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Synthetic Approaches to Trifluoromethoxy-Substituted Compounds

Anis Tlili, Fabien Toulgoat,* and Thierry Billard**

fluorine · hypervalent iodine compounds · synthetic methods
trifluoromethoxide · trifluoromethoxylation

Because of the unique properties of the trifluoromethoxy group, molecules bearing this moiety will find applications in various fields, particularly in the life sciences. However, despite the great interest in this functional group, only a small number of trifluoromethoxylated molecules are currently synthetically accessible. Over the last few years, several innovative and promising strategies for the synthesis of trifluoromethoxylated compounds have been described. This Minireview discusses these existing methods with a particular focus on more recent advances.

1. Introduction

Since their discovery in the mid-20th century, fluorinated compounds have become more and more significant for a large range of applications.[1] Especially the life sciences have benefitted from fluorinated molecules with particular properties.[1g,2] Compounds with a CF_3 group attached to a heteroatom have received growing interest over the past few years. Owing to its distinctive physicochemical properties, the trifluoromethoxy group (OCF_3) is of high value. Indeed, this moiety possesses interesting metabolic stability, a suitable lipophilicity parameter (Hansch parameter: $\pi_R = 1.04$)[3] and specific electronic properties (Hammett constants: $\sigma_p = 0.35$, $\sigma_m = 0.38$; Swain–Lupton constants: $F = 0.39$, $R = -0.04$).[4] Furthermore, trifluoromethoxylated arenes have highly specific structural features.[5] Because of these unique properties, CF_3O-containing molecules have found applications as pharmaceuticals or agrochemicals (Figure 1). For example, riluzole is the only currently approved drug for amyotrophic lateral sclerosis (Lou Gehrig's disease or Charcot's disease).[6]

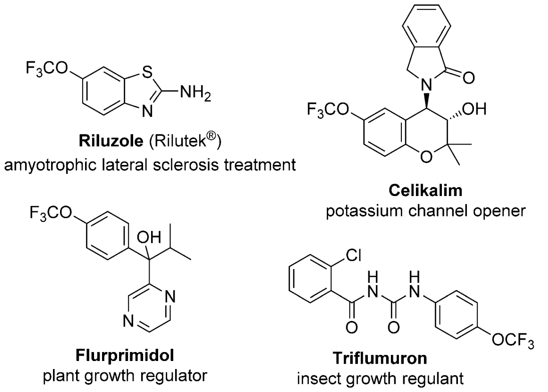

Figure 1. Some CF_3O-containing pharmaceuticals and agrochemicals.

However, despite this particular interest, there are only very limited possibilities for the synthesis of CF_3O-substituted molecules. Until recently, the only available methods were essentially based on the de novo construction of the OCF_3 moiety. Moreover, these approaches were very restricted in terms of the substrate scope (mainly arenes) and often required harsh reaction conditions and aggressive reagents (e.g., HF).[7] Over the past few years, however, new, promising strategies that are more compatible with fine chemistry have

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[*] Dr. A. Tlili, Dr. F. Toulgoat, Dr. T. Billard
Institute of Chemistry and Biochemistry (ICBMS-UMR CNRS 5246)
Univ Lyon, Université Lyon 1, CNRS
43 Bd du 11 Novembre 1918, F-69622 Villeurbanne (France)
E-mail: anis.tlili@univ-lyon1.fr
thierry.billard@univ-lyon1.fr

Dr. F. Toulgoat
CPE-Lyon, Campus LyonTech-la Doua
43 Bd du 11 Novembre 1918, F-69616 Villeurbanne (France)
E-mail: fabien.toulgoat@cpe.fr

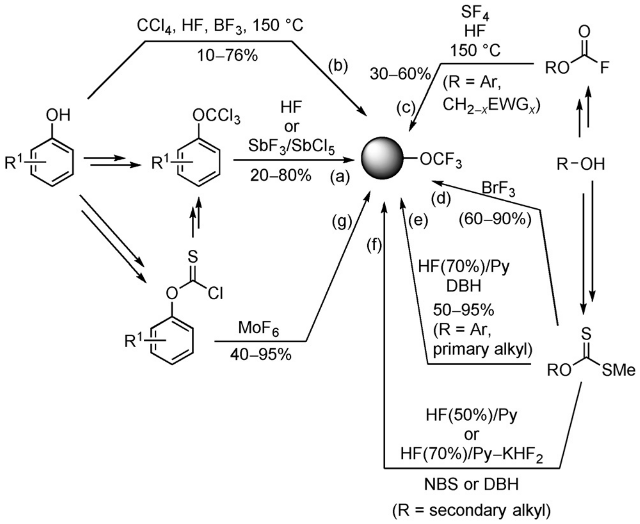
Dr. T. Billard
CERMEP—in vivo imaging
Groupement Hospitalier Est
59 Bd Pinel, F-69003 Lyon (France)

The ORCID identification numbers for the authors of this article can be found under http://dx.doi.org/10.1002/anie.201603697.

emerged owing to the impressive progress of organofluorine chemistry. In particular, methods for the direct introduction of the CF_3O group have been developed. In this Minireview, various methods for the synthesis of CF_3O-substitued molecules will be discussed, with a particular focus on recently developed approaches.

