Advances in the Development of Trifluoromethoxylation Reagents

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Abstract: This review provides a short summary of the traditional methods for synthesis of CF3-O-containing compounds, followed by a critical overview of known trifluoromethoxylating reagents, focusing on their preparation, synthetic generality and limitations.

Keywords: pharmaceutical drugs; agrochemicals; trifluoromethoxylation; trifluoromethylation; fluorination; reagents

1. Introduction

Fluorine chemistry is currently one of the most exciting areas of research, contributing to the modernization of materials [1], agriculture [2–6] and healthcare [7–14] industries. Particularly, the development of original synthetic methodology, allowing access to new fluorinated compounds with unique physicochemical and biological properties, is in very high demand in nearly every area of chemical industry [15–21]. However, the progress in the advancement of fluorine methodology was far from balanced. For instance, syntheses of aromatic C-F and C-CF3 compounds, while still enjoying a great deal of innovation, could be considered as mature areas of research [22–24]. In contrast, preparation of molecules bearing CF3-O- group is a noticeably less developed area of fluoride chemistry [25–34]. As a reflection of this apparent methodological deficit, pharmaceutical drugs and agrochemicals featuring trifluoromethoxyl substituent, constitute less than 1.5% and 2.5% of the respective fluoride-containing marketed compounds [2–14,35–38]. Examples of the corresponding pharmaceutical drugs are presented in Figure 1, and agrochemicals are shown in Figure 2. These examples clearly underscore the high interest in the trifluoromethoxy motif, which is currently recognized as an important emerging fluorinated group.

Of particular interest is the noticeably high lipophilicity of OCF3 group (OCF3: \( \pi = 1.04 \)) as compared to the OCH3 and CF3 groups (OCH3: \( \pi = -0.20 \), CF3: \( \pi = 0.88 \)), which is slightly lower to that of SCF3 group (SCF3: \( \pi = 1.44 \)) [39,40]. It should be pointed out that trifluoromethoxyl is not conjugated to unsaturated bonds (in olefines, amines). Thus, the delocalized p-electrons of oxygen atom in the \( \sigma^* \)-orbitals of the C–F bond, leads to a weakening of the C–F bond and a strengthening of the C–O bond [41,42]. Furthermore, trifluoromethoxyl adopts a particular conformation, minimizing repulsive electrostatic interactions, with the CF3 group being in a rectangular position relative to an arene residue [43]. Finally, it is worth pointing out that the trifluoromethoxy group is thermally and chemically quite stable toward bases, acids, reducing/oxidizing reagents as well as organometallic species [44–46]. Nevertheless, despite all of these exciting properties, practical and general methodology for the introduction of trifluoromethoxy group has not
been developed so far. Some success has been achieved in the preparation of aryl-O-CF$_3$ compounds based on traditional fluorination methods such as chlorine–fluorine exchange (CCl$_3$-O- to CF$_3$-O-) [47,48], fluorination of fluoroformates (FCO-O- to CF$_3$-O-) [44], desulfurization (RS-CS-O- to CF$_3$-O-) [49–52]. More recent approaches include trifluoromethylation of OH group using electrophilic Umemoto [53] and Togni [54,55] reagents.

Figure 1. Trifluoromethoxy-containing pharmaceutical drugs.

Figure 2. Trifluoromethoxy-containing agrochemicals.
These and other synthetic methods for the preparation of trifluoromethoxy-containing compounds have been extensively reviewed [56–64]. In the present article, we provide a short summary of the traditional methods, followed by a critical discussion of the most recently developed trifluoromethoxylating reagents, focusing on their synthetic generality and limitations.

2. General Approaches for Preparation of Trifluoromethoxy-Containing Compounds

2.1. Nucleophilic Fluorination

2.1.1. Chlorine-Fluorine Exchange

Aryl trifluoromethyl ethers as the first representatives of trifluoromethyl ethers were prepared in 1955 employing chlorine-fluorine exchange approach by L. Yagupolskii [65]. Synthesis of aryl trifluoromethyl ethers 3 (Scheme 1) started with side chain chlorination of anisoles 1 bearing such functional groups as fluoro, chloro, cyano and acid chloride in the presence of catalytic amount of phosphorus pentachloride at 200 °C to obtain corresponding aryl trichloromethyl ethers 2 [65,66]. At the same time, aryl trichloromethyl ethers 2 could also be prepared by chlorination of chlorothionocarbonates 5 easily combined from phenols 4 and thiophosgene under basic conditions [67]. Chlorine-fluorine exchange using antimony trifluoride and catalytic antimony pentachloride (Swarts reaction [68]) at 150 °C applied to trichloromethyl derivatives 2 with substituents at meta-, and para-positions afforded aryl trifluoromethyl ethers 3 in good yields. However, a significant decrease in the yield was observed for substrates with cyano group and chlorine substituent at ortho-position. The reaction was mediated by strong Lewis’s acid SbF₅, generated in situ by reaction of SbF₃ with SbCl₅. Synthesis of aryl trifluoromethyl ethers also employed fluorination of aryl trichloromethyl ethers 2 with hydrofluoric acid in liquid phase [69]. Screening of reaction conditions showed that liquid phase fluorination of the trichloromethoxybenzene with 2 mol% of SbCl₅ and stoichiometric amount of HF was complete after 1 h at 50 °C. It is worth mentioning that chlorothionocarbonates 5 could be directly converted to aryl trifluoromethyl ethers 3 when treated with molybdenum hexafluoride [47].

![Scheme 1. Fluorination of aryl trichloromethyl ethers.](image-url)

Chlorine-fluorine exchange strategy was also applicable to heteroaromatic compounds, such as pyridine and pyrazine derivatives. The reaction of thiophosgene with both hydroxypyridines and hydroxy.pyrazine 6 (Scheme 2) followed by chlorination and then fluorination of trichloromethoxy derivatives 7 with antimony trifluoride in the presence of catalytic antimony pentachloride allowed access to trifluoromethoxylated pyridines and pyrazine 8 which were isolated in good yields [43,70]. The presence of chlorine atoms in the heteroaryl rings was essential for the success of process.
Chlorine-fluorine exchange method was modified by in situ generation of intermediate trichloromethyl derivatives with further conversion into the final aryl trifluoromethyl ethers 3 (Scheme 3) under heating of phenols 4 with excess of tetrachloromethane, anhydrous hydrogen fluoride and catalytic amounts of boron trifluoride at 150 °C [48]. While modified procedure worked well with substrates carrying electron-withdrawing groups on aromatic ring, phenols having ortho substituents prone to hydrogen bonding with the hydroxy group failed to give corresponding trifluoromethoxy derivatives.

While chlorine-fluorine exchange strategy was widely used to prepare aryl and heteroaryl trifluoromethyl ethers, it is only recently this strategy was successfully expanded to preparation of alkyl trifluoromethyl ethers. In this case the required trichloromethyl ether intermediates 11 (Scheme 4) were obtained in excellent yields by treating β-hydroxypropionic acid derivatives and N-protected alkanolamines 9 with sodium hydride, carbon disulfide and then methyl iodide followed by chlorination of resulting xanthates 10 with elemental chlorine [71]. The chlorine-fluorine exchange was successfully accomplished with antimony trifluoride (method A) as well as hydrogen fluoride (method B) in the presence of antimony pentachloride as catalyst affording desired alkyl trifluoromethyl ethers 12. In general, trifluoromethyl ethers with protected amino group were obtained in higher yields as compared to β-hydroxypropionic acid derivatives and the lowest yield was observed for trifluoromethyl ether derived from secondary alcohol derivative.

Chlorine-fluorine exchange approach to trifluoromethyl ethers has high generality and was well described in several reviews [34,46]. It was successfully applied for aromatic, heteroaromatic and aliphatic substrates using such inexpensive industrial fluorinating reagents as antimony trifluoride and hydrogen fluoride. However, the method is limited by availability of the intermediate trichloromethyl ethers, which require extra synthetic steps for their preparation and substrate scope for heteroaromatic trifluoromethyl ethers is restricted to a few examples. Besides trifluoromethyl ethers were conventionally accessed by fluorination under harsh conditions that were incompatible with many functional groups. Nonetheless, the method is suitable for a large-scale industrial application especially for aromatic trifluoromethyl ethers.
Fluorination of alkyl trichloromethyl ethers.

Scheme 4. Fluorination of alkyl trichloromethyl ethers.

2.1.2. Oxidative Desulfurization-Fluorination

Alternative approach to synthesize both alkyl and aryl trifluoromethyl ethers is based on oxidative desulfurization-fluorination of xanthates using N-haloimides as oxidants and complex pyridine-HF as fluorine atom source [51,52]. For example, treatment of xanthates 10 and 13 (Scheme 5) derived from primary alcohols and phenols with excess of pyridine-HF 70% and 1,3-dibromo-5,5-dimethylhydantoin (DBH) afforded trifluoromethyl ethers 12 and 3 in good to excellent yields [49,50,72]. When excess of DBH was employed as the oxidant, the fluorination was accompanied by bromination of the aromatic ring. At the same time employing of such modified fluorinating reagents as pyridine-HF 70% or pyridine-HF 70% with KHF2 and N-bromosuccinimide (NBS) allowed transformation of secondary alkyl xanthates 10 to corresponding secondary alkyl trifluoromethyl ethers 12. However, fluorination of secondary alkyl xanthates 10 usually provided poor yields of the corresponding trifluoromethyl ethers 12. This method did not work in the case of benzyl xanthates.

