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Review

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 CF_3-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

Citation: Wang, Q.; Zhang, X.; Sorochinsky, A.E.; Butler, G.; Han, J.; Soloshonok, V.A. Advances in the Development of Trifluoromethoxylation Reagents. *Symmetry* **2021**, *13*, 2380. https://doi.org/10.3390/sym13122380

Academic Editor: Stefano Superchi

Received: 17 November 2021
Accepted: 3 December 2021
Published: 10 December 2021

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-CF_3 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 CF_3-O- group is a noticeably less developed area of fluorine chemistry [25–34]. As a reflection of this apparent methodological deficit, pharmaceutical drugs and agrochemicals featuring trifluoromethoxy substituent, constitute less than 1.5% and 2.5% of the respective fluorine-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 OCF_3 group (OCF_3: $\pi = 1.04$) as compared to the OCH_3 and CF_3 groups (OCH_3: $\pi = -0.20$, CF_3: $\pi = 0.88$), which is slightly lower to that of SCF_3 group (SCF_3: $\pi = 1.44$) [39,40]. It should be pointed out that trifluoromethoxyl is not conjugated to unsaturated bonds (in olefines, arenes). Thus, the delocalized p-electrons of oxygen atom in the σ*-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 CF_3 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.

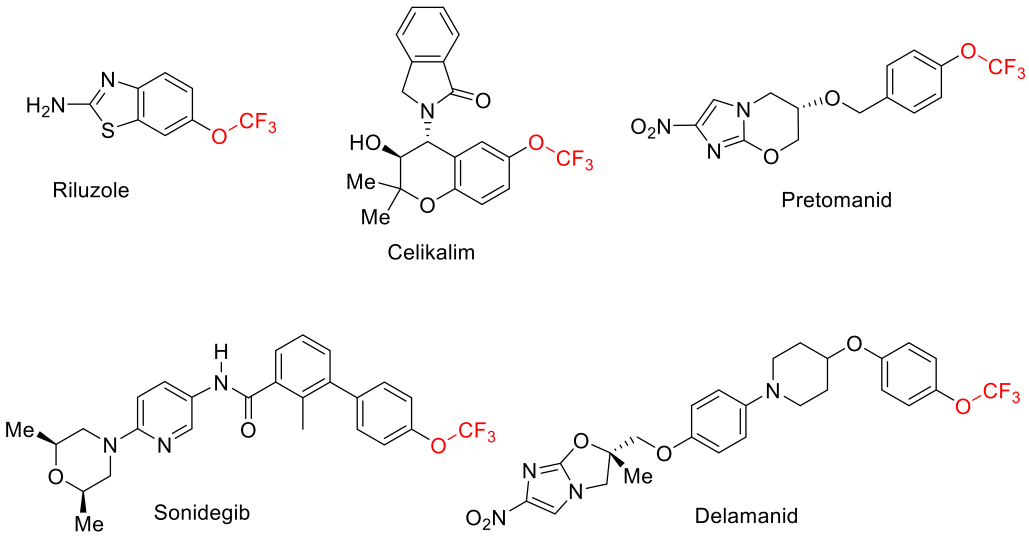


Figure 1. Trifluoromethoxy-containing pharmaceutical drugs.

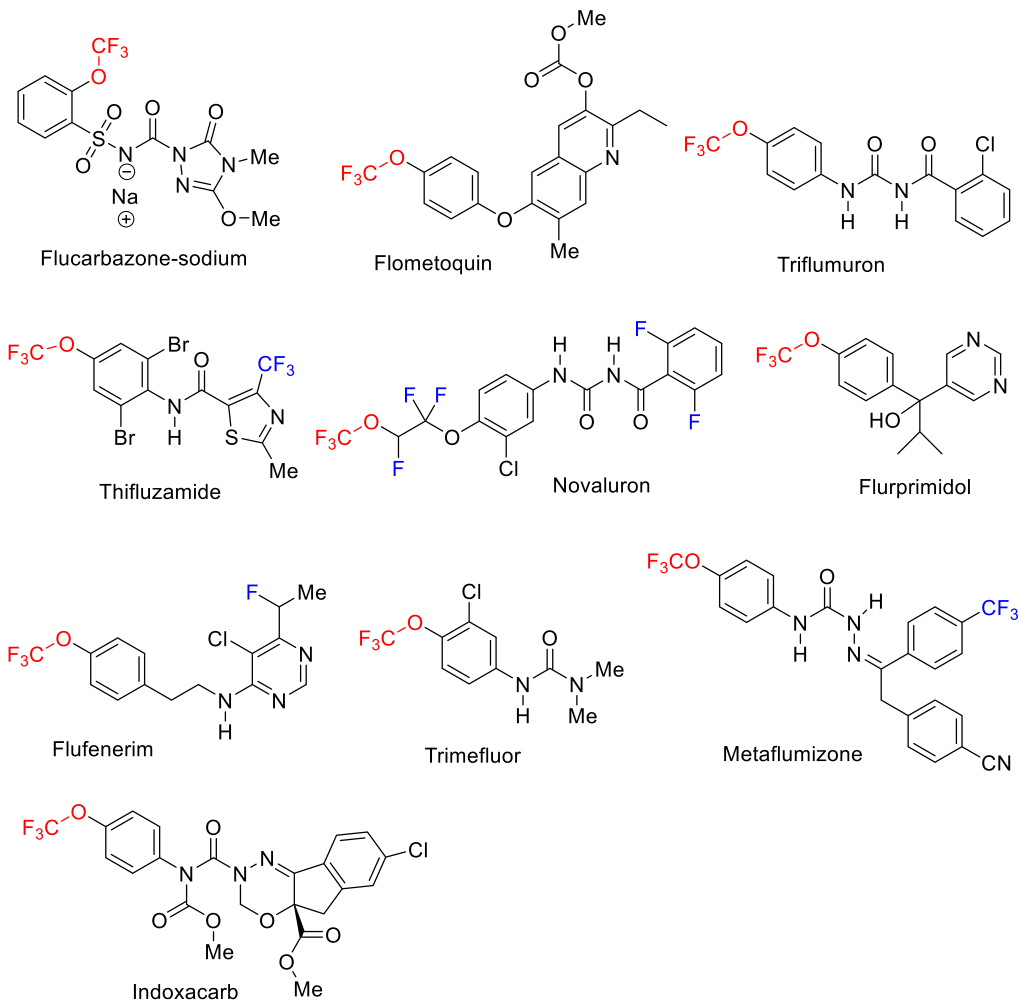


Figure 2. Trifluoromethoxy-containing agrochemicals.

