C		95
$CuSCF_3$	α-diazoesters	H_2O	MeCN		84
$(bpy)CuSCF_3$	alkyl bromides	KF	MeCN, 110 °C		77
$(Me_4N)SCF_3$	aryl and vinyl triflates	$Ni(cod)_2$, dppf	Toluene,45 °C		24
$(Me_4N)SCF_3$	(hetero)aromatic diazonium salts	CuSCN	MeCN, RT		28
$AgSCF_3$	quinones	$Cu_2(OH)_2CO_3$, $K_2S_2O_8$	MeCN, 65 °C		69
$AgSCF_3$	alkyl groups	$K_2S_2O_8$	MeCN, 60 °C		70
$AgSCF_3$	alkyl groups	$Na_2S_2O_8$	MeCN/H_2O/ DCE, 30 °C		18

View Article Online
DOI: 10.1039/C6OB00763E

$AgSCF_3$	diazoaryl acetates	CuI, H_2O	MeCN,-25 ^oC-RT		83
$AgSCF_3$	sp^2 carbons from oximes	$AgOT_f$, K_3PO_4 	DMA, 25 ^oC		98
$AgSCF_3$	sp carbon atoms from alkynoates	$K_2S_2O_8$	DMSO		107

8.-References.

1 C. Hansch, A. Leo, "Substituent constants for correlation analysis in chemistry and biology"; Wiley: New York, **1979**; p 339.

2 V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, **6**, 880–921.

3 H. Wang, D. A. Vicic, *Synlett*, 2013, **24**, 1887-1898.

4 (a) M. J. Kirby, H. Carageorgiou-Markomihalakis, P. Turner, *Br. J. Clin. Pharmacol.*, 1975, **2**, 541–542; (b) T. Silverstone, J. Fincham, J. Plumley, *Br. J. Clin. Pharmacol.*, 1979, **7**, 353–356; (c) D. C. Remy, S. F. Britcher, S. W. King, P. S. Anderson, C. A. Hunt, W. C. Randall, P. Bélanger, J. G. Atkinson, Y. Girard, C. S. Rooney, J. J. Fuentes, J. A. Totaro, J. L. Robinson, E. A. Risley, M. Williams, *J. Med. Chem.*,1983, **26**, 974–980; (d) K. J. Watling, *J. Pharm. Pharmacol.*, 1980, **32**, 778–779; (e) A. Günther, K.-H. Mohrmann, M. Stubbe, H. Ziemann (Bayer AG), DE3516630, 1986; (f) P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M. A. Coléno, A. Doble, G. Doerflinger, C. D. Hu, M. H. Donat, J. M. Duchesne, P. Ganil, C. Guérémy, E. Honoré, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. Le Blevec, M. Meunier, J. M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J. M. Stutzmann, S. Mignani, *J. Med. Chem.*, 1999, **42**, 2828–2843.

5 A. Haas, G. Möller, *Chem. Ber.*, 1996, **129**, 1383.

6 S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847.

7 (a) S. J. Tavener, D. J. Adams, J. H. Clark, *J. Fluorine Chem.*, 1999, **95**, 171-176. (b) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem.*, 2014, **126**, 1676 –1679.

8 F. Baert, J. Colomb, T. Billard, *Angew. Chem.*, 2012, **124**, 10528 – 10531; *Angew. Chem. Int. Ed.*, 2012, **51**, 10382 – 10385

View Article Online
DOI: 10.1039/C6OB00763E

9 B. Ma, X. Shao, Q. Shen, *J. Fluorine Chem.*, 2015, **171**, 73-77.

10 Q. Xiao, J. Sheng, Q. Ding, J. Wu, *Eur. J. Org. Chem.*, 2014, 217.

11 (a) K. Kang, C. Xu and Q. Shen, *Org. Chem. Front*., 2014, **1**, 294-297; (b) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed*., 2014, **53**, 9316–9320.

12 X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem*., 2013, **125**, 3541 – 3544; *Angew. Chem. Int. Ed*., 2013, **52**, 3457 – 3460.