2. De Novo Construction

The first synthesis of trifluoromethoxylated arenes was described in 1955; trichloromethoxy-substituted arenes were subjected to a Cl–F exchange reaction in the presence of anhydrous hydrogen fluoride or $SbF_3/SbCl_5$ (Scheme 1a).[8]



Scheme 1. De novo construction of the OCF_3 group starting from alcohols. DBH = 1,3-dibromo-5,5-dimethylhydantoin, EWG = electron-withdrawing group, NBS = *N*-bromosuccinimide, Py = pyridine.

This method has more recently been adapted to pyridine derivatives.[5e] A one-pot method starting directly from anisoles has also been developed, and requires the presence of CCl_4, anhydrous HF, and BF_3 (Scheme 1b).[9] However, this strategy is limited to aromatic substrates and not compatible with all functional groups. O-Aryl-substituted carbonochloridothioates and aryl fluoroformates have also been transformed into aryl trifluoromethyl ethers by treatment with MoF_6[10] or highly toxic, gaseous SF_4 under HF catalysis, respectively (Scheme 1g,c).[11] The latter approach has also been used for the first synthesis of some aliphatic trifluoromethyl ethers.[12]

Later on, the oxidative fluorodesulfurization of *S*-methyl carbonodithioates was developed to obtain trifluoromethoxylated compounds under milder conditions, namely with HF–pyridine complex in the presence of an excess of oxidant (DBH, NBS, or NIS). With this method, aromatic as well as aliphatic products with various substituents were obtained in good yields (Scheme 1e,f).[13] Similar reactions have also been performed with the unusual reagent BrF_3, which is both an oxidant and a fluorinating agent (Scheme 1d).[14]

Anis Tlili is a CNRS Research Fellow. He obtained his Ph.D. in the group of Dr. M. Taillefer (Montpellier, France) and conducted postdoctoral research with Prof. M. Beller (Rostock, Germany) and Dr. T. Cantat and Dr. A. Marinetti (Paris, France). His current research interests lie in the area of homogeneous catalysis with a particular focus on fluorine chemistry.

Fabien Toulgoat is a lecturer at the Ecole Supérieure de Chimie Physique Electronique de Lyon (CPE Lyon, France). He obtained his Ph.D. in fluorine chemistry at the University of Lyon with Dr. B. Langlois and carried out postdoctoral research with Prof. D. Enders (Aachen, Germany), Prof. A.-C. Gaumont (Caen, France), and Dr. J. Suffert (Strasbourg, France). His research focuses on fluorine chemistry and new synthetic methods based on sustainable chemistry.

Thierry Billard is a CNRS Research Director. He obtained his Ph.D. in Fluorine chemistry at the University of Lyon, France with Dr B. Langlois, and carried out postdoctoral research studies in medicinal chemistry with Prof. L. Ghosez (University of Louvain, Belgium) and in industry (Rhone-Poulenc). His research activities are interdisciplinary between chemistry and medicine with a focus on fluorine chemistry, medicinal chemistry, radiochemistry, and their application in medical imaging and the neurosciences.

Whereas some of these methods could be of interest for specific applications, their restricted scopes, the use of aggressive reagents, and the preparation of the required starting materials constitute major drawbacks. Consequently, easier strategies that are compatible with more elaborate molecules are required.

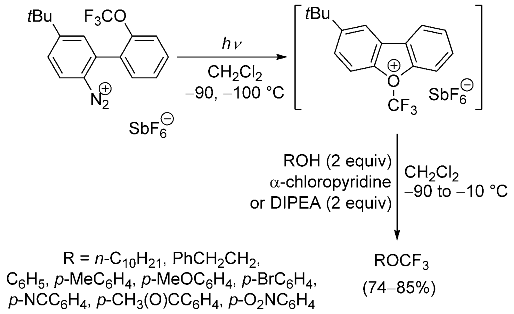
3. Indirect Approaches: Trifluoromethylation of Alcohols or Hydroxylated Compounds

A first retrosynthetic approach to trifluoromethoxy-substituted compounds entails the disconnection of the bond between the oxygen atom and the trifluoromethyl moiety. Several strategies have been developed for the corresponding bond-formation process.

3.1. Electrophilic Trifluoromethylation of Alcohols or Hydroxylated Derivatives

Among the known electrophilic trifluoromethylation reagents,[15] two families have been used for the trifluoromethylation of alcohols or derivatives thereof, namely (trifluoromethyl)dibenzochalcogenophenium salts ("Umemoto reagents")[16] and hypervalent iodine reagents ("Togni reagents").[17]