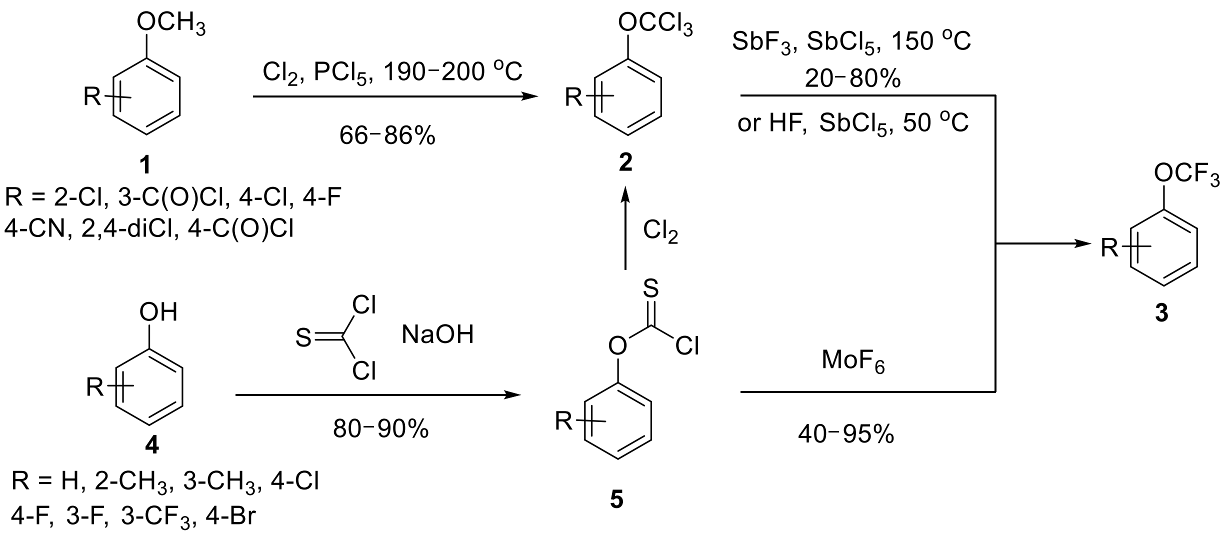
These and other synthetic methods for the preparation of trifluoromethoxy-containing compounds have been extensively reviewed [56–64]. In the present article, we provide a short summary of the traditional methods, followed by a critical discussion of the most recently developed trifluoromethoxylating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

2. General Approaches for Preparation of Trifluoromethoxy-Containing Compounds

2.1. Nucleophilic Fluorination

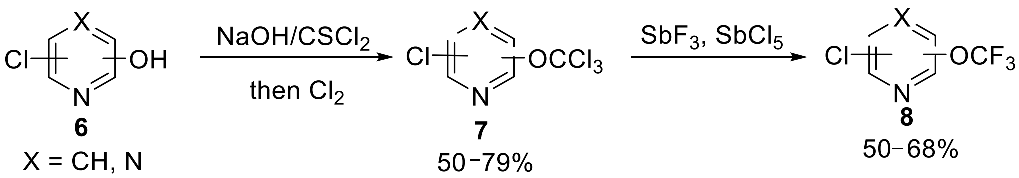
2.1.1. Chlorine-Fluorine Exchange

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 SbF_5, generated in situ by reaction of SbF_3 with $SbCl_5$. 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 $SbCl_5$ 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].



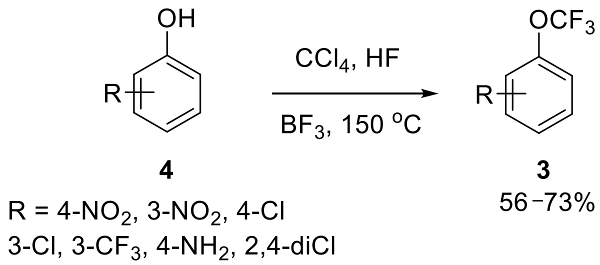
Scheme 1. Fluorination of aryl trichloromethyl ethers.

Chlorine-fluorine exchange strategy was also applicable to heteroaromatic compounds, such as pyridine and pyrazine derivatives. The reaction of thiophosgene with both hydroxypyridines and hydroxypyrazine **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.



Scheme 2. Fluorination of heteroaryl trichloromethyl ethers.

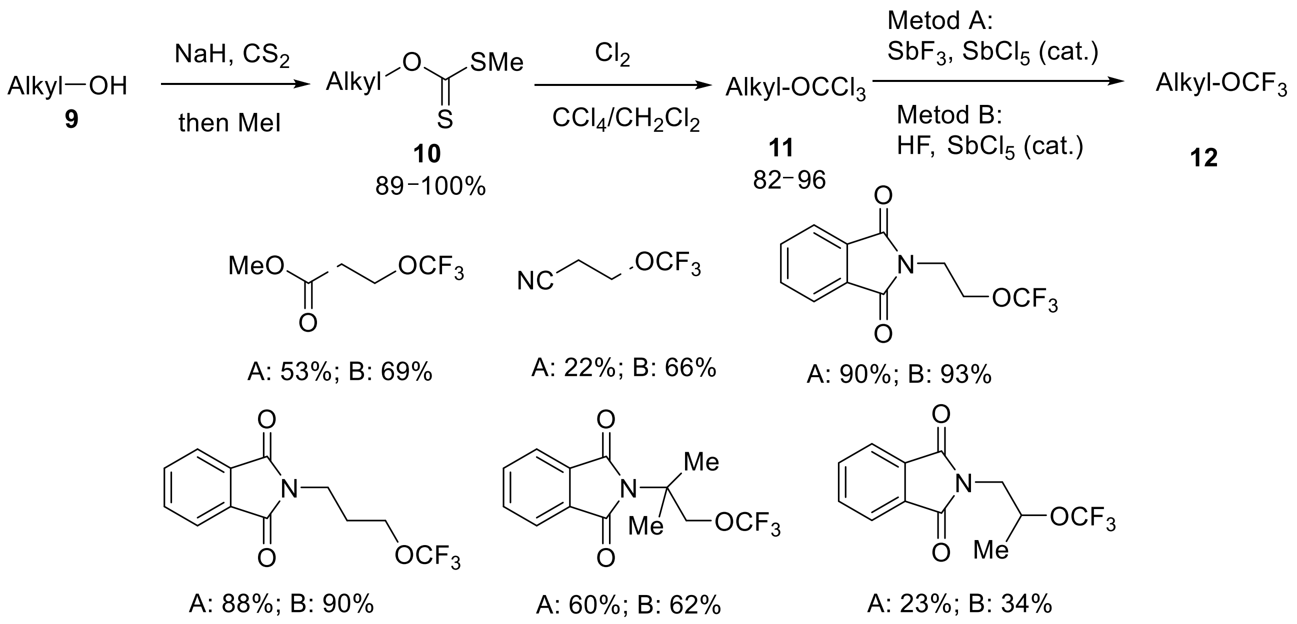
Chlorine-fluorine exchange method was modified by in situ generation of intermediate trichloromethyl derivatives with further conversion into the final aryl trifluoromethyl ethers **3** (Scheme 3) under heating of phenols **4** with excess of tetrachloromethane, anhydrous hydrogen fluoride and catalytic 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.