13 Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782 – 8785.

14 E. V. Vinogradova, P. Muller, S. L. Buchwald, *Angew. Chem., Int. Ed*., 2014, **53**, 3125

15 S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J*., 2014, **20**, 8589–8593.

16 M. Li, J. Guo, X.-S. Xue, J.-P. Cheng. **2015**. Org. Lett., DOI: 10.1021/acs.orglett.5b03433.

17 Ch. Li, K. Zhang, X.-H. Xu, F.-L. Qing, *Tetrahedron Lett.*, 2015, **56**, 6273-6275.

18 S. Guo, X. Zhang, P. Tang, *Angew. Chem. Int. Ed*., 2015, **54**, 4065 –4069.

19 L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai, W. Zhang, *Angew. Chem. Int. Ed*., 2015, **54**, 1 – 6. *Angew. Chem.*, 2015, **127**, 15178 –15182.

20 L. Zhai, Y. Li, J. Yin, K. Jin, R. Zhang, X. Fu, C. Duan, *Tetrahedron*, 2013, **69**, 10262-10266.

21 Y. Huang, X. He, H. Li, Z. Weng, *Eur. J. Org. Chem*., 2014, 7324–7328. (b) Y. Huang, J. Ding, C. Wu, H. Zheng, Z. Weng, *J. Org. Chem*., 2015, **80**, 2912−2917.

22 (a) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan, Z. Weng, *Tetrahedron*, 2013, **69**, 6046-6050; (b) C.-P. Zhang, D. A. Vicic, *Chem.Asian J*., 2012, **7**, 1756.

23 F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem*., 2014, 2415–2428.

24 A. B. Durr, G. Yin, I. Kalvet, F. Napoly, F. Schoenebeck, *Chem. Sci.*, DOI: 10.1039/c5sc03359d, **2016.**

25 T. Sekiya, Sh. Inoue, T. Shirasaka, Ch. Mijayima, H. Okushima, K. Suzuki, M. Kawai, M. Mitzuka, K. Umezu, *Chem. Pharm. Bull.*, 1994, **42**, 586.

26 S. M. Wrenn, Jr., J. S. Parks, F. W. Immermann, L. L. Rude, *Journal of Lipid Research*, 1995, **36**, 1995-1199.

27 Y. Zeng, J. Hu, *Org. Lett.*, 2016, DOI: 10.1021/acs.orglett.6b00142.

View Article Online
DOI: 10.1039/C6OB00763E

28 Ch. Matheis, V. Wagner, L. J. Goossen, *Chem. Eur. J.*, 2016, **22**, 79-82.

29 G. Ganoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.*, 2014, **5**, 1312.

30 C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F. L. Qing, *Angew. Chem., Int. Ed*., 2012, **51**, 2492.

31 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.

32 X. X. Shao, X. Q. Wang, T.Yang, L. Lu, Q. Shen, *Angew. Chem., Int. Ed*., 2013, **52**, 3457.

33 K. Kang, Ch. Xu, Q. Shen, *Org. Chem. Front*., 2014, **1**, 294.

34 Ch.-P. Zhang, D. A. Vicic, *Chem. Asian J.*, 2012, **7**, 1756.

35 R.-Y. Tang, P. Zhong, Q.-L. Lin, *J. Fluor. Chem.*, 2007, **128**, 636.

36 (a) J. L. Clavel, S. Peltai, S. Le Bars, P. Charreau, WO Patent 0,130,760 (2000); (b) G. Buntainian, L.R. Hatton, D.W. Hawkins, C.J. Pearson, D.A. Roberts, Eur. Patent 295,117 (1988).

37 Ch. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.*, 2012, **124**, 2542.

38 W. Zhong, X. Liu, *Tetrahedron Lett.*, 2014, **55**, 4909–4911.

39 Z.-J. Qiao, H. Liu, X. Xiao, Y. Fu, J.-P. Wei, Y.-X. Li, X.-F. Jiang, *Org. Lett*., 2013, **15**, 2594–2597;

40 (a) H. Oouchi, *Appl. Entomol. Zool.*, 2005, **40**, 145; (b) S. P. Lim, C. Y. Lee, *J. Ecom. Entomol.*, 2005, **98**, 2169; (c) *J. Med. Entomol.*, 1990, **27**, 913.