Scheme 5. Oxidative desulfurization-fluorination.
Desulfurization-fluorination method has been modified for preparation of aryl and heteroaryl trifluoromethyl ethers by using XtalFluor-E ([Et$_2$NSF$_2$]BF$_4$) as fluoride source in combination with trichloroisocyanuric acid (TCCA) or N-fluorobenzenesulfonimide (NFSI) [73]. Initially aryl and heteroaryl xanthates 13 and 15 (Scheme 6) were prepared from phenols 4 and heteroaromatic alcohols 6 by action of equimolar amount of 3-methyl-1-((methylthio)carbonothioyl)-1H-imidazol-3-ium iodide 14 as efficient methyldithiocarbonyl transfer reagent [74] and trimethylamine in over 90% yields under mild conditions. Crystalline XtalFluor-E was selected among many potential fluoride sources for fluorination of xanthates due to its high reactivity, good air stability and enhanced thermal stability [75]. Fluorination could be performed with XtalFluor-E, TCCA, and H$_2$O in 1,2-dichloroethane (condition A) or with XtalFluor-E and NFSI in 1,2-dichloroethane (condition B). While both electron-poor and electron-rich aromatic xanthates were smoothly fluorinated under both conditions giving the respective CF$_3$O-compounds 3 in good to high yield, heteroaromatic xanthates containing pyridine, quinoline or pyrazole rings formed trifluoromethyl ethers 8 in modest yield. Generally, fluorination of aromatic substrates bearing amide and nitrile groups as well as heteroaromatic substrates proceeded in higher yield under condition A than under condition B.

**Scheme 6.** Trifluoromethoxylation of phenols and heteroaryl alcohols using XtalFluor-E.

Recent articles were described the use of the Fluolead (4-tert-butyl-2,6-dimethylphenylsulfur trifluoride) combined with SbCl$_3$ for simple fluorination of aromatic and aliphatic xanthates giving the respective CF$_3$O compounds in high yield [76,77]. Substrates with high level of complexity were also tolerated under reaction conditions, as exemplified by efficient fluorination of xanthate 16 (Scheme 7) delivering aryl trifluoromethyl ether 17. In addition, bromine trifluoride or p-nitrophenylsulfur chlorotetrafluoride were used as both oxidant and fluorinating agents for transformation of xanthates derived from primary alcohols to the corresponding primary alkyl trifluoromethyl ethers [78,79]. In the aliphatic series desulfurization-fluorination of carbonofluoridothioates by treatment with a mixture of TBAH$_2$F$_3$ and various oxidants also gave rise to the alkyl trifluoromethyl ethers [80].
Oxidative desulfurization-fluorination of xanthates now is the most general method being applicable for synthesis as aromatic as well as aliphatic trifluoromethyl ethers. Xanthate intermediates can be prepared by simple procedures using commercially available reagents. Although fluorination of xanthates with large excess of liquid pyridine-HF complex requires special equipment, it shows wide scope, functional group tolerance, low cost and is suitable for industrial scale production of aromatic and aliphatic trifluoromethyl ethers. In this regard, it is interesting to mention the recent applications of THF-HF complex that can be used instead of the pyridine-HF [81,82]. In addition, XtalFluor-E is employed as inexpensive commercially available reagent to convert a range of aromatic xanthates under atmospheric conditions on a large scale. However, limitation of this method is low efficiency for synthesis of heteroaromatic and secondary alkyl trifluoromethyl ethers.

2.1.3. Deoxofluorination of Fluoroformates

Aryl trifluoromethyl ethers were accessible by other fluorination method, the reaction of corresponding fluoroformates with sulfur tetrafluoride [44]. The aryl fluoroformates 18 (Scheme 8) were prepared from phenols 4 and fluorophosgene and without isolation treated by sulfur tetrafluoride. Deoxofluorination could be accomplished at 160–175 °C affording aryl trifluoromethyl ethers 3 in yields ranging from 9 to 81% for two steps. Hydrogen fluoride generated at the first step served as a catalyst for the sulfur tetrafluoride reaction. Functional groups including nitro and halogens were tolerated under the reaction conditions. Aliphatic alcohols 9 could be converted to corresponding trifluoromethyl ethers 12 by reaction with fluorophosgene followed by treatment of the resulting fluoroformates 19 with sulfur tetrafluoride in 15–72% yield for two steps when one or more electron-withdrawing groups, such as F, Cl, Br, were present in β-position (Scheme 8) [45].
Sulfur tetrafluoride as fluorinating agent is capable of performing deoxofluorinations of aryl fluoroformates to corresponding aryl trifluoromethyl ethers. However, deoxofluorination using sulfur tetrafluoride is carried out under pressure and require high temperatures (typically 100–200 °C). Practically, harsh reaction conditions and high toxicity of sulfur tetrafluoride as well as intermediate aryl fluoroformates has prevented the use of deoxofluorination method for industrial scale production. Moreover, its applicability has limited to synthesis of aryl trifluoromethyl ethers.

2.2. Fluorodecarboxylation of Aryloxydifluoroacetic Acids

2.2.1. Silver-Catalyzed Fluorodecarboxylation

Attractive approach to aryl trifluoromethyl ethers represents silver-catalyzed Hunsdiecker-type exchange of carboxylic group in aryloxydifluoroacetic acids with fluorine [83]. Wide range of starting aryloxydifluoroacetic acids 20 (Scheme 9) were easily prepared from phenols 4 and both chloro- and bromodifluoroacetic acids in excellent yields [84,85].

![Scheme 9. O-Carboxydifluoromethylation of phenols 4.](image)

The reactions of carboxylic acids 20 (Scheme 10) with Selectfluor II in the presence of catalytic amounts of silver(I) salt and such additives as HBF₄ or HOTf in biphasic solvent system afforded aryl trifluoromethyl ethers 3 in moderate to high yields [84]. Employing of Selectfluor II as a fluorine source and silver nitrate or silver iodide as catalysts was significant for the success of the reaction. The presence of water allowed the dissolution of reaction components. The reaction provided access to aryl trifluoromethyl ethers 3 bearing electron-withdrawing substituents on aromatic ring in good yields, while decrease in the yields was observed for substrates bearing electron-donating substituents. Alkyl, aryl, esters, ketones, and halides substituents were well tolerated under reaction conditions. Thus, method exhibited broad substrate scope enabling the synthesis of various aryl trifluoromethyl ethers 3.

![Scheme 10. Silver-catalyzed fluorodecarboxylation of ArOCF₂COOH with Selectfluor II.](image)
Analogous fluorodecarboxylation of acids 20 (Scheme 11) was also carried out employing Selectfluor as a fluorine source in the presence of AgOTf and TFA or H$_3$PO$_4$ as additives [85]. Biphasic system CH$_2$Cl$_2$/H$_2$O in ratio 9:1 as solvent was necessary for successful transformation. When H$_3$PO$_4$ was used as an additive for the fluorodecarboxylation of aryldifluoroacetic acids 20 with tert-butyl substituent the corresponding products 3 was observed in 2–4% yield, whereas in the presence of TFA the products were produced in 53–61% yield. Halogen substituted substrates provided products in yield ranged from 19 to 60%.

In the case of methoxy group no fluorodecarboxylated product was detected.

Silver-catalyzed decarboxylative fluorination leads to wide array of aryl trifluoromethyl ethers containing different functional groups. This process uses and available reagents as Selectfluor and Selectfluor II under mild conditions and can be applied for the large-scale experiments.

2.2.2. Fluorodecarboxylation with Silver(II) Fluoride

The decarboxylative fluorination of aryloxydifluoroacetic acids 20 (Scheme 12) could be conducted with AgF$_2$ [86] as a reagent to form aryl trifluoromethyl ethers 3 [87]. The reactions proceeded with either AgF$_2$ or combination of AgF$_2$, AgF and pyridine ligand under mild conditions with a broad substrate scope. The addition of substoichiometric amounts of AgF and 2,6-difluoropyridine ligand substantially increased the reaction yield and allowed synthesis of aryl trifluoromethyl ethers containing alkyl, carbomethoxy, cyano, carbamoyl, phenacyl and halogen substituents on aromatic ring in 41–98% yield. The AgF served as a source of fluorine to generate the fluorodecarboxylation products, while addition of 2,6-difluoropyridine increased solubility and reactivity of AgF$_2$.

AgF$_2$ is light sensitive, strong fluorinating and oxidising agent and requires special teflon or passivated metal equipment. While AgF$_2$ find laboratory experiments application, it is too expensive for large scale industry use.
Fluorodecarboxylation with Xenon Difluoride

Strong oxidizing fluorinated reagent xenon difluoride [88] effectively promoted the decarboxylation of aryloxydifluoroacetic acids 20 (Scheme 13) and fluorine transfer to afford aryl trifluoromethyl esters 3 under mild conditions [89]. The reaction proceeded very rapidly within a few minutes with 1 equiv. of XeF$_2$ in CDCl$_3$ at room temperature. It should be noted that yield of products significantly improved the use of special polypropylene plastic vessel. Good yields of aryl trifluoromethyl ethers 3 were obtained for alkyl-, chloro-, bromo-, fluoro-, and trifluoromethyl substrates 20, but disubstituted substrates 20 afforded 3 in lower yield. On the other hand, acids 20 bearing alkoxy substituent provided poor yields of the corresponding fluorodecarboxylation products 3. Generally, yields of the aryl trifluoromethyl ethers were on the same level with those obtained by fluorodecarboxylation with AgF$_2$.

Fluorodecarboxylation of aryloxydifluoroacetic acids with xenon difluoride is narrow substrate scope. Beside xenon difluoride is expensive and requires special plastic equipment due to its high reactivity. Thus, this transformation is not easily scalable.
2.3. O-Trifluoromethylation
2.3.1. Electrophilic O-Trifluoromethylation

Umemoto Oxonium Reagent

The first direct electrophilic trifluoromethylation of both aliphatic and aromatic alcohols was successfully accomplished by Umemoto using 2-tert-butyl-O-(trifluoromethyl)-dibenzofuranium hexafluoroantimonate 22 (Scheme 14) [53,90]. This thermally unstable compound 22 was obtained by photochemical decomposition of diazonium salt 21 at −90 to −100 °C. Aliphatic alcohols 9 and phenols 4 were smoothly trifluoromethylated with 22 at −90 to −10 °C in the presence of di(isopropyl)ethylamine as a base to give corresponding trifluoromethyl ethers 12 and 3 in high yields. However, in situ generation of the trifluoromethylation reagent 22 by photochemical decomposition at low temperature of diazonium salt 21 limited the broad application of this method.