Scheme 3. One-pot synthesis of aryl trifluoromethyl ethers.

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.

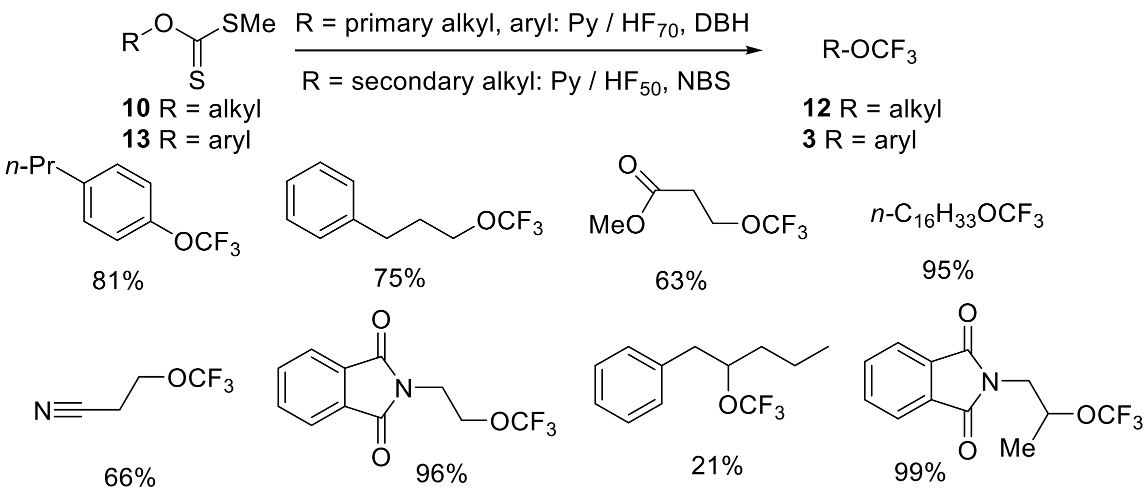
Chlorine-fluorine exchange approach to trifluoromethyl ethers has high generality and was well described in several reviews [34,46]. It was successfully applied for aromatic, heteroaromatic and aliphatic substrates using such inexpensive industrial fluorinating reagents as antimony trifluoride and hydrogen 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.



Scheme 4. Fluorination of alkyl trichloromethyl ethers.

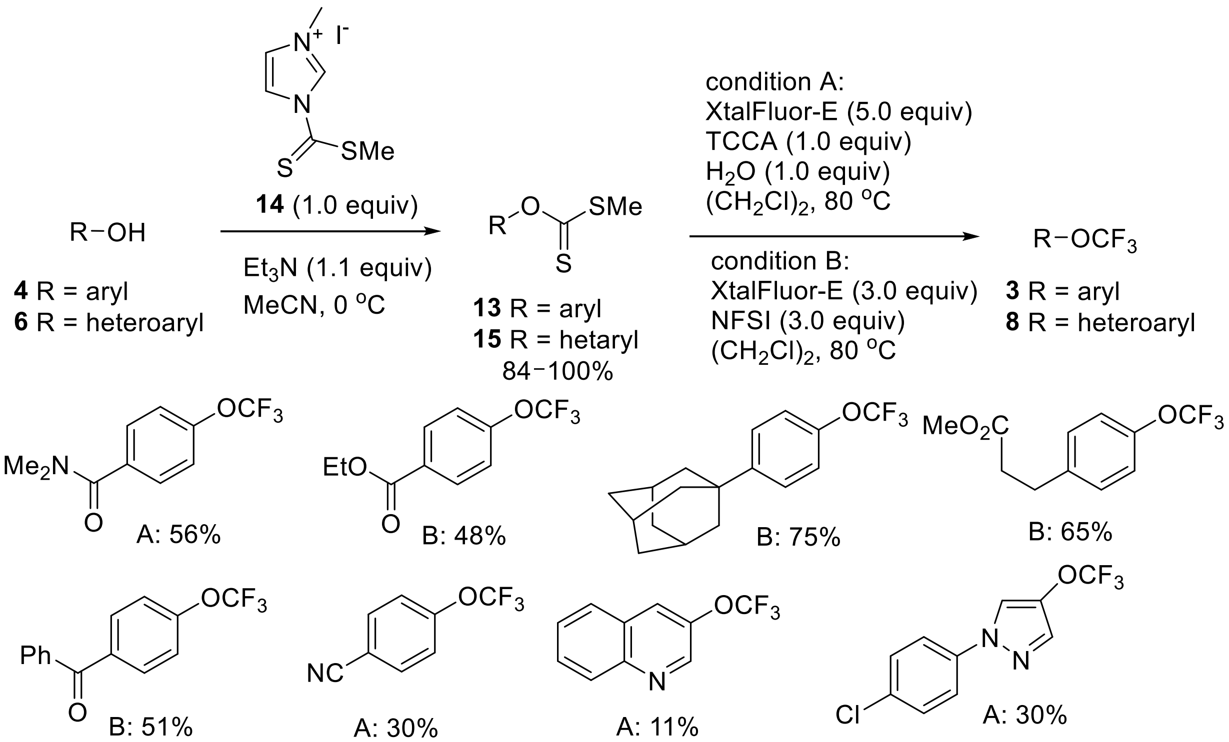
2.1.2. Oxidative Desulfurization-Fluorination

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-$HF_{50\%}$ or pyridine-$HF_{70\%}$ with KHF_2 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.