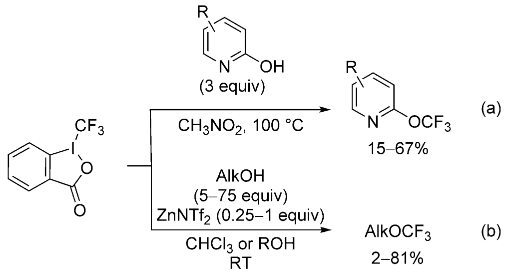
However, when trifluoromethylation was attempted with Umemoto reagents, C-trifluoromethylation was found to be favored over O-trifluoromethylation.[16,18] To reverse the selectivity, O$-$CF$_3$ onium salts were considered as alternative electrophilic trifluoromethylating reagents. Indeed, the oxygen-based salts are expected to feature a more positively charged CF$_3$ group than the other chalcogen salts owing to their relative electronegativities ($O > S > Se > Te$). Several O$-$CF$_3$ reagents were thus synthesized in situ by photochemical decomposition of the corresponding 2-trifluoromethoxy-2′-diazoniumbiphenyl salts (Scheme 2).[16,18] Although all of these salts were found to be thermally unstable above −70 °C,[18] they were successfully used for the trifluoromethylation of aliphatic alcohols and phenols (Scheme 2).[16,18]



Scheme 2. Trifluoromethylation of alcohols using OCF$_3$ onium salts.

A two-step reaction at very low temperature (addition of the alcohol and a base to the O$-$CF$_3$ onium salt preformed in situ) was found to be superior to the thermal decomposition of the 2-trifluoromethoxy-2′-diazoniumbiphenyl salts in the presence of an equimolar amount of the alcohol. In case of phenol, similar results were observed regardless of whether it was used as the solvent or in large excess. This method was also adapted to the trifluoromethylation of sulfonic acids in the presence of pyridine or sulfonate salts.[18]

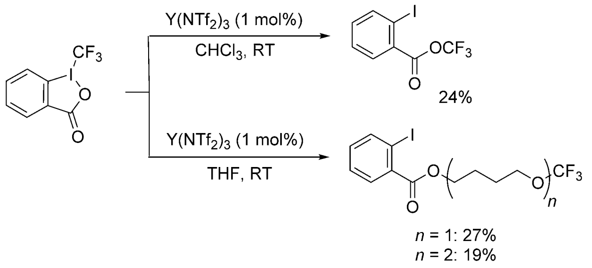
Similarly, C-trifluoromethylation was initially found to be favored during phenol trifluoromethylation with the Togni reagent.[19] In fact, the O-trifluoromethylation of N-heteroaromatic phenols was achieved only recently (Scheme 3 a), and required a high reaction temperature and an excess of substrate.[20] The acidic phenolic proton was assumed to be crucial for the activation of the Togni reagent, which reacts further through a single electron transfer (SET) mechanism. Nevertheless, amino-substituted pyridines still preferentially underwent C-trifluoromethylation.



Scheme 3. Synthesis of trifluoromethyl ethers with the Togni reagent.

The trifluoromethylation of aliphatic alcohols with the Togni reagent was achieved in the presence of zinc triflimide at room temperature (Scheme 3 b).[21] Despite its low nucleophilicity, the triflimide anion was trifluoromethylated when the alcohol/Zn(NTf$_2$)$_2$ molar ratio was decreased to 5:1. An excess of alcohol was thus required to achieve good yields.

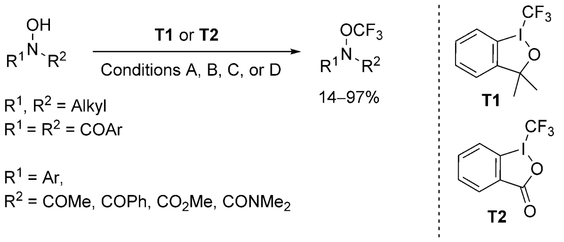
During the optimization of this reaction, it was found that the released 2-iodobenzoic acid reacts with THF through a formal ring opening/esterification/oligomerization/trifluoromethylation process to give trifluoromethyl ethers in low yield (Scheme 4).[22]



Scheme 4. Trifluoromethyl esters and ethers formed with the Togni reagent.

The trifluoromethylation of other hydroxylated compounds were also investigated. Owing to their high acidity, sulfonic acids are able to activate the Togni reagent in the absence of any additives. Thus a series of sulfonic acids were successfully trifluoromethylated in good yields.[23] Similarly, less acidic hydrogen phosphates were trifluoromethylated in moderate yields (22–44 %).[24]

Hydroxylamines were also subjected to trifluoromethylation with hypervalent iodine reagents (derived from iodobenzoic acid or iodophenyl propyl alcohol).[25] The best results were achieved when the reagent was activated with a Lewis acid while the substrate is deprotonated (Scheme 5).[25] However, this double activation was not always necessary (Scheme 5). Indeed, N-protected *N*-aryl hydroxylamines could be trifluoromethylated with the Togni reagent in the presence of a catalytic amount of base and without any Lewis acid (Scheme 5, conditions D).[26]



Conditions A: **T1** (1.5 equiv), $CHCl_3$, −20 °C to RT

Conditions B: **T1** (1.1 equiv), $(NMe_2)_2C{=}NH$ (1 equiv), TMSOTf (1.1 equiv), CH_2Cl_2, −78 °C to RT

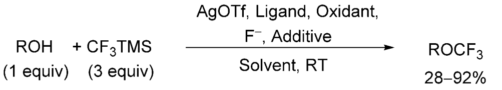
Conditions C: **T2** (1.5 equiv), Et_3N (1 equiv), CH_2Cl_2, 0 °C to RT

Conditions D: **T2** (1.2 equiv), Cs_2CO_3 (10 mol%), $CHCl_3$, RT

Scheme 5. Trifluoromethylation of *N*-hydroxylamines with Togni reagents.