41 P. Nikolaienko, T. Yildiz, M. Rueping, *Eur. J. Org. Chem.*, 2016, 1091–1094.

42 G. Yin, I. Kalvet, and F. Schoenebeck, *Angew. Chem. Int. Ed*., 2015, **54**, 6809 –6813.

43 M. Jereb, K. Gosak, *Org. Biomol. Chem.*, 2015, **13**. 3103.

44 Alazet, L. Zimmer, Th. Billard, *J. Fluorine Chem.*, 2015, **171**, 78-81.

45 (a) L. Jiang, J. Qian, W. Yi, G. Lu, Ch. Cai, W. Zhang, *Angew. Chem., Int. Ed.*, 2015, **127**, 15178. (b) For the seminal report of trifluoromethanesulfenate reagent, see: (a). For its applications, see: (b) X. Q.Wang, T. Yang, X. L. Cheng, Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 12860; (c) T. Yang, Q. Shen, L. Lu, *Chin. J. Chem.*, 2014, **32**, 678-680; (d) B. Ma, X. Shao, Q. Shen, *J. Fluorine Chem*., 2015, **171**, 73; (e) For the report of *N*-trifluoromethylthiosaccharin reagent, see: (i) C. F. Xu, B. Q. Ma, Q. Shen, Angew. *Chem.*,

View Article Online
DOI: 10.1039/C6OB00763E

Int. Ed., 2014, **53**, 9316. For its applications, see: (ii) Q. Wang, Z. Qi, F. Xie, X. Li, *Adv. Synth. Catal*., 2015, **357**, 355. (iii) M. Maeno, N. Shibata, D. Cahard, *Org. Lett*., 2015, **17**, 1990. (iv) C. Xu, Q. Shen, *Org. Lett*., 2015, **17**, 4561. (f) X. Shao, C. Xu, L. Lu, Q. Shen, *J. Org. Chem.*, 2015, **80**, 3012-3021.

46 X. Ji, H. Huang, W. Xiong, K. Huang, W. Wu, H. Jiang, *J. Org. Chem*., 2014, **79**, 7005–7011.

47 R. Honeker, J. B. Ernst, F. Glorius, *Chem. Eur. J.*, 2015, **21**, 8047.

48 S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. H. Wagner, H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847.

49 C.-P. Zhang, D. A. Vicic, *Chem. Asian J.*, 2012, **7**, 1756.

50 Y. Zhao, *Annu. Rev. Plant Biol.*, 2010, **61**, 49.

51 J. Wagner, M. L. Wagner, *Sleep Med. Rev*., 2000, **4**, 551.

52 (a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* 2005, **105**, 827; (b) B. Manteau, S. Pazenok, J. P. Vors, F. R. Leroux, *J. Fluorine Chem.* 2010, **131**, 140; (c) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.*, 2015, **115**, 731. (d) C.-F. Ni, M.-Y. Hu, J.-B. Hu, *Chem. Rev.*, 2015, **115**, 765.

53 (a) K. Shimizu, *Jpn. J. Antibiot.*, 1988, **12**, 1809; (b) M. Ito, T. Ishigami, *Infection*, 1991, **19**, S253.

54 J. J Fourie, I. G. Horak, V de la Puente Redondo, *Vet. Rec.*, 2010, **167**, 442.

55 T. Yoshimura, M. Nakatani, S. Asakura, R. Hanai, M. Hiraoka, S. Kuwahara, *J. Pestic. Sci.*, 2011, **36**, 212.

56 P. C. C. Feng, Th. G. Ruff, Patent US006107549A, 2000.

57 C. Perrot-Rechenmann, R. M. Vapier, *Vitam. Horm.*, 2005, **72**, 203.

58 R. E. Armer, M. R. Ashton, E. A. Boyd, Ch. J. Brennan, F. A. Brookfield, L. Gazi, Sh. L. Gyles, Ph. A. Hay, M. G. Hunter, D. Middlemiss, M. Whittaker, L. Xue, R. Pettipher, J. Med. Chem., 2005, **48**, 6174.