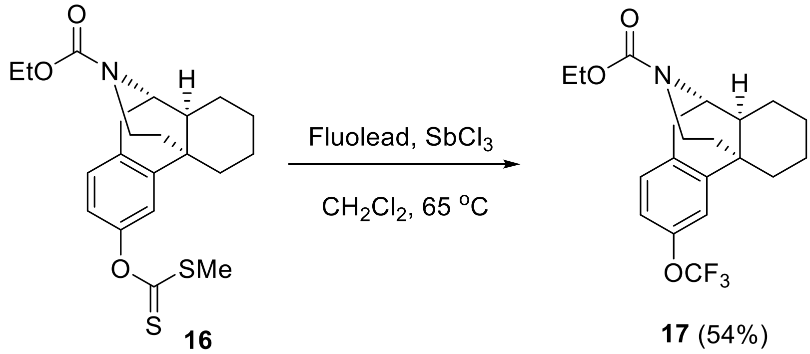
Scheme 5. Oxidative desulfurization-fluorination.

Desulfurization-fluorination method has been modified for preparation of aryl and heteroaryl trifluoromethyl ethers by using XtalFluor-E ([Et_2NSF_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)-1*H*-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_2O 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_3O-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_3O 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 $TBAH_2F_3$ and various oxidants also gave rise to the alkyl trifluoromethyl ethers [80].

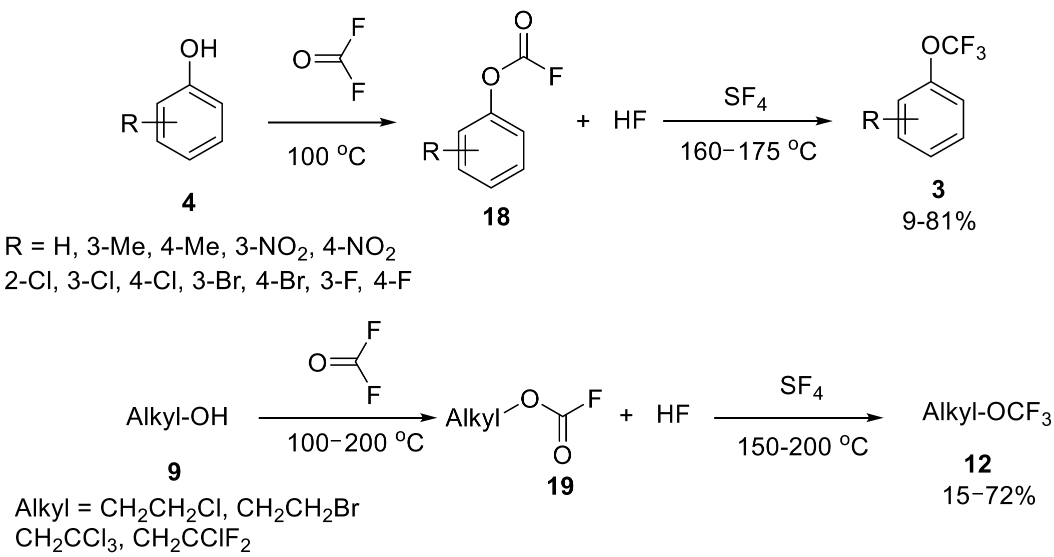


Scheme 7. Synthesis of trifluoromethyl ether analogue of dextromethorphan.

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. Deoxyfluorination 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, C1, Br, were present in β-position (Scheme 8) [45].



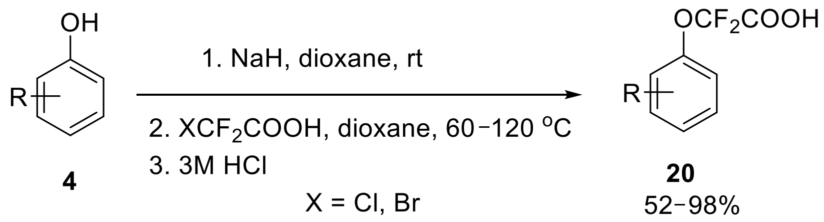
Scheme 8. Deoxyfluorination of aryl fluoroformates.

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*

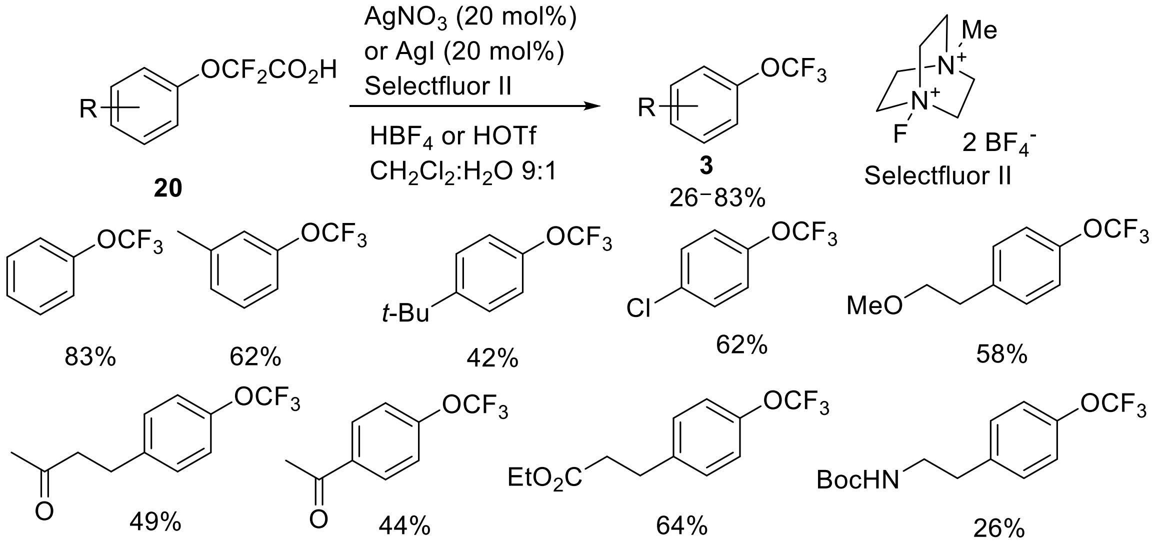
2.2.1. Silver-Catalyzed Fluorodecarboxylation

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].