3.2. Oxidative Couplings between Alcohols and Nucleophilic Trifluoromethylating Reagents

Oxidative couplings with nucleophilic reagents such as the Ruppert–Prakash reagent ((trifluoromethyl)trimethylsilane) represent an alternative to electrophilic trifluoromethylation.[27] This approach was recently adopted by Qing and co-workers for a breakthrough synthesis of trifluoromethyl ethers.[28] Phenols were trifluoromethylated in the presence of a combination of several components, which have to be used in excess, at room temperature (Scheme 6).[28a] In particular, two oxidants (*N*-fluorobenzenesulfonamide (NFSI) and Selectfluor) had to be used simultaneously to promote the oxidation of $[Ag^{I}CF_3]$ into $[Ag^{III}CF_3(F)]$. The subsequent substitution of the fluoride with an alkoxide to form $[Ag^{III}(CF_3)(OR)]$ was proposed to be the key step of this transformation. Whereas moderate to good yields were achieved with phenols bearing electron-withdrawing groups, those initially achieved with electron-rich phenols were not optimal as side products were detected. In fact, two reactions compete with the desired oxidative coupling, namely the formation of the corresponding benzenesulfonate of the phenol starting material and C-trifluoromethylation of the aromatic ring. To increase the efficiency of the process and promote the formation of the desired trifluoromethyl ethers, another electron-rich phenol, 2,4-di-*tert*-butylphenol, had to be added (Scheme 6).[28a] Extending this approach to N-heteroaromatic phenols initially failed, probably owing to coordination of the nitrogen atom to the metal center. To prevent this undesired process, the nitrogen atoms were simply protonated, and the corresponding pyridinium ions were then trifluoromethylated in moderate yields (Scheme 6).[28a] This oxidative coupling was also adapted to the trifluoromethylation of aliphatic alcohols (Scheme 6).[28b]



Conditions for ArOH: AgOTf (3 equiv), 2-fluoropyridine (5 equiv), Selectfluor (2 equiv), NFSI (2 equiv), CsF (6 equiv), 2,4-di-*tert*-butylphenol (0–2 equiv), TfOH (1 equiv with HetArOH), $PhCF_3/PhCH_3$ (2:1)

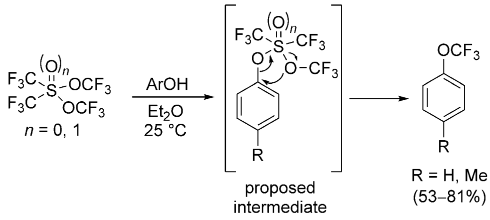
Conditions for AlkOH: AgOTf (3 equiv), 2-fluoropyridine (3 equiv), Selectfluor (1.5 equiv), KF (4 equiv), 2,4-di-*tert*-butylphenol (0–2 equiv), EtOAc

Scheme 6. Oxidative trifluoromethylation of alcohols. NFSI = *N*-fluorobenzenesulfonamide, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

Moreover, this method could also be used for the late-stage trifluoromethylation of various elaborate alcohols.[28] Considering other hydroxylated derivatives, no preparative methods have been reported. Nevertheless, the formation of *N*-trifluoromethoxy-*N*-phenylacetamide (through oxidative trifluoromethylation of the corresponding hydroxylamine) as a side product during the oxytrifluoromethylation of alkenes with sodium trifluoromethanesulfinate and a hydroxylamine has been detected by GC-MS and ^{19}F NMR spectroscopy.[29]

3.3. Phenol Trifluoromethylation through Phenol Activation and ipso *Trifluoromethoxylation*

The synthesis of (trifluoromethoxy)benzene and *para*-trifluoromethoxytoluene was achieved using sulfurane or sulfurane oxide (Scheme 7).[30] A mechanism based on nucleophilic attack of the phenol on the sulfurane followed by intramolecular rearrangement was proposed. However, this method could not be employed for the trifluoromethylation of secondary or tertiary alkyl alcohols as only the corresponding alkenes were formed.



Scheme 7. Trifluoromethylation of phenols using sulfurane derivatives.

3.4. Radical Trifluoromethylation

Only few reports describe radical trifluoromethylation reactions that lead to trifluoromethyl ethers. For example, a small amount of bis(trifluoromethoxy)benzene was observed in the reaction mixture of the photoreaction of *para*-benzoquinone with $Te(CF_3)_2$.[31] Bis(trifluoromethyl)nitroxyl has been trifluoromethylated with trifluoromethyl phosphine, arsine, and stibine derivatives.[32] However, this reaction has not been extended to other nitroxyl compounds since these early reports.