Scheme 14. O-Trifluoromethylations of aliphatic alcohols and phenols with Umemoto reagent 22.

Togni Hypervalent Iodine Reagents

One of the recent achievements in the area of fluorine chemistry was development by Togni trifluoromethylated hypervalent iodine compounds 23 and 24 (Scheme 15) for trifluoromethylation of carbon and heteroatom nucleophiles [91]. Reagent 23 was found to react with 2,4,6-trimethylphenol 4 affording desired aryl trifluoromethyl ether 3 in low yield along with mixture of C-trifluoromethylated major products [55]. The investigation of other phenols with unsubstituted ortho- or para-positions showed that corresponding products of aromatic electrophilic substitution were obtained in moderate yield.

Activation of reagent 23 by Zn(NTf2)2 allowed to transfer the electrophilic trifluoromethyl group to aliphatic alcohols 9 (Scheme 16) [54]. Aliphatic alcohols 9 could be used as both solvent and substrate in reaction affording excellent yields of corresponding trifluoromethyl ethers 12 with respect to reagent 23, while a molar ratio of 5:1 between the alcohol 9 and reagent 23 was also acceptable for solid or expensive substrates. Secondary alcohols also underwent $O$-trifluoromethylation cleanly affording a trifluoromethyl ether of ethyl lactate as well as trifluoromethoxyxyclohexane while tert-butyl alcohol could not be $O$-trifluoromethylated. Stable adduct of reagent 24 with HCl in the presence of phase transfer catalyst was also capable of $O$-trifluoromethylation of primary and secondary alcohols affording corresponding trifluoromethyl ethers under mild conditions in modest yields [92].
Scheme 15. O-Trifluoromethylation of 2,4,6-trimethylphenol with Togni reagent 23.

![Scheme 15. O-Trifluoromethylation of 2,4,6-trimethylphenol with Togni reagent 23.](image)

Scheme 16. O-Trifluoromethylation of aliphatic alcohols with Togni reagent 23.

One-step method for the synthesis of ortho-N-heteroaromatic trifluoromethoxy derivatives 8 (Scheme 17) starting from N-heteroaromatic alcohols 6 and reagent 23 was described [93]. The optimal reaction conditions including combination of substrates 6, reagent 23 in MeNO$_2$ at 100 °C enabled the synthesis of a wide range of six or five-membered N-heteroaromatic trifluoromethoxy compounds 8 containing one or two heteroatoms. The reaction was applicable to substrates containing a wide range of functional groups including ester, cyano, acetyl, ether, halide, alkyl, and aryl underdeveloped conditions. However, this method required a high reaction temperature and an excess of substrates.

The two most popular trifluoromethylated hypervalent iodine reagents 23 and 24 are air-stable crystalline solids and could be easily prepared from readily available 2-iodobenzoic acid making them available on a kilogram scale. Although, hypervalent iodine reagents 23 and 24 are expensive, advantages of their industrial application for production of alkyl and heteroaryl trifluoromethyl ethers include simplicity, mild conditions, wide substrate scope and compatibility with a variety of functional groups.
2.3.2. Oxidative O-Trifluoromethylation

Silver triflate-mediated oxidative trifluoromethylation of phenols and heteroaromatic alcohols with nucleophilic CF$_3$SiMe$_3$ as the CF$_3$ source in the presence of oxidants constituted one of the most straightforward methods for synthesis of trifluoromethyl esters under mild reaction conditions. The variety of phenols 4 and heteroaromatic substrates 6 (Scheme 18) bearing electron-withdrawing groups were efficiently reacted with CF$_3$SiMe$_3$ in the presence of Csf, AgOTf, 2-fluoropyridine as a ligand, Selectfluor and N-fluorobenzenesulfonylimide as an oxidant at room temperature affording the desired O-trifluoromethylated products 3 and 8 in 42–77% yield [94]. Screening of oxidants showed that usage of both Selectfluor and NFSI as an oxidant is critical to the success of the trifluoromethylation reaction. Despite the complex reactive mixture, this method exhibited excellent scope: ester, cyano, nitro, sulfanyl, ether groups and $\beta$-lactam moiety were tolerated under the mild reaction conditions. Moreover, coumarins and thiophene derivatives 8 were also isolated in good yields. It should be noted that excellent selectivity was observed for phenol O-trifluoromethylation in the case of estradiol.

Scheme 17. O-Trifluoromethylation of ortho-N-heteroaromatic alcohols.

Scheme 18. Silver-mediated O-trifluoromethylation electron-poor phenols and heterocycles.
The oxidative O-trifluoromethylation could be extended to nitrogen-containing heteroaromatic substrates 6 as well as phenols 4 (Scheme 19) substituted with an electron-donating group or bromine with minor modification of the reaction conditions. The reactions of pyridinium salts of such substrates as pyridines, quinolines, and benzothiazoles 16 proceeded smoothly affording desired heteroaryl trifluoromethyl ethers 8 in synthetically useful yields. On the other hand, conversion of electron-rich phenols 4 into the corresponding aryl trifluoromethyl ethers required addition of 2,4-di-tert-butylphenol to prevent competitive trifluoromethylolation of phenyl ring with electrophilic CF<sub>3</sub> radicals easily generated from the combination of TMSCF<sub>3</sub>/CsF/AgOTf and increased the yield to 52–83%. For example, the reaction of protected tyrosine under modified conditions provided corresponding trifluoromethyl ether in an excellent yield.

![Scheme 19. Silver-mediated O-trifluoromethylation of electron-rich phenols and heterocycles.](image)

Silver-mediated oxidative O-trifluoromethylation with nucleophilic TMSCF<sub>3</sub> found application for aliphatic alcohols. Trifluoromethylation of aliphatic alcohols 25 (Scheme 20) was conducted in presence of AgOTf, 2-fluoropyridine, Selectfluor, TMSCF<sub>3</sub>, and KF at room temperature [95]. Reactions proceeded smoothly, furnishing corresponding trifluoromethyl ethers 26 in moderate to excellent yields. The primary and secondary alcohols 25 were both effective in this transformation. The reactions of alcohols containing the electron-rich aryl group were sharply improved by the addition of 2,6-di-tert-butylphenol. All oxidative O-trifluoromethylation reactions tolerate a wide range of functional groups, affording structurally diverse trifluoromethyl ethers 26. Moreover, O-trifluoromethylation of a series of complex natural products and bioactive compounds proceeded efficiently under developed mild reaction conditions. Mechanistically, O-trifluoromethylation of alcohols and phenols proceed through silver-mediated oxidative cross-coupling reactions.

Oxidative trifluoromethylation provides access to structurally diverse trifluoromethyl ethers from aryl, heteroaryl, and aliphatic alcohols using commercially available and stable CF<sub>3</sub>SiMe<sub>3</sub> as a nucleophilic reagent. All these oxidative trifluoromethylation reactions tolerate a wide range of functional groups and provide alternative to electrophilic trifluoromethylation. The mild process was also applied to trifluoromethylation of substrates with high level of complexity and attractive for large-scale applications. However oxidative trifluoromethylation is limited by using of large excess of silver salt, CF<sub>3</sub>SiMe<sub>3</sub> and oxidants which make the method extremely expensive for industrial application.
2.3.3. Radical O-Trifluoromethylation

A two-step route to aryl trifluoromethyl ethers included O-trifluoromethylation of N-aryl-N-hydroxylamines followed by thermally induced intramolecular rearrangement of the intermediate N-aryl-N-(trifluoromethoxy)amines. Various protected N-aryl-N-hydroxylamines 27 (Scheme 21) were shown to undergo O-trifluoromethylation with Togni reagent 23 in the presence of catalytic amount of Cs2CO3 furnishing protected N-aryl-N-(trifluoromethoxy)amines 28 in moderate to good yields under very mild reaction conditions [96]. Substrates 27 with acetyl, benzoyl, and methoxycarbonyl N-protecting groups showed similar activities. Mechanistic studies with radical trap 3,5-di-tert-butyl-4-hydroxytoluene demonstrated that the reaction followed a radical pathway with the formation of N-hydroxyl and trifluoromethyl radical intermediates. Heating of N-aryl-N-(trifluoromethoxy)amines 28 in nitromethane at 80 °C enabled intramolecular OCF3 migration affording trifluoromethoxylated aniline derivatives 3 with excellent ortho selectivity and functional-group tolerance. This migration reaction proceeds via the sequence of heterolytic cleavage of the N-O bond and trifluoromethoxylation at ortho-position of phenyl moiety. Moreover, two-step method was modified to one-pot procedure by treatment of protected N-aryl-N-hydroxylamines 27 with slight excess of reagent 23 and NaH without the isolation of the intermediates 28.

Further investigations showed that this method could be applied to heteroaromatic substrates. Togni reagent 24 (Scheme 22) was employed for O-trifluoromethylation of N-protected hydroxylamines 29 derived from pyridines and pyrimidines and both O-trifluoromethylation and OCF3 migration was performed in one pot without isolation of the intermediate N-heteroaryl-N-(trifluoromethoxy)amines [97,98]. Heterocyclic compounds 29 with electron-donating and electron-withdrawing substituents including complex molecules were tolerated under the reaction conditions and gave the trifluoromethoxylated pyridine and pyrimidine derivatives 8, containing ortho-OCF3 substituent to the amino group in good to excellent yields. Using pyridines 29 with electron-donating substituent in α-position to nitrogen atom significantly facilitates the OCF3 migration step and rearrangement proceeded at room or below temperature. Electron-deficient heteroaromatic substrates 29 required heating to perform rearrangement stage.