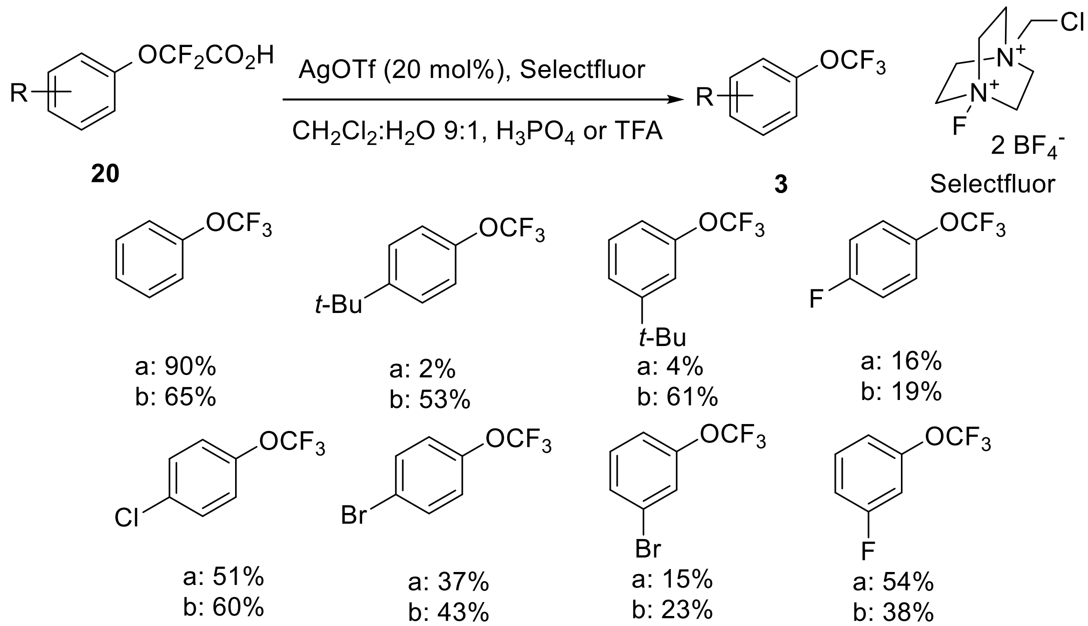
Scheme 9. *O*-Carboxydifluoromethylation of phenols **4**.

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 HBF_4 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-catalized fluorodecarboxylation of $ArOCF_2COOH$ with Selectfluor II.

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_3PO_4 as additives [85]. Biphasic system CH_2Cl_2/H_2O in ratio 9:1 as solvent was necessary for successful transformation. When H_3PO_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%.



Scheme 11. Silver-catalized fluorodecarboxylation of $ArOCF_2COOH$ with Selectfluor (a: and b: represent the yields, when H3PO4 and TFA were used as additives, respectively).

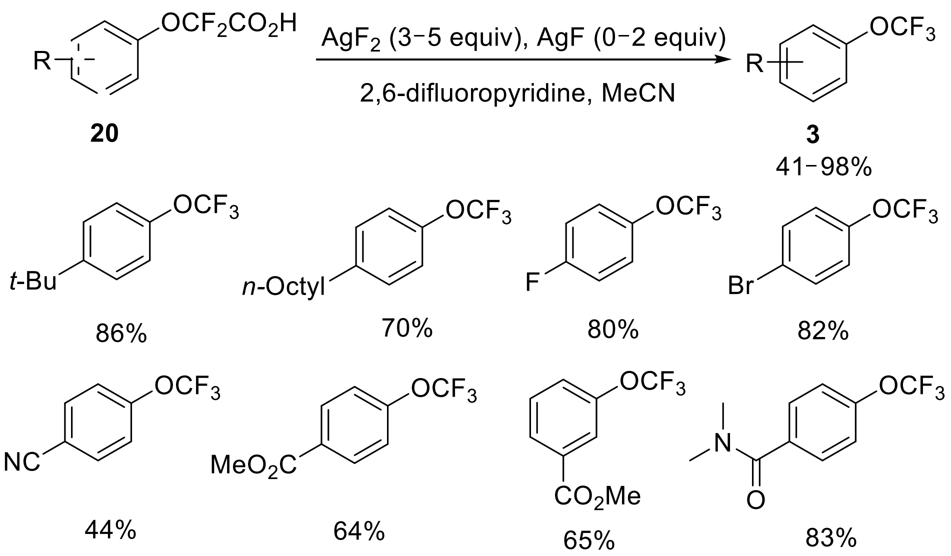
In the case of methoxy group no fluodecarboxylated product was detected.

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.