In addition, the TEMPO radical has also been trifluoromethylated.[33] TEMPO is commonly employed as a radical trap, and $TEMPOCF_3$ is thus formed under a broad range of radical trifluoromethylation conditions that generate

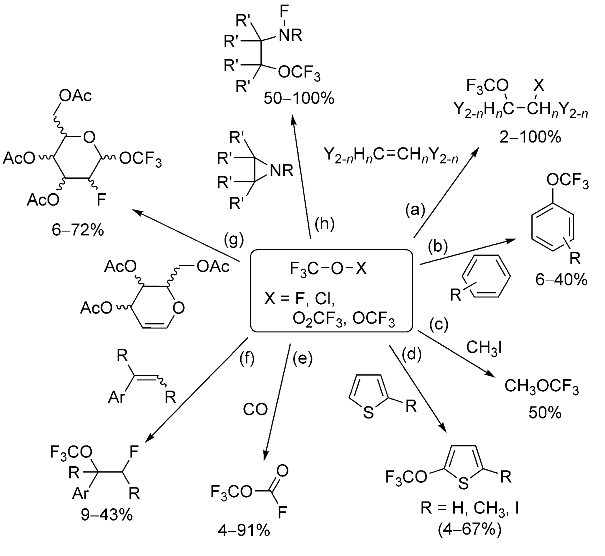
CF_3 radicals.[34] Its detection has often been used to confirm that a radical pathway is operating, but it is almost never isolated.[33,34]

4. Direct Trifluoromethoxylation

Even if some of the previous indirect methods constitute valuable approaches to various CF_3O-substituted molecules, their scopes are generally restricted to specific substrates. From a retrosynthetic point of view, another strategy entails the direct disconnection of the R–OCF_3 bond. However, this approach requires the development of CF_3O donor reagents, which still constitutes a challenge.

4.1. Radical Trifluoromethoxylation

The radical trifluoromethoxylation of perhalogenated alkenes was achieved using trifluoromethyl hypofluorite (Scheme 8 a).[35] However, the toxicity and potential explosiveness of hypofluorite are major drawbacks of this reagent.[36] Trifluoromethyl hypofluorite has to be diluted in nitrogen or used at very low temperatures to avoid explosions as observed with acetylene or even ethene.[35a] Moreover, addition reactions to alkenes sometimes suffer from selectivity issues.[35i] Whereas trifluoromethyl hypofluorite has been reported to be a mild electrophilic arene fluorination reagent, it has recently also been used for arene trifluoromethoxylation (Scheme 8 b).[36] When a halogenated substrate (iodomethane) was reacted with trifluoromethyl hypochlorite, the corresponding trifluoromethyl methyl ether was obtained in 50 % yield (Scheme 8 c).[37] The trifluoromethoxy moiety was also introduced into the four products (mono-, di-, tri-, and tetramers) formed during the reaction of dichlorodifluoroethene with $CF_3O_3CF_3$.[38]



Scheme 8. Trifluoromethoxylation with CF_3OX.

Bis(trifluoromethyl) peroxide, which has been seldom observed in reactions involving trifluoromethyl hypofluorite,[35e,h] reacts with 2-substituted thiophenes at 200 °C to afford the corresponding 2-substituted 5-trifluoromethoxythiophenes in moderate yields (Scheme 8 d).[39]

Furthermore, (trifluoromethyl)fluoroformate has been prepared from trifluoromethyl hypofluorite and carbon monoxide (Scheme 8 e).[40] Several trifluoromethyl carbonates ($CF_3OC(O)OR$) have also been obtained from photochemical reactions of trifluoroacetic anhydride in the presence of CO and O_2.[41]

4.2. Concomitant Electrophilic Halogenation and Trifluoromethoxylation

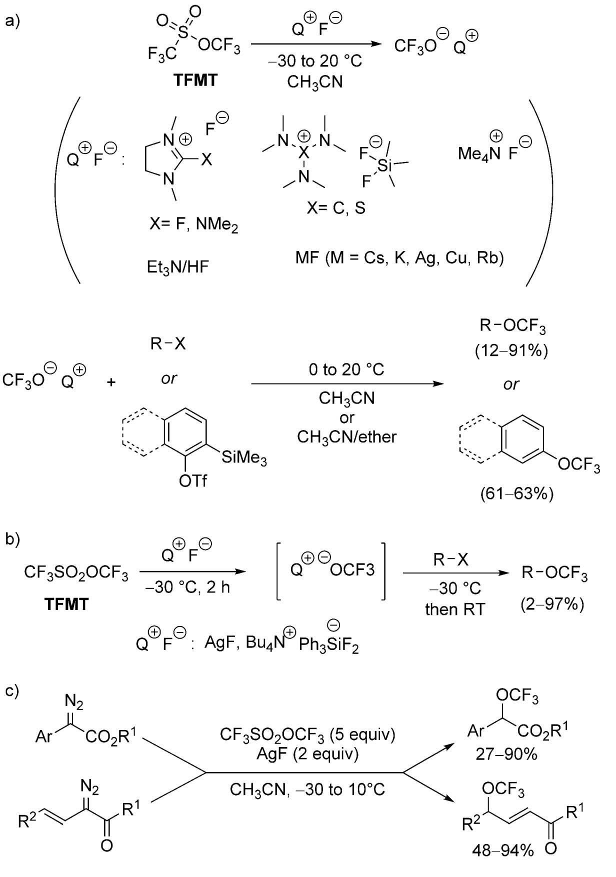
Aside from the radical mechanism proposed for reactions involving trifluoromethyl hypofluorite, concerted electrophilic fluorination/trifluoromethoxylation can also occur.[42] This pathway is in accordance with the major *syn* products formed during reactions with styrene derivatives[42a] and with the regioisomers obtained from carbohydrates (Scheme 8 f, g).[43] In several cases, difluoro-substituted compounds were formed in addition to the trifluoromethyl ethers owing to the decomposition of trifluoromethanolate into fluoride and difluorophosgene. The ring opening of aziridines with trifluoromethyl hypofluorite proceeds in a similar fashion (Scheme 8 h).[44] In a comparison of the addition of trifluoromethyl hypofluorite and hypochlorite to alkenes, DesMarteau and Johri concluded that electrophilic halogenation/trifluoromethoxylation is more pronounced with the latter reagent.[35i] However, isomeric mixtures were still obtained in most cases.[35i,45] One example of the chlorotrifluoromethoxylation of isocyanides has also been reported.[46]