Scheme 20. Silver-mediated trifluoromethylation of aliphatic alcohols.
Photocatalytic procedure using \( N \)-aryl-\( N \)-hydroxylamides 27 (Scheme 23) and commercially available trifluoromethyl iodide instead of expensive Togni reagents to access a range of aryl trifluoromethyl ethers 3 was recently developed [99,100]. In this transformation, \( \text{Ru(bpy)}_3(\text{PF}_6)_2 \) was used as a photoredox catalyst in the presence of potassium carbonate as a base in acetonitrile upon irradiation with blue LED light. Photocatalytic procedure under optimized conditions was applicable to aromatic hydroxylamides 25 bearing such functional groups as \textit{tert}-butyl, bromo, esters and carbamates with yield ranging from 45% to 66%.

**Scheme 21.** O-Trifluoromethylation/OCF\(_3\)-migration of protected \( N \)-aryl-\( N \)-hydroxylamines.

**Scheme 22.** O-Trifluoromethylation/OCF\(_3\)-migration reaction of protected \( N \)-heteroaryl-\( N \)-hydroxylamines.
The regioselective trifluoromethoxylation of functionalized anilines, pyridines and pyrimidines is operationally simple and displayed high levels of functional group tolerance. However, this method is limited by preparation of protected N-(hetero)aryl-N-hydroxylamines precursors. Besides the products obtained by this method always contain OCF$_3$-substituent in ortho-position to amino group. Furthermore, using of high cost Togni reagents for large-scale applications is expensive. Further development of the photocatalytic radical strategy using N-aryl-N-hydroxylamines and commercially available as well as inexpensive trifluoromethyl iodide represents promising solution for industrial application in term of cost.

3. Trifluoromethoxylation Reagents

3.1. Nucleophilic Reagents

3.1.1. Trifluoromethyl Trifluoromethanesulfonate (TFMT)

Trifluoromethyl trifluoromethanesulfonate 36 (Scheme 24) usually referred to as TFMT, was first synthesized in 1965 by Noftle and Cady [101] by decomposition of bis(trifluoromethylsulfury) peroxide 30 (Scheme 24, Equation (1)). Some other known methods for preparation of TFMT 36 are collected in Scheme 24 [102–108]. Most of these approaches were based on in situ formation and decomposition of triflic anhydride using dangerously reactive reagents under rather forcing reaction conditions requiring specialized equipment. One can also notice generally low yields and high cost of the reagents. Nevertheless, the procedures presented in Equation (5), acid-catalyzed decomposition of Tf$_2$O [107] and Equation (6), the reaction of triflic anhydride with SbF$_5$ [108], can be scaled up and considered as relatively “convenient” for commercial preparation of TFMT. Quite remarkably, TFMT 36 is unreactive with water at ambient temperature and thus, can be safely handled in the open air. Furthermore, noticeable decomposition of TFMT 36 with 0.1 mol/L solution of aqueous sodium hydroxide is observed at 100 °C. It seems that the major inconvenience in production and application of TFMT 36 is that this reagent is a gas at ambient temperature, showing the melting point of −108.2 °C and the boiling point of 18 °C [101–108].

![Scheme 23. Photocatalytic radical coupling reaction of N-aryl-N-hydroxylamides with trifluoromethyl iodide.](image-url)
TFMT 36 reacts with nucleophiles, especially hard ones, to give CF$_3$-O$^-$ anion, which undergoes decomposition into COF$_2$ and F$^-$ anion. For example, even catalytic amounts of F$^-$ anion can lead to the complete decomposition of 36. In 2008, Kolomeitsev et al. discovered that some anhydrous fluoride containing salts can cleave the S-O bond of 36 giving rise to the corresponding trifluoromethoxide derivatives 38 and trifluoromethanesulfonyl fluoride 39 (Scheme 25) [109]. Usually, the reactions were conducted in acetonitrile at low (-30 °C) to ambient temperature, generating derivatives 38 in situ followed by the reaction with electrophiles. However, some salts 38 were stable in solid state, allowing their isolation and full structural characterization. For example, single-crystal X-ray structure of tris(dimethylamino)sulfonium trifluoromethoxide 38 (TAS-OCF$_3$, melting point is 214–216 °C) was reported by Farnham and Dixon et al. [110]. These trifluoromethoxide salts 38 could be used to realize trifluoromethoxylation of primary triflate and iodide, activated secondary triflates as well as benzyl bromide to give corresponding trifluoromethyl ethers 39 (Scheme 25) [109].
The combination of TFMT 36 (Scheme 26) with silver fluoride or n-tetrabutylammonium triphenyldifluorosilicate was also successful for synthesis of trifluoromethyl ethers 39 from various alkyl halides [42]. In this way primary aliphatic bromides and iodides, primary and secondary benzylic and allylic bromides as well as benzoxy bromide were efficiently trifluoromethoxylated under mild conditions and silver trifluoromethoxide was usually afforded better yields than n-tetrabutylammonium trifluoromethoxide. Additionally, this approach was successfully applied for trifluoromethoxylation of α-bromoketones [111,112]. However, low yields were obtained from secondary aliphatic bromides and no reaction was observed with secondary aliphatic iodides as well as tertiary aliphatic bromides. The transformation of alkyl chlorides into the corresponding trifluoromethoxylated products is restricted to benzyl chloride and allyl chloroformate in modest yield.

![Scheme 26. Trifluoromethoxylation of alkyl bromides and iodides with trifluoromethoxide salts 38.](image)

A silver-mediated direct trifluoromethoxylation of α-diazo esters was also performed using TFMT as trifluoromethoxide anion source for α-trifluoromethoxylation of esters under mild reaction conditions [113,114]. The reaction of alkyl α-diazo arylacetates 40 (Scheme 27) was typically carried out with TFMT 36 and AgF in MeCN at −30 to 10 °C providing α-trifluoromethoxyl arylacetates 42 in up to 90% yield. Both, moderately electron-donating or electron-withdrawing substituents on the phenyl ring had no significant influence on the yields of trifluoromethoxylated products. However, the strong electron-withdrawing substituents could result in a drop in reaction yields. Thiophenyl and indolyl derivatives were well-tolerant in this trifluoromethoxylation reaction. When the ester group was changed from ethyl to methyl, isopropyl, butyl, tert-butyl, benzyl, and allyl esters there was no significant drop of the products yields. Trifluoromethoxylation of alkyl α-diazo vinylacetates 41 using TFMT 36 and AgF proceed at the vinylogous position of 41 to form E-isomers of γ-trifluoromethoxy α,β-unsaturated esters 43 in up to 94% yield with good regio- and stereoselectivities. The reaction was also applicable to α-diazo ketosteroid, affording the desirable trifluoromethoxylated product in moderate yield. Mechanistically, TFMT first reacts with AgF to form in situ AgOCF3. Interaction of Ag+ ion with α-diazo esters generates the key alkyl–Ag+ intermediate which could be further trifluoromethoxylated by CF3O− anion and the final products were obtained by quenching with water.
luoromethyl ethers

Scheme 27. Trifluoromethoxylation of α-diazo esters 40 and 41 with TFMT 36 and AgF.

The convenient synthesis of aryl trifluoromethyl ethers 3 (Scheme 28) was achieved by silver-mediated trifluoromethoxylation of aryl stannanes 44 as well as arylboronic acids 45 using TAS-OCF₃ 38 prepared in situ from TFMT 36 [115]. Treatment of aryl stannanes 44 with TAS-OCF₃ 38, oxidant Selectfluor-PF₆, and silver(I) hexafluorophosphate at −30 °C afforded aryl trifluoromethyl ethers 3 in 59−88% yield. The optimized conditions increased the yield of trifluoromethoxylation by preventing formation of fluorodestannylation, hydroxydestannylation, protodestannylation, and homocoupling by-products. At the same time, arylboronic acids 45 afforded aryl trifluoromethyl ethers 3 according two-step procedure including their transformation with sodium hydroxide and AgPF₆ in methanol into corresponding aryl silver complexes which were treated with TAS-OCF₃ 38 and Selectfluor-PF₆ in THF/acetone mixture. The trifluoromethoxylation reactions tolerated a broad range of functional groups, especially, halogens, esters, ethers, alkenes, and ketones with the exception of basic substituents such as amines or pyridines. Besides, this method also was applied in late-stage functionalization of bioactive compounds including estrone and morphine.

Scheme 28. Trifluoromethoxylation of aryl stannanes 44 and arylboronic acids 45.
A mild method for the regioselective C2-trifluoromethoxylation of N-oxides of 8-substituted quinolines 46 (Scheme 29) was developed employing TFMT 36 as a trifluoromethoxide anion source, AgF, 3,3-dimethylbutan-2-one as additive and DME as the solvent [116]. Screening of the substitution effect showed that substituent at the 8-position played a crucial role in the achieving good yields of corresponding trifluoromethyl ethers 8. While quinoline N-oxides 46 bearing electron-donating (Me, i-Pr, MeO) and electron-withdrawing (F, Cl, Br) groups afforded corresponding products 8 in yields ranging from 31% to 66%, quinoline N-oxide lacking the 8-substituent gave less than 5% yield of the trifluoromethyl ether. Furthermore, the reaction also worked well with penanthridine N-oxides. The authors showed that TFMT 36 performed the dual role in this process to form OCF$_3$ anion as well as N-triflate cation that was more electrophilic than starting heterocyclic N-oxides 46.