59 E. Ismalaj, D. Le Bars, T. Billard, *Angew. Chemie, Int. Ed*., 2016, **55**. Doi: 10.1002/anie.201601280.

60 A. B. Dounay, L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945.

61 (a) S. Sakai, N. Aimi, K. Yamaguchi, H. Ohhira, K. Hori, J. Haginiwa, *Tetrahedron Lett.*, 1975, **16**, 715 – 718; (b) N. Aimi, K. Yamaguchi, S. Sakai, J. Haginiwa, A. Kubo,

View Article Online
DOI: 10.1039/C6OB00763E

Chem. Pharm. Bull., 1978, **26**, 3444 – 3449; (c) S. Sakai. N. Aimi, K. Yamaguchi, E. Yamanaka, J. Haginiwa, *J. Chem. Soc. Perkin Trans. 1*, 1982, 1257 – 1262.

62 O. Dideberg, J. Lamotte-Brasseur, L. Dupont, H. Campsteyn, M. Vermeire, L. Angenot, *Acta Crystallogr. Sect. B*, 1977, **33**, 1796 – 1801.

63 (a) C. B. Cui, H. Kakeya, H. Osada, *Tetrahedron*, 1996, **52**, 12651 – 12666; (b) C. B. Cui, H. Kakeya, H. Osada, *J. Antibiot.*, 1996, **49**, 832 – 835.

64 T. Yang, Q. Shen, L. Lu, *Chin. J. Chem*., 2014, **32**, 678.

65 M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merkens, *Chem. Commun.*, 2014, **50**, 2508.

66 D. Zhu, Y. Gu, L. Lu, Q. Shen, *J. Am. Chem. Soc.*, 2015, **137**, 10547.

67 R. H.Thomson, in *Naturally Occurring Quinones IV*; Blackie Academic, London, **1997**.

68 (a) J. Koyama, *Recent Pat. Anti-Infect. Drug Disc.* 2006, **1**, 113; (b) R. P. Verma, *Anti-Cancer Agents Med. Chem.*, 2006, **6**, 489; (c) P. Babula, V. Adam, L. Havel, R. Kizek, *Ceska Slovens. Farm.*, 2007, **56**, 114; (d) I. C. F. R. Ferreira, J. A. Vaz, M. H. Vasconcelos, A. Martins, *Mini-Rev. Med. Chem.*, 2010, **10**, 424; (e) P. R. Dandawate, A. C. Vyas, S. B. Padhye, M. W. Singh, J. B. Baruah, *Mini-Rev. Med. Chem.*, 2010, **10**, 436.

69 Ch. Li, K. Zhang, X.-H. Xu, F.-L. Qing, *Tetrahedron Lett.*, 2015, **56**, 6273-6275

70 H. Wu, Zh. Xiao, J. Wu, Y. Guo, J.-Ch. Xiao, Ch. Liu, Q.-Y. Chen, *Angew. Chem. Int. Ed.*, 2015, **127**, 4142.

71 (a) D. A. House, *Chem. Rev.*, 1962, **62**, 185; (b) J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc*., 1970, **92**, 1651; (c) A. Kumar, P. Neta, *J. Am. Chem. Soc*., 1980, **102**, 7284; (d) S. Seo, J. B. Taylor, M. F. Greaney, *Chem. Commun*., 2012, **48**, 8270.