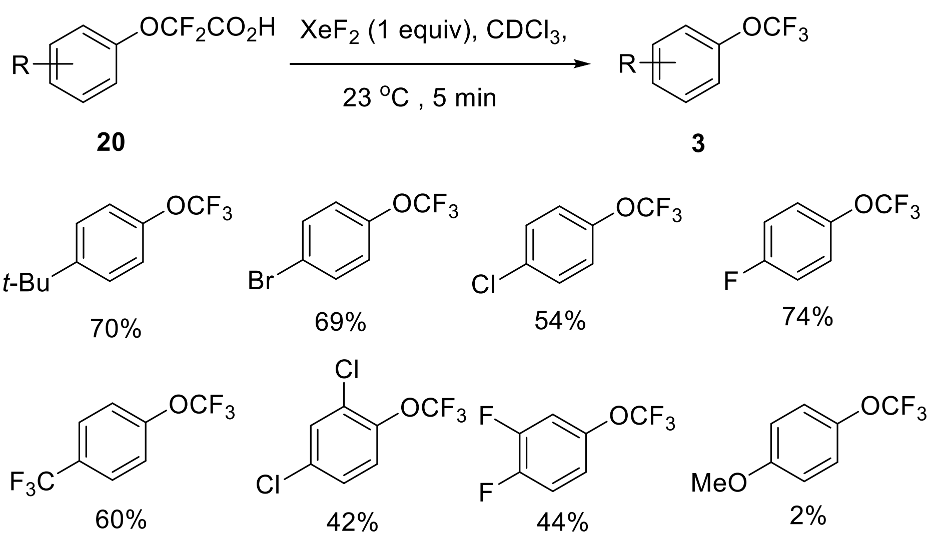
AgF_2 is light sensitive, strong fluorinating and oxidising agent and requires special teflon or passivated metal equipment. While AgF_2 find laboratory experiments application, it is too expensive for large scale industry use.



Scheme 12. AgF_2 induces fluorodecarboxylation of aryloxydifluoroacetic acids **20**.

2.2.3. 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.



Scheme 13. Preparation of aryl trifluoromethyl ethers **3** using XeF_2.

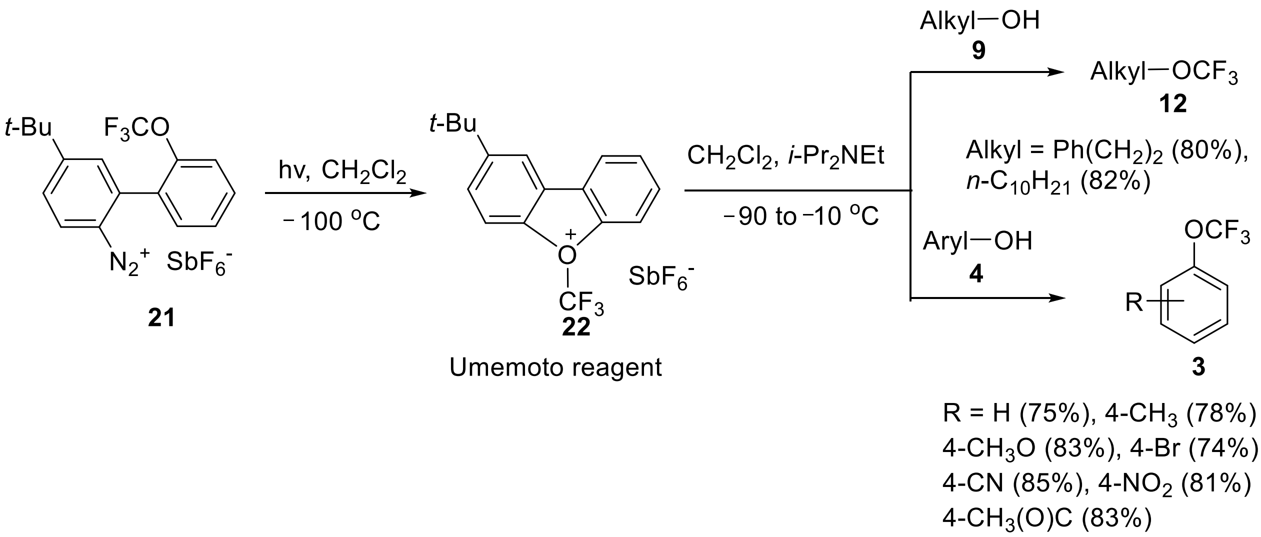
Fluorodecarboxylation of aryloxydifluoroacetic acids with xenon difluoride is narrow substrate scope. Beside xenon difluoride is expensive and requires special plastic equipment due to its high reactivity. Thus, this transformation is not easily scalable.

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.

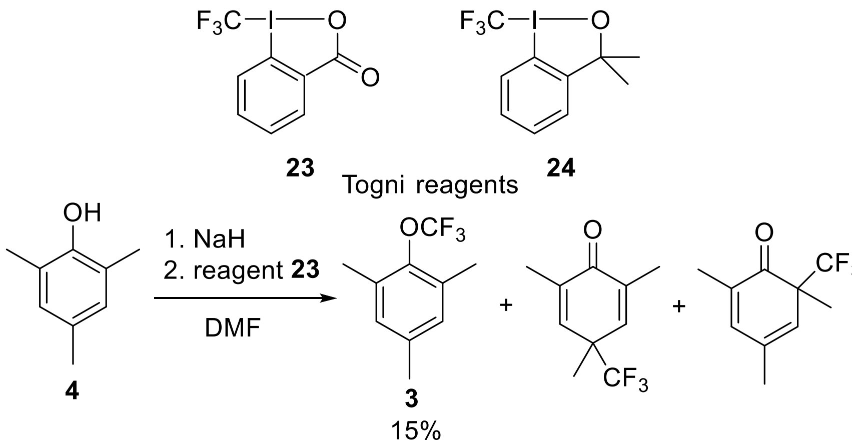


Scheme 14. *O*-Trifluoromethylations of aliphatic alcohols and phenols with Umemoto reagent **22**.