Thus, TFMT was the first reagent which promoted the development of the field of trifluoromethoxylation and employed with fluoride anion to prepare alkyl, aryl, and heteroaryl trifluoromethyl ethers. In addition, TFMT was a precursor of trifluoromethoxide salts AgOCF$_3$ [117–122] and CsOCF$_3$ [123,124], which in turn could be used as trifluoromethoxylation reagents. However, the high volatility of TFMT (bp 19 °C) severely limits its synthetic application.

3.1.2. Trifluoromethyl Nonafluorobutanesulfonate (TFNf)

Recently, TFNf was developed as reactive and scalable nucleophilic trifluoromethoxylation reagent. The new reagent is odorless, thermally stable, and non-flammable liquid with a boiling point 87–89 °C allowing its easy handling and storage [125]. TFNf was resistant to 3 M HCl solution for 150 h and considerable decomposition of TFNf was observed only after treatment with 3 M KOH solution for 150 h. TFNf 50 (Scheme 30) was easily prepared in large scale starting from 2,8-difluoro- or 2,3,7,8-tetrafluoro-S-(trifluoromethyl)dibenzothiophenium triflates 47a,b (Umemoto reagents) [126,127] using two simple anion exchange steps and subsequent thermolysis of neat nonaflates 49. When triflates 47 were treated with tetrabutylammonium chloride in acetonitrile at room temperature, fast reactions occurred to produce the chlorides 48 as precipitates in high yields. Nonaflates 49 were prepared in good yields from chlorides 48 by treating with potassium nonafluorobutanesulfonate in water. The direct conversion of triflates 47 to nonaflates 49 did not proceed well. The effective thermolysis of nonaflates 49 was possible because of their low decomposition points compared to starting triflates 47 as well as distillation of TFNf 50 during the thermolysis process. Activation of TFNf 50 by fluoride for nucleophilic trifluoromethoxylation generated CF$_3$O$^-$ anion along with nonafluoryl fluoride, which could easily be recovered after preparation of trifluoromethyl ethers and recycled.
TFNf was appropriate for the introduction of trifluoromethoxyl group into alkyne derivatives such as 1-haloalkynes, alkynyl sulfones, and alkynyl esters. For example, TFNf 50 (Scheme 31) in combination with AgF was used for the hydrotrifluoromethoxylation of 1-chloroalkynes 51 in the presence of tetramethylammonium bromide in MeCN/DME as mixed solvent system giving rise regio- and stereoselectively to formation of Z-isomers of chlorotrifluoromethoxyalkenes 52 in good to excellent yields [125]. AgF played a double role in this reaction: on one hand, activating TFNf 50 and on the other enhancing the reactivity of 1-chloroalkynes 51. At the same time quaternary ammonium salt additives improved the AgF solubility and stabilized the CF₃-O⁻ anion. This silver-mediated reaction was characterized by excellent functional group tolerance including chloroalkynes with heterocyclic substituents. Under standard reaction conditions, hydrotrifluoromethoxylation of natural product (L-phenylalanine and estrone) and pharmaceutical (Probenecid and Febuxostat) derivatives was achieved, which successfully afforded the corresponding chloroalkyne tethered compounds. It is noteworthy that further functionalization of Z-chlorotrifluoromethoxyalkenes 52 could be performed by means of transition metal-catalysed coupling reactions. In addition to 1-chloroalkynes, hydrotrifluoromethoxylation of various alkynyl sulfones proceeded with good yields and high regio- and stereoselectivity, while simple alkynes did not react.

Scheme 31. Hydrotrifluoromethoxylation of 1-chloroalkynes 51.
Furthermore, the procedure for the regio- and stereoselective bromotrifluoromethoxylation of various alkynyl sulfones was developed where TFNf 50 (Scheme 32) was used in the presence of N-bromosuccinimide as electrophilic halogenating reagent [125]. The bromotrifluoromethoxylation of aryl- and alkyl-substituted alkynyl sulfones 53 with TFNf 50/NBS and the assistance of silver salt yielded predominantly E-isomers of tetrasubstituted alkenes 54 in good to excellent yields and common functionalities, such as ester, ethers, and halide were well-tolerated. On the other hand, trichloroisocyanuric acid and N-iodosuccinimide have been used in this transformation, which afforded the corresponding chloro- and iodotrifluoromethoxylated products. The scope of the process was not restricted to alkynyl sulfones and alkynyl esters could also be converted to bromotrifluoromethoxylated alkenoates in good yields. The reaction between TFNf and AgF generated in situ AgOCF$_3$, which was converted to the corresponding vinyl-silver intermediate by trans-addition to alkyne derivatives bearing activating and regio-directing electron-withdrawing group. It should be mentioned that the by-products trifluoromethoxylated alkenes also were observed in this transformation.

![Scheme 32. Halotrifluoromethoxylation of alkynyl sulfones 53.](image)

TFNf 50 (Scheme 33) under AgF-activation was found to be effective reagent for conversion of benzyl bromide and alkyl triflate to the alkyl trifluoromethyl ethers in excellent yields [125]. Furthermore, TFNf 50 could act as a nucleophilic trifluoromethoxylating reagent to perform one-pot synthesis of alkyl trifluoromethyl ethers from primary and secondary alcohols via triflates in high yields.
Trifluoromethylation of arylsulfonic acids using Togni reagent 23 [128] and thermally prepared Umemoto reagent 56 [53,90]. For example, when aryl sulfonic acids 55 were mixed with the hypervalent iodine reagent 23, formation of TFMS 57 took place under mild conditions in good to excellent yields. The presence of a strong Brønsted acid was critical to the success of the reaction, as trifluoromethylation of sodium, potassium or ammonium toluenesulfonates failed. In addition, aryl sulfonic acids bearing an internal basic group failed to give the desired trifluoromethylated products. Availability and thermal stability of TFMS 57 made them attractive trifluoromethoxylation reagents [63].

**Scheme 33.** Application of TFNf 50 for trifluoromethylation of alkyl halides and triflate.

**Scheme 34.** Trifluoromethylation of arylsulfonic acids 55 using Togni reagent 23 and Umemoto reagent 56.
Initially, TFMS 57 (Scheme 35) were employed as efficient nucleophilic trifluoromethoxylation reagents under activation with fluoride anions for enantioselective silver-catalyzed bromotrifluoromethoxylation of alkenes 58 [129]. In this DBH as electrophilic bromine source activated the alkenes 58 to form a reactive bromonium intermediate while TFMS 57 with cesium fluoride generated in situ the trifluoromethoxide anion which transformed into Ag(I)OCF$_3$ in the present of AgF. The reaction proceeded by attack of Ag(I)OCF$_3$ on bromonium intermediate in the presence of chiral ligands, in particular, the bis-cinchona alkaloid (DHQD)$_2$PHAL to give bromotrifluoromethoxylated products 59 in moderate to high yields from styrenes, non-activated alkenes and several more complex systems including heteroaromatic substrates, amino acid derivatives, steroids and cinchona alkaloids. Screening of reaction conditions showed that trifluoromethyl 4-fluorobenzenesulfonate 57 was the most effective as a trifluoromethoxylation reagent in terms of reaction yield, although the enantioselectivity was not satisfactory. Generally, the electron-deficient substrates showed higher enantioselectivities, while electron-rich substrates gave lower enantioselectivities.

![Scheme 35. Asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes 58.](image)

In addition, N-iodosuccinimide (NIS) was used instead of DBH with TFMS 57 (Scheme 36), CsF and bis-cinchona alkaloid (DHQD)$_2$PHAL as additive for silver-mediated intermolecular iodotrifluoromethoxylation of alkenes 58 [130]. Styrenes with various functional groups provided the corresponding products 60 with yields up to 92%. Although internal alkenes 58 underwent iodotrifluoromethoxylation diastereoselectively, no enantioselectivity was observed under reaction conditions.
The reactivity of TFMS 57 (Scheme 37) with the range of terminal alkynes 61 was further explored [131]. The dibromotrifluoromethoxylated products 62 were obtained in the presence of KF, electrophilic bromination reagent and silver salt (Ag$_2$CO$_3$ or AgF) at low loadings (0.2 equiv), which was proved to be very important for the reaction. The 18-crown-6 was also critical for this transformation and modest yields of products were observed without crown ether. Among electrophilic bromination reagents N-bromophthalimide (NBP) was optimal for dibromotrifluoromethoxylation of terminal alkynes. Under the optimized conditions a great number of substrates 61 including phenylacetylene derivatives were successfully transformed into 1,1-dibromo-2-(trifluoromethoxy)alkenes 62 with yields ranging from 37 to 88% and high regioselectivity. This method proved tolerant to such functional groups as halides, epoxide, aldehyde, ketone, carboxyl acid, nitrile, nitro, and silicon. Additionally, the method was compatible with substrates containing heterocycles including benzofuran, thiaphen, and pyridine providing corresponding 1,1-dibromo-2-(trifluoromethoxy)alkenes in 70 to 77% yield. It was noteworthy that under reaction conditions 1,2-diphenylacetylene was transformed into mixture of E- and Z-isomers of bromotrifluoromethoxylated 1,2-diphenylethene in ratio 3.33:1. Efficient access to 1,1-dibromo-2-(trifluoromethoxy)alkenes allowed their further modification by transition-metal catalyzed cross-coupling reactions with terminal alkyne, arylboronic acids, and thiophenols as well as reduction reactions. Mechanistic studies revealed that initially silver salts promoted generation of 1-bromoalkyne intermediates. Subsequent activation of triple bond by treatment of electrophilic bromination reagent resulted in bromonium ions which reacted with trifluoromethoxy anion to give the final product.
Combination of silver catalysis and ruthenium photoredox catalysis allowed to realize vicinal azidotrifluoromethoxylation of styrenes 63 (Scheme 38) with TFMS 57 and azidoiodane 64 [132]. The application of a photoredox catalyst [Ru(bpy)_3](PF_6)_2 and visible light irradiation gave azidotrifluoromethoxylated products 65 with isolated yields ranging from 28% to 72%. Reactions worked well for styrenes 63 bearing functional groups including ether, ester, amide, nitrile, sulfonyl, and halogen. Electron-withdrawing functional groups generally diminish yields of azidotrifluoromethoxylated products 65 compared to substrates with electron-donating groups. Moreover, azidotrifluoromethoxylation of complex substrates as well as benzothiophene and quinoline derivatives under the standard light-promoted conditions also provided the corresponding products with moderate yields. However, low yields of azidotrifluoromethoxylated products were observed with aliphatic alkenes. Possible reaction mechanism included silver fluoride activation of TFMS to generate reactive Ag(I)OCF_3. On the other hand, under visible-light irradiation in the presence of [Ru(bpy)_3](PF_6)_2, azidoiodane 64 was activated by electron transfer to generate azide radical. Addition of the azide radical to styrene generated benzyl radical intermediate which was further oxidized to a benzyl cation intermediate. Finally, this carbocation intermediate reacted with Ag(I)OCF_3 to afford azidotrifluoromethoxylated products 65.