4.3. Nucleophilic Trifluoromethoxylation with Difluorophosgene

The trifluoromethanolate anion is known to be relatively unstable and rapidly collapses to difluorophosgene and a fluoride anion.[47] However, this degradation process is an equilibrium, which can be shifted with an excess of reagent. This strategy has been applied to prepare some trifluoromethoxide salts[47,48] and for a few nucleophilic substitution reactions.[37,49] However, the use of gaseous and toxic difluorophosgene considerably restricts the applicability of this method.

4.4. Nucleophilic Trifluoromethoxylation Starting from Trifluoromethyl Trifluoromethanesulfonate

Although the synthesis of trifluoromethyl trifluoromethanesulfonate (TFMT) has been known for a long time,[50] it has only really been used in fluorine chemistry in the last ten years. The quantitative decomposition of TFMT into difluorophosgene (COF_2), through degradation of transient trifluoromethanolate (CF_3O^-), was observed with various nucleophiles, including fluoride anions.[50j] The formation of this unstable anion from TFMT in the presence of fluoride sources at low temperature (−30 °C) has also been exploited.[51] Whereas several trifluoromethanolate salts have been isolated (Scheme 9 a),[51a–c,e] the trifluoromethoxide anion (from silver and tetrabutylammonium trifluoromethoxide) can also be generated in situ (Scheme 9 b).[51d] Both methods have enabled the trifluoromethoxylation of alkyl halides or pseudohalides (I, Br, OTf), especially for primary or activated secondary starting materials; however, almost no reactivity was observed with unactivated secondary as well as tertiary alkyl halides. This strategy could be extended to the preparation of an α-trifluoromethoxylated ketone on multigram scale.[52]

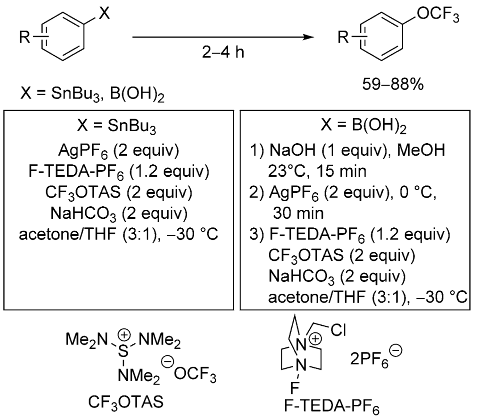


Scheme 9. Nucleophilic trifluoromethoxylation with trifluoromethyl trifluoromethanesulfonate (TFMT).

However, nucleophilic aromatic substitution was not successful using isolated CF_3OM salts. Instead of C−OCF_3 bond formation, only C−F bond formation was observed owing to the decomposition of the reagent into difluorophosgene and fluoride.[51a] On the other hand, the trifluoromethoxylation of two arynes, formed in situ from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate derivatives, was indeed successful.[51a] It should, however, be noted that direct fluorination of the aryne was also observed.

Very recently, the trifluoromethoxylation of α-diazo esters was achieved by using a combination of TFMT and AgF.[53] In the case of vinylic diazo carbonyl compounds, an S_N2'-like reaction was observed (Scheme 9 c).

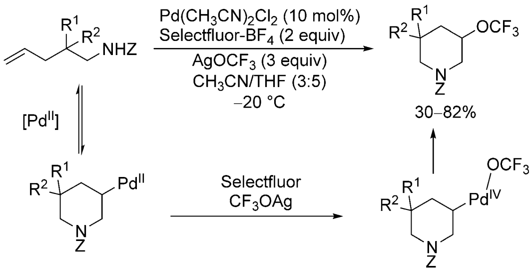
A breakthrough was achieved by Ritter and co-workers, who described the first direct approach for the trifluoromethoxylation of arenes in 2011.[54] Aryl stannane derivatives underwent trifluoromethoxylation under oxidative conditions with F-TEDA-PF_6 in the presence of tris(dimethylamino)sulfonium trifluoromethoxide (CF_3OTAS), which was prepared from TFMT,[47] as the trifluoromethoxylation agent (Scheme 10). The reactions were carried out in the presence of two equivalents of silver hexafluorophosphate and sodium bicarbonate in a THF/acetone mixture at −30 °C. Electron-deficient and electron-rich arenes underwent trifluoromethoxylation in very good to excellent yields. Moreover, challenging compounds, such as a morphine derivatives, were also suitable substrates for this process, and the corresponding product was isolated in 59 % yield. Unfortunately, the fluorodestannylated as well as protodestannylated side products were obtained alongside the desired product.