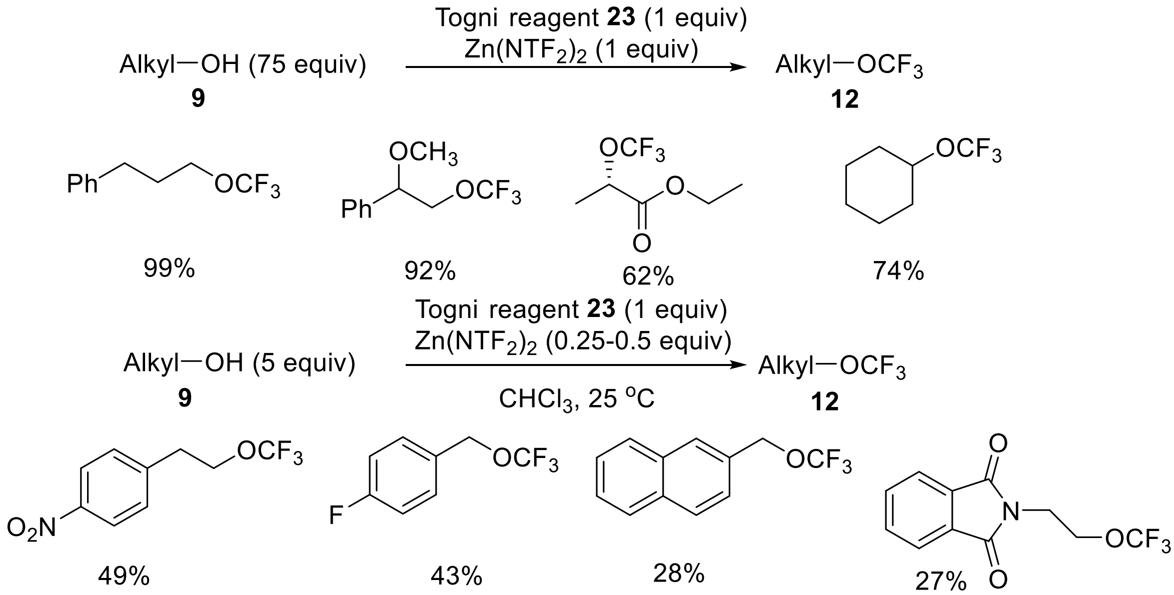
Togni Hypervalent Iodine Reagents

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 $Zn(NTf_2)_2$ 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 trifluoromethoxycyclohexane 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].



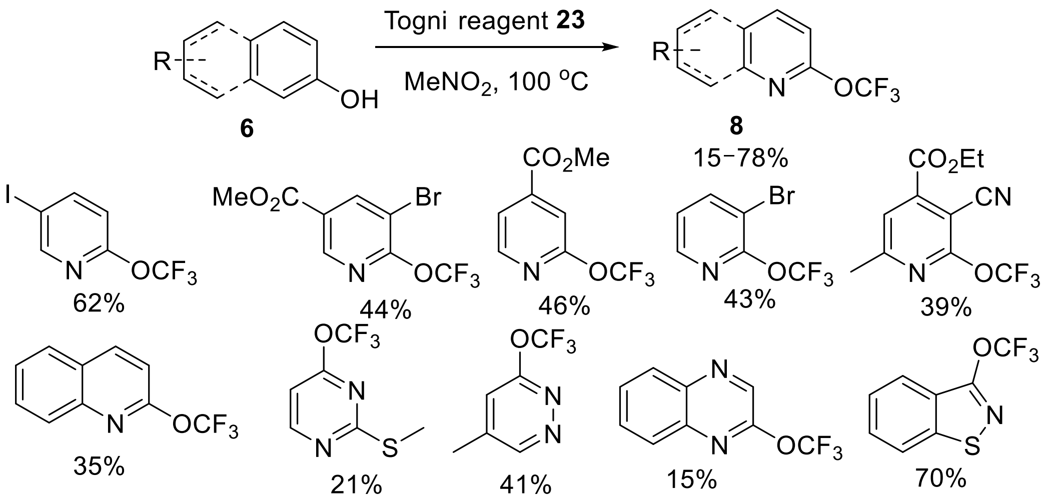
Scheme 15. *O*-Trifluoromethylation of 2,4,6-trimethylphenol with Togni reagent **23**.



Scheme 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.

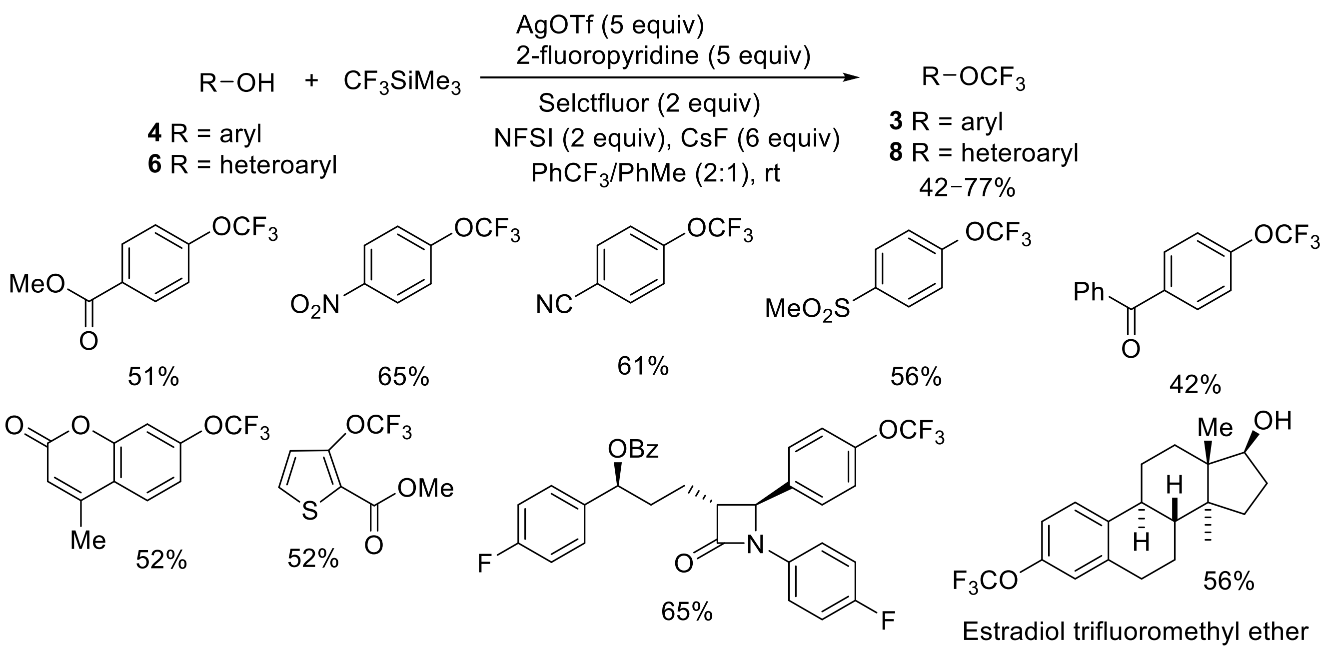
The two most popular trifluoromethylated hypervalent iodine reagents **23** and **24** are air-stable crystalline solids and could be easily prepared from readily available 2-iodobenzoic acid making them available on a kilogram scale. Although, hypervalent iodine reagents **23** and **24** are expensive, 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.