Activation of TFMS by fluoride anion with formation of the trifluoromethoxide anion was also used for dehydroxytrifluoromethoxylation of alcohols [133]. The reaction included in situ generation of alkyl fluoroformate intermediates from alcohols, followed by nucleophilic trifluoromethoxylation affording trifluoromethyl ethers. Alkyl fluoroformates were formed from alcohols and fluorophosgene which in turn was generated by decomposition of the trifluoromethoxide anion. When primary, allyl, benzyl, propargyl, as well as secondary alcohols 66 (Scheme 39) were treated under optimized conditions with TFMS 57, CsF as a source of fluorine and tetramethylammonium bromide to improve the solubility of CsF and nucleophilicity of trifluoromethoxide anion the corresponding trifluoromethoxylation products 67 were formed in moderate to good yields. However, no desired products were observed with tertiary alcohols. The reaction was scalable and tolerated a wide range of functional groups.
Scheme 38. Ag/Ru-catalyzed azidotrifluoromethoxylation of styrenes 63.

Activation of TFMS by fluoride anion with formation of the trifluoromethoxide anion was also used for dehydroxytrifluoromethoxylation of alcohols. The reaction included in situ generation of alkyl fluoroformate intermediates from alcohols, followed by nucleophilic trifluoromethoxylation affording trifluoromethyl ethers. Alkyl fluorofor-mates were formed from alcohols and fluorophosgene which in turn was generated by decomposition of the trifluoromethoxide anion. When primary, allyl, benzyl, propargyl, as well as secondary alcohols (Scheme 39) were treated under optimized conditions with TFMS, CsF as a source of fluorine and tetramethylammonium bromide to improve the solubility of CsF and nucleophilicity of trifluoromethoxide anion the corresponding trifluoromethoxylation products were formed in moderate to good yields. However, no desired products were observed with tertiary alcohols. The reaction was scalable and tolerated a wide range of functional groups.

Scheme 39. Dehydroxytrifluoromethoxylation of alcohols 66.

Cobalt-catalyzed trifluoromethoxylation of epoxides 68 was achieved by activation of TFMS 57 (Scheme 40) with 2,4-dinitrophenates. The use of n-Bu4N+DNP− instead of fluorides to activate TFMS enhanced nucleophilicity and stability of trifluoromethoxy anion as well as avoided formation of fluorinated byproducts. Under optimized conditions with TFMS 57, catalyst I, n-Bu4N+DNP− at room temperature ring-opening of meso and racemic epoxides 68 afforded vicinal trifluoromethoxy-hydrins 69 with excellent regioselectivities and yields range from 45% to 95%. However, poor regioselectivity was observed for ring-opening of 2-phenyloxirane. Stereoselective transformation of enantiomerically pure epoxides was also reported.
Cobalt-catalyzed trifluoromethoxylation of epoxides

Trifluoromethoxylation of alkylsilanes 70 (Scheme 41) by TFMS 57 could be performed in the presence of a strong oxidant Selectfluor and silver fluoride as mediator as well as fluoride source [135]. The desired trifluoromethoxylated products 12 were obtained in good, isolated yields from primary alkylsilanes 70 in the presence of 3,4,7,8-tetramethyl-1,10-phenanthroline as a ligand. This reaction tolerated a wide range of functional groups under mild reaction conditions. The method was also proved efficient for substrates containing heteroaromatic rings. However, low yields were observed with secondary alkylsilanes 70. Possible reaction mechanisms of silver-mediated oxidative trifluoromethoxylation of alkylsilanes were proposed to involve radical processes.

Analogous trifluoromethoxylation of alkyl trifluoroborates 71 (Scheme 42) by TFMS 57 was achieved under silver-catalyzed conditions [136]. This reaction was performed in the presence of AgOTf (30 mol %) and Selectfluor in anisole at 30 °C. Optimization experiments revealed that phenanthroline could promote this trifluoromethoxylation and...
18-crown-6 was added as phase transfer catalysts to improve the solubility of KF and alkyl trifluoroborates 71 in anisole. After optimization of the reaction conditions desired trifluoromethyl ethers 12 were accessed in yields from 32% to 91%. Silver-catalyzed trifluoromethoxylation reaction could be extended to alkyl trifluoroborates 71 containing functions like hydroxyl, cyano, nitro, amide, ketone, aldehyde, bromo, ether and ester groups. However, trifluoromethoxylation of secondary alkylborates 71 provided poor yields of the corresponding trifluoromethyl ethers 12. These conditions were applicable to scale up synthesis while maintaining its efficacy. Mechanistic experiments suggested oxidation of silver salt in the presence of Selectfluor to produce Ag(III)F, which was converted by TFMS reagent into FAg(III)OCF₃. This complex reacted with alkylborates to give alkyl radical and Ag(II)OCF₃ via single-electron oxidation. Finally, an alkyl radical was involved in a reaction with Ag(II)OCF₃ to form the desired trifluoromethyl ethers and regeneration of Ag(I).

TFMS were also employed in silver-promoted oxidative trifluoromethylation of benzylic C-H bond. Utilizing AgOTf as catalyst, various substrates 72 containing electron-donating and electron-withdrawing groups underwent trifluoromethylation of benzylic C-H bonds with trifluoromethyl TFMS 57 (Scheme 43) in the presence of such oxidants as K₂S₂O₈, F-TEDA-OTf or AgF₂ providing corresponding trifluoromethoxylated products 73 in 28–81% yield [137]. Moreover, the ligand proved to be essential for the reaction, as low yield of trifluoromethoxylated products resulted without the ligand. The reactions were applicable to trifluoromethylation of primary as well as secondary benzylic C-H bonds. Heteroaromatic-substituted substrates 72 were also successfully employed to provide the corresponding trifluoromethyl ethers 73 in good yields. However, substrates 72 with varied substituents on the aromatic ring required to use different reaction conditions. It is worth noting that simultaneously benzylic C-H trifluoromethoxylation and fluorination were observed for substrates 72 bearing electron-donating groups when F-TEDA-OTf was used as an oxidant. The reactions were operationally simple and amenable to gram-scale synthesis. A mechanism involving generation of benzyl radical, which was subsequent oxidized to benzyl carbocation trapping by the OCF₃ anion could explain the results of the process.
Simultaneous activation of TFMS 57 (Scheme 44) and ortho-(trimethylsilyl)aryl triflates 74 by potassium fluoride in the presence of crown ethers and iodination reagents led to the formation of 2-iodoaryl trifluoromethyl ethers 3 in moderate to high yields [138]. Trifluoromethoxylation of aryne species in situ-generated from ortho-(trimethylsilyl)aryl triflates 74 with TFMS 57 allowed to form the intermediate aryl anion, which further trapped with iodination reagents to give 2-trifluoromethoxylated iodoarenes 3 as useful synthetic building blocks for many applications. Functional groups such as alkyl, phenyl, methoxy, and fluoride are compatible in this transformation. In cases of unsymmetrical arynes the regioselectivity was definitely low.

Photoredox-catalyzed and copper-mediated trifluoromethoxylation with TFMS allowed the introduction of trifluoromethoxy group into a variety of arenediazonium tetrafluoroborates 75 (Scheme 45) [139]. Extensive screening of various combinations of photocatalysts, copper salts, fluoride sources, and solvents revealed that white LED irradiation of a
mixture of aryl diazonium salts 75, trifluoromethyl 4-fluorobenzenesulfonate 57, CuOTf (1.0 equiv), CsF, and [Ru(bpy)3]([PF6]2 afforded the desired aryl trifluoromethyl ethers 3 with yields ranging from 27% to 81%. Electron-rich and electron-poor substrates 75 were efficiently trifluoromethoxylationed, but decreased yield was observed in the case of ortho-substituted products 3. The scope of the reaction was wide tolerating functional groups such as halogen, nitro, cyano, ketone, ester, amide, amine, and sulfone. This strategy could be used for the introduction of the trifluoromethoxy group in sulfamethoxazole and estrone derivatives. However, heteroaryl diazonium salts did not give trifluoromethoxylationed products under the reaction conditions. The mechanistic study indicated that Cu(II)(OCF3)2 complex generated from trifluoromethyl arylsulfonate, CsF and CuOTf reacted with aryl radical generated from the excited state of photocatalyst and aryl diazonium salt to provide the aryl trifluoromethyl ether and regenerate Cu(I).