Scheme 10. Silver-mediated trifluoromethoxylation of aryl stannanes and aryl boronic acids.

This method was further developed into a one-pot three-step approach with aryl boronic acids as the starting materials. The formation of the required arene silver(I) complexes was achieved in two steps by 1) addition of NaOH (1 equiv) to the aryl boronic acid in methanol at room temperature and stirring for 15 min and 2) addition of silver hexafluorophosphate (2 equiv) at 0 °C. After 30 min, CF_3OTAS and F-TEDA-PF_6 were added to obtain the desired products also in very good yields. Once again, arenes with electron-withdrawing as well as electron-donating groups were suitable substrates for this reaction.

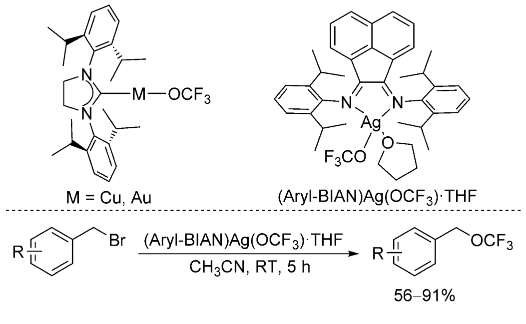
The effectiveness of palladium-catalyzed direct trifluoromethoxylation reactions was first disclosed by Liu and coworkers in 2015, who employed CF_3OAg prepared from TFMT as the key reagent (Scheme 11).[55] The use of palladium in high oxidation states was key to the success of the reaction as potential β-fluoride elimination, which is often observed with trifluoromethoxylated transition-metal complexes, was prevented. Indeed, intramolecular aminotrifluoromethoxylation of N-tosylated alkenylamines yielded



Scheme 11. Palladium-catalyzed intramolecular aminotrifluoromethoxylation of alkenes.

3-OCF_3-substituted piperidine derivatives under mild reaction conditions. The authors further demonstrated that the reaction proceeds through reversible aminopalladation followed by oxidation with Selectfluor, which yields a high-valent alkyl−Pd(OCF_3) complex that undergoes reductive elimination.

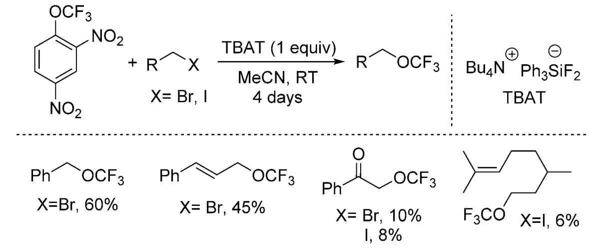
Whereas the crystal structures of several alkali-metal-based trifluoromethanolate complexes ($MOCF_3$, M = K, Rb, Cs) have been known for many years,[56] the first crystal structures of discrete copper or gold analogues were only reported in 2012 by Vicic and Zhang.[57] These authors also highlighted the high sensitivity of the complexes towards oxygen as well as their thermal sensitivity. To render the CF_3O−M bond more covalent, NHC ligands were added to obtain well-defined copper and gold complexes (Scheme 12).[57] The bulkiness of the NHC ligand appeared to be crucial. Indeed, when [(SIPr)CuCl] or [(SIPr)AuCl] (see Scheme 12, left) was treated with $AgOCF_3$ (prepared from TFMT) at −30 °C, the desired complex was isolated, and crystal data could be collected. With the less bulky NHC ligand SIMes (1,3-dimesitylimidazolin-2-ylidene), the corresponding complexes could be formed in situ, but isolation failed. Furthermore, the silver analogues were found to be even more sensitive than the copper ones as the addition of SIPr as well as 1,10-phenanthroline led to decomposition.[57] To this day, these complexes have not been implied in trifluoromethoxylation reactions even though a well-defined silver(I) trifluoromethoxide complex was finally synthesized in 2015.[58] This complex was prepared in 75 % yield from $AgOCF_3$ (from TFMT) and a bis(arylimino)acenaphthene (Aryl-BIAN, 1 equiv) at room temperature, and was used for the trifluoromethoxylation of benzyl bromides. Very good to excellent yields were achieved regardless of the electronic nature of the substituents (electron-donating or -withdrawing) on the aromatic ring.[58] The presence of benzyl chloride, however, was detrimental to the trifluoromethoxylation process.



Scheme 12. Transition metal/trifluoromethoxide complexes and their application in trifluoromethoxylation reactions.