72 F. Yin, X. S. Wang, *Org. Lett*., 2014, **16**, 1128.

73 (a) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 4258; (b) F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc*., 2012, **134**, 10401; (c) Z. Li, L. Song, C. Li, *J. Am. Chem. Soc*., 2013, **135**, 4640; (d) C. Zhang, Z. Li, L. Zhu, L. Yu, Z. Wang, C. Li, *J. Am. Chem. Soc*., 2013, **135**, 14082; (e) Z. Li, Z. Wang, L. Zhu, X. Tan, C. Li, *J. Am. Chem. Soc.*, 2014, **136**, 16439; (f) Z. Li, C. Zhang, L. Zhu, C. Liu, C. Li, *Org. Chem. Front*., 2014, **1**, 100; (g) L. Zhu, H. Chen, Z. Wang, C. Li, *Org. Chem. Front*., 2014, **1**, 1299.

View Article Online
DOI: 10.1039/C6OB00763E

74 D. Kong, Zh. Jiang, Sh. Xin, Zh. Bai, Y. Yuan, Zh. Weng, *Tetrahedron*, 2013, **69**, 6046-6050.

75 E. Th. Theimer, US Patent N°3712947A, **1973**.

76 A. Elentner, D. Ortner, C. Bjoern, F. J. Gonzalez, P. M. Fernandez-Salguero, M. Schmuth, S. Dubrac, *Experimental Dermatology*, 2015, **24**(11), 835-840.

77 Q. Lin, L. Chen, Y. Huanga, M. Ronga, Y. Yuaa, Z. Weng, *Org. Biomol. Chem*., 2014, **12**, 5500–5508.

78 J. Zheng, L. Wang, J.-H. Lin, J.-C. Xiao, S. H. Liang, *Angew. Chem. Int. Ed*., 2015, **54**, 13236 –13240.

79 (a) J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, *Chem. Commun*., 2013, **49**, 7513 – 7515; (b) Y. Qiao, T. Si, M.-H. Yang, R. A. Altman, *J. Org. Chem*., 2014, **79**, 7122 – 7131; (c) V. V. Levin, A. L. Trifonov, A. A. Zemtsov, M. I. Struchkova, D. E. Arkhipov, A. D. Dilman, *Org. Lett*., 2014, **16**, 6256 – 6259.

80 J.-B. Liu, X.-H. Xu, Z.-H. Chen, and F.-L. Qing, *Angew. Chem. Int. Ed*., 2015, **54**, 897 – 900.

81 M. Rong, D. Li, R. Huang, Y. Huang, X. Han, Zh. Weng, *Eur. J. Org. Chem.*, 2014, 5010.

82 R. M. DeMarinis, J. R. E. Hoover, G. L. Dunn, P. Actor, J. V. Uri, J. A. Weisbach, *J. Antibiot.*, 1975, **28**, 463–470.

83 X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.*, 2014, 3093.

84 Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.*, 2014, **50**, 6617.

85 (a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.*, 1971, **71**, 525; (b) R. Filler, *Biomedical Aspects of Fluorine Chemistry*, Kodansha, Tokyo, 1982; (c) L.M. Yagupol'skii, A. Ilchenko, N. V. Kondratenko, *Russ. Chem. Rev.*, 1974, **43**, 32; (d) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.

86 (a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.*, 2005, **105**, 827; (b) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.*, 2010, **131**, 140; (c) X.-H., Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (d) J. Hu, *J. Fluorine Chem.*, 2009, **130**, 1130.