One can see that essential progress was made in trifluoromethoxylation of functionalized aromatic derivatives using TFMS. Nevertheless, the most effective route for the preparation of CF3O-substituted arenes would be direct trifluoromethoxylation of C−H bonds. Recently direct C-H trifluoromethoxylation of arenes 76 and heteroarenes 77 (Scheme 46) was performed with complexe Ag(II)OCF3 obtained by the combination of AgF2 as the silver salt, Selectfluor as the oxidant, and TFMS 57 [140]. In addition, CsF was used as fluoride source for generation of CF3O− anion from trifluoromethyl TFMS 57. This method was applicable for selective ortho- and para-trifluoromethoxylation of electron-rich arenes 76 with 4-tert-butyl-2,6-bis(4-tert-butylpyridin-2-yl)pyridine as the ligand furnishing the corresponding products 3 in satisfactory yields and heteroaromatic substrates 77, such as quinoline, indole, thiophene, chromone, and coumarin were well tolerated in the process. Besides, pyridines 77 with electron-donating substituents provided selectively ortho-trifluoromethoxylationed products 8 in good yields. This method could be also extended to pyridines 77 with electron-withdrawing substituents using AgF2 as the oxidant and fluoride source. Thus, electron-deficient pyridines were selectively ortho-trifluoromethoxylationed in moderate yields. The method tolerated a large range of functional groups, and several pharmaceutical and natural products could be directly trifluoromethylationed to achieve the corresponding trifluoromethoxylationed products.

Scheme 45. Trifluoromethoxylation of aryl diazonium salts 75.

One can see that essential progress was made in trifluoromethoxylation of functionalized aromatic derivatives using TFMS. Nevertheless, the most effective route for the preparation of CF3O-substituted arenes would be direct trifluoromethoxylation of C−H bonds. Recently direct C-H trifluoromethoxylation of arenes 76 and heteroarenes 77 (Scheme 46) was performed with complexe Ag(II)OCF3 obtained by the combination of AgF2 as the silver salt, Selectfluor as the oxidant, and TFMS 57 [140]. In addition, CsF was used as fluoride source for generation of CF3O− anion from trifluoromethyl TFMS 57. This method was applicable for selective ortho- and para-trifluoromethoxylation of electron-rich arenes 76 with 4-tert-butyl-2,6-bis(4-tert-butylpyridin-2-yl)pyridine as the ligand furnishing the corresponding products 3 in satisfactory yields and heteroaromatic substrates 77, such as quinoline, indole, thiophene, chromone, and coumarin were well tolerated in the process. Besides, pyridines 77 with electron-donating substituents provided selectively ortho-trifluoromethoxylationed products 8 in good yields. This method could be also extended to pyridines 77 with electron-withdrawing substituents using AgF2 as the oxidant and fluoride source. Thus, electron-deficient pyridines were selectively ortho-trifluoromethoxylationed in moderate yields. The method tolerated a large range of functional groups, and several pharmaceutical and natural products could be directly trifluoromethylationed to achieve the corresponding trifluoromethoxylationed products.
Scheme 46. Direct C-H trifluoromethoxylation of arenes and heteroarenes (a): AgF\textsubscript{2} (1.0 equiv), 57 (3.0 equiv), Selectfluor (2.0 equiv), CsF (3.0 equiv), DMC, 35 °C; (b): AgF\textsubscript{2} (4.0 equiv), 57 (4.0 equiv), MeCN, 10 °C; (c): AgF\textsubscript{2} (1.0 equiv), 57 (4.0 equiv), Selectfluor (2.0 equiv), CsF (4.0 equiv), 4-tert-butyl-2,6-bis(4-tert-butyl-pyridin-2-yl)pyridine (0.1 equiv). DMC, 35 °C; (d): AgF\textsubscript{2} (4.0 equiv), 57 (4.0 equiv), dif(pyridin-2-yl)methanone (0.1 equiv), MeCN, 10 °C.

The broad substrate scope, simple and mild reaction conditions, tolerance to a wide range of functional groups make TFMS valuable trifluoromethoxylation reagents for academic research on constructing of aryl, heteroaryl, and alkyl trifluoromethyl ethers. TFMS also allow efficient trifluoromethoxylolation of complex drugs, and natural products. However, the preparation of TFMS is currently based on trifluoromethylation of sulfonic acids using expensive Togni reagents. Besides the high cost of TFMS, common trifluoromethoxylation procedures demand a large excess of reagent, silver salt, oxidant, and fluoride sources, which hamper their application on a large scale.

3.1.4. Trifluoromethyl Benzoate (TFBz)

TFBz 80 (Scheme 47) is a thermally stable liquid, which can be easily activated by fluoride anion to release CF\textsubscript{3}O anion. The preparation of TFBz 80 included treatment of difluorophosgene 78 with KF and catalytic amount of 18-crown-6 in THF for generation of trifluoromethoxide salt, followed by addition of benzyl bromide to furnish the final product 80 in 70% yield after column chromatography purification [141]. In this process, difluorophosgen 79 could be prepared from triphosgene 78 as a phosgene precursor by halogen exchange in the presence of potassium fluoride and catalytic amount of 18-crown-6 in acetonitrile.

Scheme 47. Preparation of TFBz 80.

Synthesis of a series of ortho-bromoaryl trifluoromethyl ethers 3 (Scheme 48) involving arylene intermediates in situ generated from ortho-(trimethylsilyl)aryl triflates 74 was carried out with TFBz 80 by analogy to TFMS 57 [141]. Combination of KF/cis-dicyclohexano-18-crown-6
and phenylethynyl bromide, C₆F₁₂Br or C₆F₅Br as electrophilic bromination reagents in EtOAc was found to be the optimum conditions for trifluoromethoxylation–bromination of arynes. Under these reaction conditions, a wide range of ortho-(trimethylsilyl)aryl triflates 74 underwent trifluoromethoxylation–bromination to give corresponding products 3 in moderate to good yields and indolynes were also tolerated in the process. Furthermore, using of C₆F₁₂I and CCl₄ as halogenation reagents afforded ortho-trifluoromethoxylated iodo- and chloroarenes respectively while in the absence of a halogenation reagent trifluoromethoxylation–bromination products were formed in good yield.

It was also shown that TFBz 80 in the presence of AgF could be employed for efficient trifluoromethoxylation of primary alkyl iodide, benzyl bromide, and α-bromoacetyl derivatives (Scheme 49) [141]. Silver-catalyzed asymmetric bromotrifluoromethoxylation of alkenes and silver-mediated cross-coupling of aryl stannanes with TFBz 80 were also performed.
The TFBz 80 as stable and inexpensive trifluoromethoxylation reagent has good substrate scope and tolerates various functionalities. A limitation for the practical use of TFBz 80 is the process of its preparation involving highly toxic fluorophosgene.

3.1.5. 2,4-Dinitro(Trifluoromethoxy)Benzene (DNTFB)

DNTFB is inexpensive, commercially available high boiling liquid. The reaction between DNTFB 81 (Scheme 50) and tetrabutylammonium triphenyldifluorosilicate released trifluoromethoxide salt through nucleophilic aromatic substitution in activated aromatic ring [142]. Then in situ generated trifluoromethoxide salt was used for reactions with benzylic bromide and cinnamyl bromide 82 affording the corresponding trifluoromethyl ethers 83 in 45–60% yields. The scope of the reactions was limited to activated electrophiles such as benzylic or allylic bromides because unactivated alkyl iodides as well as α-halo carbonyl compounds were not effective for the preparation of trifluoromethoxylated products.

\[
\text{R-Br} \quad _{0.9 \text{ equiv}} \quad \begin{array}{c}
\text{NO}_2 \\
\text{OCF}_3
\end{array} \quad \text{Bu}_4\text{N}^+\text{Ph}_3\text{SiF}_2^- \quad (1 \text{ equiv}) \quad \text{MeCN, rt} \quad \text{R-OCF}_3
\]

\[
\begin{array}{c}
\text{NO}_2 \\
\text{OCF}_3
\end{array} \quad \text{81} \quad 2 \text{ equiv} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{THF, rt} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{84} \quad 90\% \text{ isolated yield}
\]

\[
\text{R-Br} \quad \begin{array}{c}
\text{NO}_2 \\
\text{OCF}_3
\end{array} \quad \text{81} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{THF, rt} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{84} \quad \text{R-OCF}_3
\]

Thus, DNTFB showed low reactivity and very limited scope. Nevertheless, isolable pyridinium trifluoromethoxide salt 84 was easily prepared from the reaction of DNTFB 81 (Scheme 51) with 4-dimethylaminopyridine [143]. This salt was an effective trifluoromethoxide source for SN2 reactions to form trifluoromethyl ethers.

\[
\begin{array}{c}
\text{NO}_2 \\
\text{OCF}_3
\end{array} \quad \text{81} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{THF, rt} \quad \begin{array}{c}
\text{Me} \\
\text{N}^+ \text{Me}
\end{array} \quad \text{84} \quad \text{R-OCF}_3
\]

3.1.6. (E)-O-Trifluoromethylbenzaldoximes (TFBO)

TFBO 87 are stable often crystalline trifluoromethoxylation reagents which were conveniently prepared in two steps starting from N-hydroxyphthalimide 85 as exemplified in Scheme 52 [56]. Copper(II)-catalyzed trifluoromethylation of N-hydroxyphthalimide 85 with sodium trifluoromethanesulfinate as a radical CF3 source and phenylidodine(III) diacetate as the stoichiometric oxidant led to O-trifluoromethylated product 86 in good yield. Heating of N-trifluoromethoxy phthalimide 86 and aryl aldehydes in water under acidic conditions gave the TFBO 87 with yield ranging from 11 to 59%.
Scheme 52. Preparation of TFBO 87.