4.5. Nucleophilic Trifluoromethoxylation with 2,4-Dinitro(trifluoromethoxy)benzene

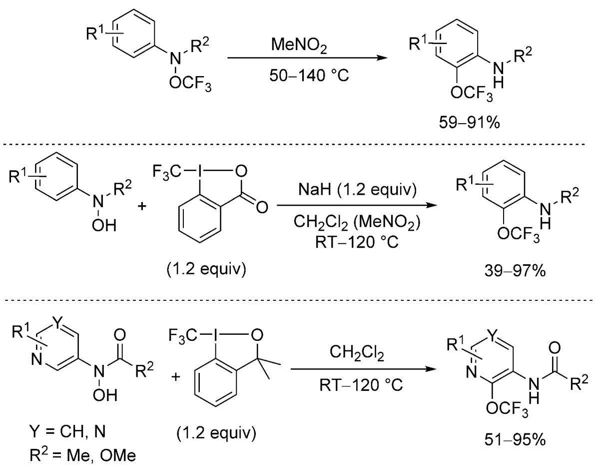
Whereas TFMT has shown versatile reactivity in various trifluoromethoxylation reactions, it is still expensive and difficult to handle owing to its low boiling point (21 °C) and high volatility. An alternative approach has thus been proposed for the generation of trifluoromethoxide anions: In the presence of a fluoride source, 2,4-dinitro(trifluoromethoxy)benzene can release a trifluoromethoxide anion by forming 2,4-dinitrofluorobenzene through an S_NAr pathway.[59] Benzyl bromide could thus be trifluoromethoxylated, and the best reaction conditions entailed the use of TBAT (tetrabutylammonium triphenyldifluorosilicate) as the fluoride source (Scheme 13). The expected product was formed in 60 % yield after four days at room temperature or after 20 h when heated to 50 °C. Unfortunately, activated substrates are still required to achieve moderate to very good yields in this process. Alternatively, benzyl bromide could be trifluoromethoxylated under microwave conditions (100 °C, 20 min) to yield the desired product in 70 % yield.



Scheme 13. Nucleophilic trifluoromethoxylation with 2,4-dinitro(trifluoromethoxy)benzene.

4.6. Intramolecular Nucleophilic Trifluoromethoxylation

In 2014, Ngai and co-workers developed an original strategy for the formation of $C(sp^2)$−OCF_3 bonds. Their method is based on the trifluoromethylation of protected *N*-aryl-*N*-hydroxylamines followed by an intramolecular migration of the OCF_3 group to the aryl ring.[26,60] The starting trifluoromethoxylated hydroxylamines were prepared following a procedure described in Section 3.1 (see Scheme 5). When the isolated products were heated at 80 °C in $MeNO_2$, the OCF_3 moiety could migrate and a new C−OCF_3 bond was formed (Scheme 14). Migration to both the *ortho* and *para* positions with respect to the amine group was observed. This intramolecular C−OCF_3 bond formation was also conducted



Scheme 14. Intramolecular *ortho* trifluoromethoxylation through OCF_3 migration.

in a in one-pot two-step fashion. By using a slight excess of NaH (1.2 equiv), the desired reaction could be performed without purification of the N–OCF_3 intermediate. In some cases, simply heating the reaction mixture to 50 °C was enough to obtain the desired products. For other substrates, replacement of CH_2Cl_2 by $MeNO_2$ as well as heating up to 120 °C was necessary (Scheme 14). It should be highlighted that the reaction is easily scalable, and that the authors were able to obtain more than 2 g of a trifluoromethoxylated arene.[26]

These methods could be easily applied to the direct trifluoromethoxylation of pyridine and pyrimidine derivatives (Scheme 14). Interestingly, no additive was required with these starting materials.[61] Heterocyclic compounds with electron-donating and electron-withdrawing substituents were tolerated under the reaction conditions and gave the desired products in very good to excellent yields.

The authors proposed that the reaction proceeds by single electron transfer (SET) between the *N*-aryl-*N*-hydroxylamine anion and the Togni reagent. The OCF_3 migration step, however, is currently believed to proceed by heterolytic cleavage of the N–OCF_3 bond via formation of a nitrenium ion and a trifluoromethoxide anion. The intramolecular nature of this OCF_3 migration was confirmed by a crossover experiment.[62]

5. Conclusion

Even though the trifluoromethoxy group has been known for a long time, the synthetic methods available to obtain CF_3O-substituted molecules were extremely limited until recently and essentially restricted to aromatic compounds. Therefore, the exciting properties of the trifluoromethoxy group have hardly been explored.

However, with the significant developments in fluorine chemistry over the past few years, new innovative methods have emerged for the synthesis of a broad range of trifluoromethoxylated compounds. Furthermore, the mild experimental conditions of these approaches are more suitable to more elaborate, often sensitive, substrates. This has contributed to the renewed interest in CF_3O-substituted molecules and enables the use of the CF_3O moiety as an important fluorine-containing functional group.

Nevertheless, even though significant advances have been achieved, there is still a long way to go before we have an efficient toolbox for the trifluoromethoxylation of any compound in hand. In particular, direct trifluoromethoxylation still appears to be dramatically underdeveloped even though it should be a promising direction for further advances. In particular, the development of stable, easy-to-handle, and efficient CF_3O donor reagents could lead to new breakthroughs in this field of research.

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