View Article Online
DOI: 10.1039/C6OB00763E

87 L. Candish, L. Pitzer, A. Gomez-Suarez, F. Glorius, *Chem. Eur. J.*, 2016, DOI: 10.1002/chem.201600421.

88 F. Hu, X. Shao, D. Zhu, L. Lu, Q. Shen, *Angew. Chemie., Int. Ed.*, 2014, **53**, 6105.

89 S. Alazet, E. Ismalaj, Q.Glenadel, D. Le Bars, Th. Billard, *Eur. J. Org. Chem.*, 2015, 4607.

90 A. Ghatak, J. M. Dorsey, Ch. M. Garner, K. G. Pinney, *Tetrahedron Lett.*, 2003, **44**, 4145.

91 K. Monostory, V. Tamasi, L. Vereczkey, P. Perjesi, *Toxicology*, 2003, **184**, 203.

92 N. Arumugam, R. Raghunathan, V. Shanmugaiah, N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3698.

93 H. Bayer, Ch. Batzl, R. W**.** Hartmann, A. Mannschreckt, *J. Med. Chem.*, 1991, **34**, 2685.

94 Ch. Yin, W. Cao, L. Lin, X. Liu, X. Fenga, *Adv. Synth. Catal.*, 2013, **355**, 1924.

95 X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 12860.

96 (a) F. Dzierszinski, A. Coppin, M. Mortuaire, E. Dewally, C. Slomianny, J.-C. Ameisen, F. DeBels, S. Tomavo, *Antimicrob. Agents Chemother.*, 2002, **46**, 3197; (b) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly, F. Gago, *J. Med. Chem.*, 2005, **48**, 3796.

97 (a) R. Yamada, M. Seto, U. S. Patent 201093789, **2010**; (b) Q. Zeng, C. C. Yuan, G. Yao, X. Wang, S. Tadesse, D. J. S. Jean Jr., A. Reichelt, Q. Liu, F.-T. Hong, N. Han, C. Fotsch, C. Davis, M. P. Bourbeau, K. S. Ashton, J. G. Allen, WO 201083246, 2010; (c) K. Matsubara, A. Iesato, A. Oomura, K. Kawasaki, R. Yamada, M. Seto, U. S. Patent 200948223 A1, **2009**.

98 Q. Xiao, J. Sheng, Q. Ding, J. Wu, *Eur. J. Org. Chem.*, **2014**, 217.

99 A. Tlili, T. Billard, *Angew. Chem. Int. Ed.*, 2013, **52**, 6818 – 6819.

100 (a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.*, 2004, **104**, 3079 – 3160; (b) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.*, 2011, **111**, 2937 – 2980; (c) Acetylene Chemistry: Chemistry, Biology and Material Science (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, 2005; (d) H.C. Kolb, K.B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128 – 1137; (e) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.*, 2003, **125**, 3192 – 3193.

101 S. Alazet, L. Zimmer, Th. Billard, *Angew. Chem. Int. Ed.*, 2013, **125**, 11014.

View Article Online
DOI: 10.1039/C6OB00763E

102 R. S. Keri, S. A. Patil, S. Budagumpi, B. M. Mallanna, *Chemical Biology & Drug Design*, 2015, **86**(4), 410-423.

103 R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **126**, 1676.

104 X. Bantreil, C. Vaxelaire, Th. Godet, E. Parker, C. Sauer, Ph. Belmont, *Org. Biomol. Chem.*, 2011, **9**, 4831.

105 Ch. A. Demerson, L. G. Humber, Patent 4,108,998, US, 1978

106 (a) T. Pengsuparp, M. Serit, S. H. Hughes, D. D. Soejarto, J. M. Pezzuto, *J. Nat. Prod.*, 1996, **59**, 839; (b) E. B. B. Ong, N. Watanabe, A. Saito, Y. Futamura, K. H. Abd EI Galil, A. Koito, N. Najimudin, H. Osada, *J. Biol. Chem.*, 2011, **286**, 14049; (c) T. Taechowisan, C. Lu, Y. Shen, S. Lumyong, *Microbiology*, 2005, **151**, 1691; (d) T. Taechowisan, C. Lu, Y. Shen, S. Lumyong, *Food Agric. Immunol.*, 2007, **18**, 203; (e) M. Itoigawa, C. Ito, H. T.-W. Tan, M. Kuchide, H. Tokuda, H. Nishino, H. Furukawa, *Cancer Lett.*, 2001, **169**, 15; (f) C. Rappl, P. Barbier, V. Bourgarel-Rey, C. Gregoire, R. Gilli, M. Carre, S. Combes, J. Finet, V. Peyrot, *Biochemistry*, 2006, **45**, 9210; (g) C. Bailly, C. Bal, P. Barbier, S. Combes, J. Finet, M. Hildebrand, V. Peyrot, N. Wattez, *J. Med. Chem.*, 2003, **46**, 5437; (h) R. Argotte-Ramos, G. Ramírez-Avila, M. C. Rodríguez- Gutiérrez, M. Ovilla-Muñoz, H. Lanz-Mendoza, M. H. Rodríguez, M. González-Cortazar, L. Alvarez, *J. Nat. Prod.*, 2006, **69**, 1442.