Activation of TFBO 87 (Scheme 53) with Cs₂CO₃ as optimal base in DMA, followed by reaction of the resulting CsOCF₃, (detected by ^1⁹F NMR) with unactivated alkyl iodides, bromide, and chloride 88 without any metal assistance allowing preparing the corresponding trifluoromethyl ethers 89 with yields ranging from 30 to 98% and many functional groups including halogen, ester, ether, ketone, and aldehyde were tolerated under reaction conditions [56]. In particular, the process could also be applied to heteroaromatic and amino acid derivatives and amenable to large-scale synthesis. Generally, secondary alkyl halides gave lower yields of trifluoromethoxylated products than primary alkyl halides. Moreover, allyl, benzyl, and propargyl products were prepared in good to excellent yield. The main disadvantage of this method was that tertiary alkyl halides were nonreactive under the reaction conditions.

Scheme 53. Base-promoted trifluoromethoxylation of alkyl halides with TFBO 87.

3.2. Radical Reagents
3.2.1. N-Trifluoromethoxybenzimidazole 93

1-Trifluoromethoxybenzimidazole 93 (Scheme 54) is a stable crystalline reagent that can undergo homolytic cleavage of N-OFC₃ bond providing •OCF₃ radical and N-centered benzimidazole radical under mild reaction conditions. This radical trifluoromethoxylation reagent was afforded through three-step synthesis starting from commercially available 2-chloro-1,3-dinitro-5-(trifluoromethyl)benzene 90 and (3,5-bis(trifluoromethyl)-phenyl)methanamine 91 [59,60,144]. Nucleophilic displacement of the chlorine atom of 90 by the reaction with
benzyamine 91 in DMF followed by base-promoted cyclization of resulting N-benzyl-2,6-
dinitro-4-trifluoromethylaniline which was facilitated by the presence of two nitro groups in
the aromatic ring afforded the corresponding 1-hydroxybenzimidazole derivative 92 in 71% yield over 2 steps. Finally, O-trifluoromethylation reaction of 1-hydroxybenzimidazole derivative 92 using Togni reagent 24 in CH2Cl2 at 40 °C led to 1-trifluoromethoxybenzimidazole 93 in good yield.

![Scheme 54. Preparation of 1-trifluoromethoxybenzimidazole 57.](image)

Reaction of 1-trifluoromethoxybenzimidazole 93 (Scheme 55) with arenes 76 in the presence of a redox-active catalyst under irrigation with violet LED light in MeCN at room temperature afforded aryl trifluoromethyl ethers 3 in moderate to good yields [59,60,144]. Use of the photocatalyst [Ru(bpy)3](PF6)2 (bpy = 2,2′-bipyridine) provided the best yields. However, 10 equivalents of arenes were used in the reactions to prevent formation of bis-trifluoromethoxylated side products. Trifluoromethoxylation conditions were tolerant towards a variety of functional groups, including halogen, ester, nitrite, ether, and phosphine oxide. The potential of this method was also demonstrated preparing trifluoromethoxylation products 8 from such heteroarenes 77 as pyridine, pyrimidine, and thiophene. Furthermore, structurally complex compounds such as fructose and trans-androsterone derivatives were also successfully trifluoromethoxylated using only 1 equivalent of substrates. As expected for a homolytic aromatic substitution, the regioselectivity of OCF3 radical reactions was generally low and complicated by the formation of 3–10% yield of N-arylated side products. The mechanistic study of the reaction indicated photocleavage of 1-trifluoromethoxybenzimidazole 93 followed by a homolytic cleavage of the N-OCF3 bond to generate OCF3 radical that reacted with arenes. Finally, oxidation of the generated cyclohexadienyl radicals and followed by deprotonation provided the trifluoromethoxylated products.

3.2.2. N-Trifluoromethoxytriazolium Salt 96

Further screening of potential reagents for radical trifluoromethylation of arenes and heteroarenes demonstrated that 3-methyl-1-trifluoromethoxybenzotriazolium triflate 96 (Scheme 56) could generate OCF3 radical in selective manner under visible light photocatalytic conditions at room temperature [145]. The synthesis of reagent 96 was accomplished by heating 2-chloro-1,3-dinitro-5-(trifluoromethyl)benzene 90 with excess of hydrazine monohydrate, sodium acetate, and acetic acid in ethanol under reflux followed by O-trifluoromethylation of resulting 1-hydroxybenzotriazole 94 using Togni reagent 24 to yield 1-trifluoromethoxybenzotriazole 95. Alkylation of 95 was conducted using methyl triflate to form 3-methyl-1-trifluoromethoxybenzotriazolium triflate 60 in 92% yield.
Preparation of 3-methyl-1-trifluoromethoxybenzotriazolium triflate to form 3-methyl-1-trifluoromethoxybenzotriazolium triflate by reaction of methyl triflate with benzotriazole in the presence of Ru(bpy)$_3$(PF$_6$)$_2$ (0.03 mol%) in MeCN, 23 °C and 10 W LED (402 nm). When amount of arenes 76 was reduced to 1 equivalent, it afforded 3 in lower yield and accompanied by 15% of bis-trifluoromethoxylated products. Various mono-, di-, and trisubstituted benzene derivatives 76 were successfully transformed into the corresponding trifluoromethoxyalted arenes 3 as mixtures of regioisomers. The trifluoromethoxylation could be applied to electron-rich arenes and benzene derivatives bearing alkyl substituents were accessible to the reaction affording the products in reasonable yields. The method had broad heteroarenes scope (pyridine, pyrimidine, and thiophene), including a number of examples of late-stage trifluoromethylation. The mechanistic study of the reaction indicated that it proceed via the electron transfer from the triplet-excited state of photoredox catalysis to 1-trifluoromethoxybenzotriazolium triflate 96 and then formation of •OCF$_3$ radical and Ru(bpy)$_3$$^{3+}$. Addition of trifluoromethoxy radical to arene forming...
the cyclohexadienyl radical followed by oxidation with Ru(bpy)$_3^{3+}$ and deprotonation afforded the trifluoromethoxylated product.

![Scheme 57](image)

Scheme 57. Photoredox-catalyzed intermolecular C–H trifluoromethoxylation of arenes and heteroarenes with reagent 96.

3.2.3. N-Trifluoromethoxy pyridinium Salt 98

4-Cyano substituted N-trifluoromethoxy pyridinium salt 98 (Scheme 58) is solid, thermally stable source of trifluoromethoxyl radical in the presence of strongly reducing photocatalyst Ru(bpy)$_3$(PF$_6$)$_2$. This reagent was available on multigram scale by trifluoromethylation of 4-cyanopyridine N-oxide 97 using Togni reagent 24 [146]. Activation of Togni reagent 24 with N-trimethylsilyl bis(trifluoromethanesulfonyl) imide allowed to be obtained 4-cyano-N-trifluoromethoxypyridinium salt 98 in 63% yield.

![Scheme 58](image)

Scheme 58. Trifluoromethylation of 4-cyanopyridine N-oxide.

Reaction of arenes 76 or heteroarenes 77 (Scheme 59) with N-trifluoromethoxy pyridinium salt 98 as trifluoromethoxylating reagent required ruthenium photocatalyst Ru(bpy)$_3$(PF$_6$)$_2$ (5.0 mol%) and irradiation with blue LED light in MeCN. Under the optimized reaction conditions trifluoromethoxylation of excess number of substrates 76 and 77 was achieved in 21–66% yields. A wide range of aryl 3 and heteroaryl 8 trifluoromethyl ethers bearing common functional groups (halides, aldehydes, ketones, esters, imides, and benzylic moieties) were prepared using trifluoromethoxylation with N-trifluoromethoxy pyridinium salt 98. This method was also applicable to late-stage functionalization of complex structures. However, the drawback of trifluoromethoxylation reaction using N-trifluoromethoxypyridinium salt 98 was formation of N-aryl pyridination byproducts (~15%). The reduction of pyridinium reagent 98 and the oxidation of Ru(bpy)$_3^{3+}$ to Ru(bpy)$_3^{2+}$ occurred in a single electron transfer step to produce 4-cyanopyridinium radical, which fragmentation led to trifluoromethoxy radical and neutral pyridine. Following addition of the OCF$_3$ radical to the arene, oxidation of cyclohexadienyl radicals with Ru(bpy)$_3^{3+}$ and deprotonation afforded final trifluoromethoxylated product.
Scheme 59. Visible light photoredox-catalyzed C–H trifluoromethoxylation of arenes with reagent 98.

The radical direct trifluoromethoxylation of arenes and heteroarenes in catalytic reactions provides short and convenient route to a wide range of trifluoromethoxylated compounds under mild conditions without the need for prefunctionalized substrates such as aryl or heteroaryl halides, silanes, and boronic acid derivatives. Nevertheless, the newly developed radical trifluoromethoxylation of aromatic systems cannot be used for the large-scale production of aryl and heteroaryl trifluoromethyl ethers due to generating mixtures of regioisomers and requirement for large excess of substrates.

4. Conclusions

As one can see from the data discussed, a number of efficient reagents have been developed to facilitate the preparation of organic compounds featuring such an emerging fluorinated motif as trifluoromethoxy group. These include the reagents for nucleophilic as well radical pathway for introduction of a CF₃-O function. From the standpoint of substrate generality, these reagents show exceptional synthetic value working via variety of mechanisms and reaction types, usually with excellent chemical yields. However, virtually all discussed reagents, both the nucleophilic and the radical, share one principal disadvantage necessitating the use of electrophilic trifluoromethylating reagents as step in their preparation. Thus, most typically used Umemoto and Togni reagents are quite expensive and unsuitable for large-scale preparations. Therefore, the traditional approaches represented by, for example, chlorine-fluorine exchange, oxidative desulfurization-fluorination and deoxofluorination of fluoroformates, are still currently being used for industrial production of trifluoromethoxy-containing compounds. One may agree that this field of research is only getting started and new generation of trifluoromethoxylating reagents will be developed to overcome the current shortcoming.

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