107 Y.-F. Zeng, D.-H. Tan, Y. Chen, W.-X. Lv, Xu-Ge Liu, Q. Li, H. Wang, *Org. Chem. Frontiers*, 2015, **2**, 1511.

108 (a) R. D. Barry, *Chem. Rev.*, 1964, **64**, 229; (b) E. Napolitano, *Org. Prep. Proced. Int.* 1997, **29**, 631; (c) S. Pal, V. Chatare, M. Pal, *Curr. Org. Chem.*, 2011, **15**, 782; (d) K. M. Meepagala, G., Sturtz, D. E. Wedge, *J. Agric. Food Chem.*, 2002, **50**, 6989; (e) D. Engelmeier, F. Hadacek, O. Hofer, G. Lutz-Kutschera, M. Nagl, G. Wurz, H. Greger, *J. Nat. Prod.*, 2004, **67**, 19.

109 Y. Li, G. Li, Q. Ding, *Eur. J. Org. Chem.*, **2014**, 5017-5022.

110 (a) J. E. Saxton, *Nat. Prod. Rep.*, 1997, **14**, 559; (b) M. Toyota, N. Ihara, *Nat. Prod. Rep.*, 1998, **15**, 327 and references therein; (c) J. A. Joule, *Product Class 13: Indole and Its Derivatives*, Thieme, Stuttgart, 2001; (d) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761; (e) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.*, **2006**, **106**, 2875; (f) D. F. Taber, P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195.

View Article Online
DOI: 10.1039/C6OB00763E

111 J. Sheng, Sh. Lia, J. Wu, *Chem. Commun.*, 2014, **50**, 578.

112 For selected examples, see: (a) Y. Dong, D. Tang, N. Zhang, Y. Li, C. Zhang, L. Li, M. Li, *Chem. Cent. J.*, 2013, **7**, 124; (b) J. R. Clem, D. K. Farver, J. R. Fischer, T. J. Johnson, *Curr. Drug Saf.*, 2010, **5**, 251; (c) K. M. Zareba, *Drugs Today*, 2006, **42**, 75; (d) T. Ohtsuka, Y. Aoki, *Drugs Future*, 2003, **28**, 143; (e) S. O. Simonetti, E. L. Larghi, A. B. J. Bracca, T. S. Kaufman, *Nat. Prod. Rep.*, 2013, **30**, 941; (f) M. V. Kulkarni, G. M. Kulkarni, C.-H. Lin, C.-M. Sun, *Curr. Med. Chem.*, 2006, **13**, 2795; (g) S. Thareja, S. Aggarwal, T. R. Bhardwaj, M. Kumar, *Med. Res. Rev.*, 2012, **32**, 459; (h) M. A. Musa, M. O. F. Khan, J. S. Cooperwood, *Curr. Med. Chem.*, 2007, **14**, 1249; (i) A. S. Verkman, G. L. Lukacs, L. J. V. Galietta, *Curr. Pharm. Des.*, 2006, **12**, 2235.

113 J. Sheng, C. Fan, J. Wu, *Chem. Commun.*, 2014, **50**, 5494.

114 S. Alazet, K. Ollivier, Th. Billard, *Beilstein J. Org. Chem.*, 2013, **9**, 2345-2357.

115 G. L. Grunewald, M. R. Seim, S. R. Bhat, M. E. Wilson, K. R. Criscione, *Bioorg. Med. Chem.*, 2008, **16**, 542.

116 M. Jereb, D. Dolenc, *RSC Advances*, 2015, **5**, 58292.

117 A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *J. Org. Chem.*, 2008, **73**, 9362–9365.