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

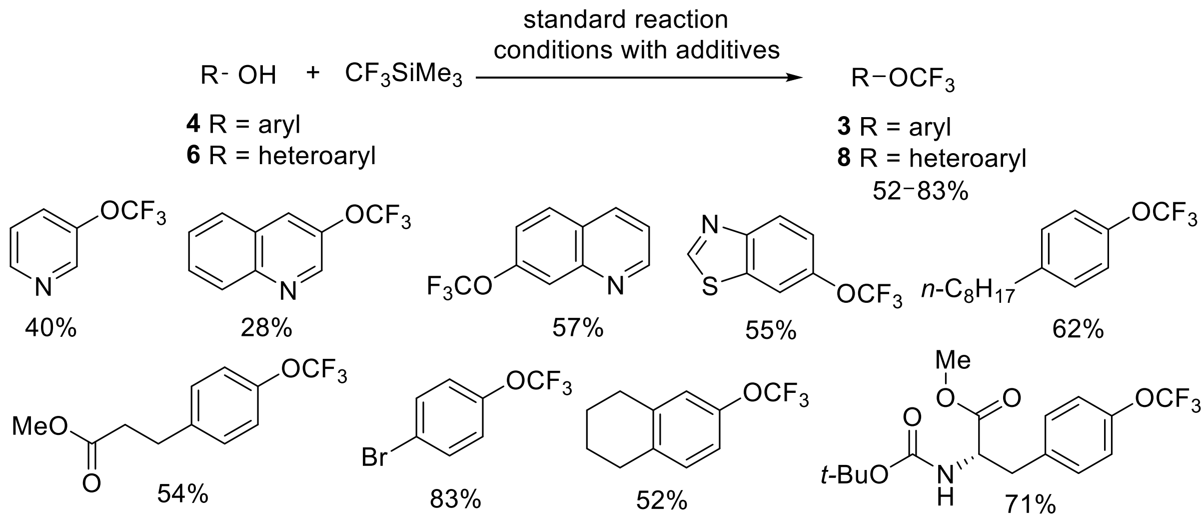
2.3.2. Oxidative O-Trifluoromethylation

Silver triflate-mediated oxidative trifluoromethylation of phenols and heteroaromatic alcohols with nucleophilic CF_3SiMe_3 as the CF_3 source in the presence of oxidants constituted one of the most straightforward methods for synthesis of trifluoromethyl esthers under mild reaction conditions. The variety phenols **4** and heteroaromatic substrates **6** (Scheme 18) bearing electron-withdrawing groups were efficiently reacted with CF_3SiMe_3 in the presence of CsF, AgOTf, 2-fluoropyridine as a ligand, Selectfluor and *N*-fluorobenzenesulfonimide 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, sulfonyl, ether groups and β-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 18. Silver-mediated *O*-trifluoromethylation electron-poor phenols and heterocycles.

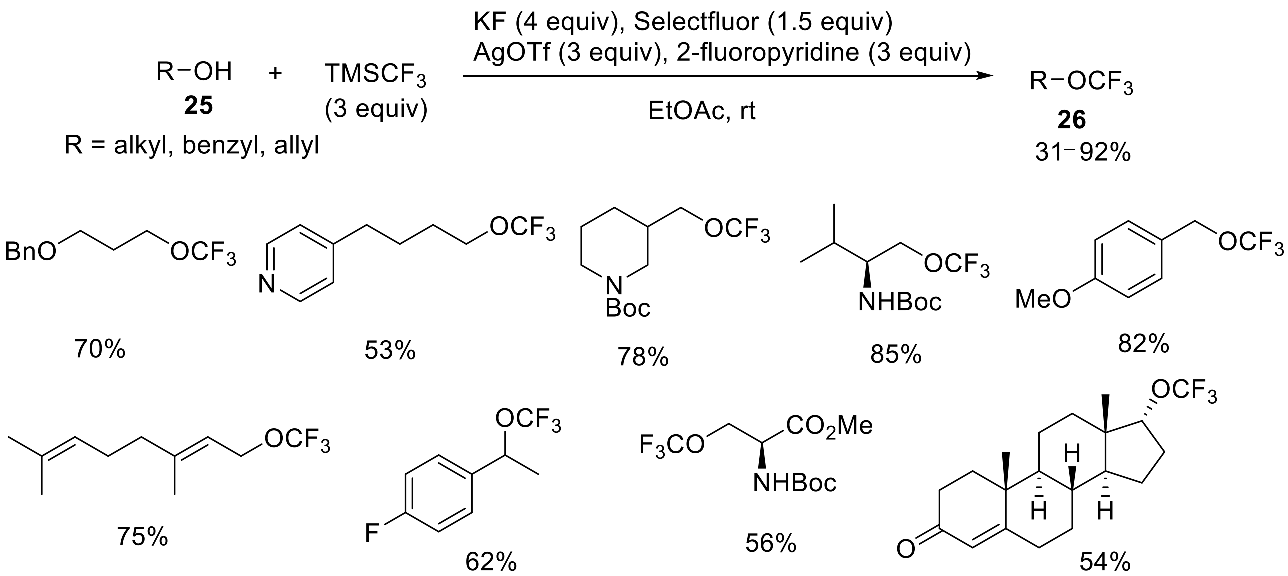
The oxidative *O*-trifluoromethylation could be extended to nitrogen-containing heteroaromatic substrates **6** as well as phenols **4** (Scheme 19) substituted with an electron-donating group or bromine with minor modification of the reaction conditions. The reactions of pyridinium salts of such substrates 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 trifluoromethyaltion of phenyl ring with eletrophilic CF_3 radicals easily generated from the combination of $TMSCF_3$/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.

Silver-mediated oxidative *O*-trifluoromethylation with nucleophilic $TMSCF_3$ found application for aliphatic alcohols. Trifluoromethylation of aliphatic alcohols **25** (Scheme 20) was conducted in presence of AgOTf, 2-fluoropyridine, Selectfluor, $TMSCF_3$, 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_3SiMe_3 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_3SiMe_3 and oxidants which make the method extremely expensive for industrial application.

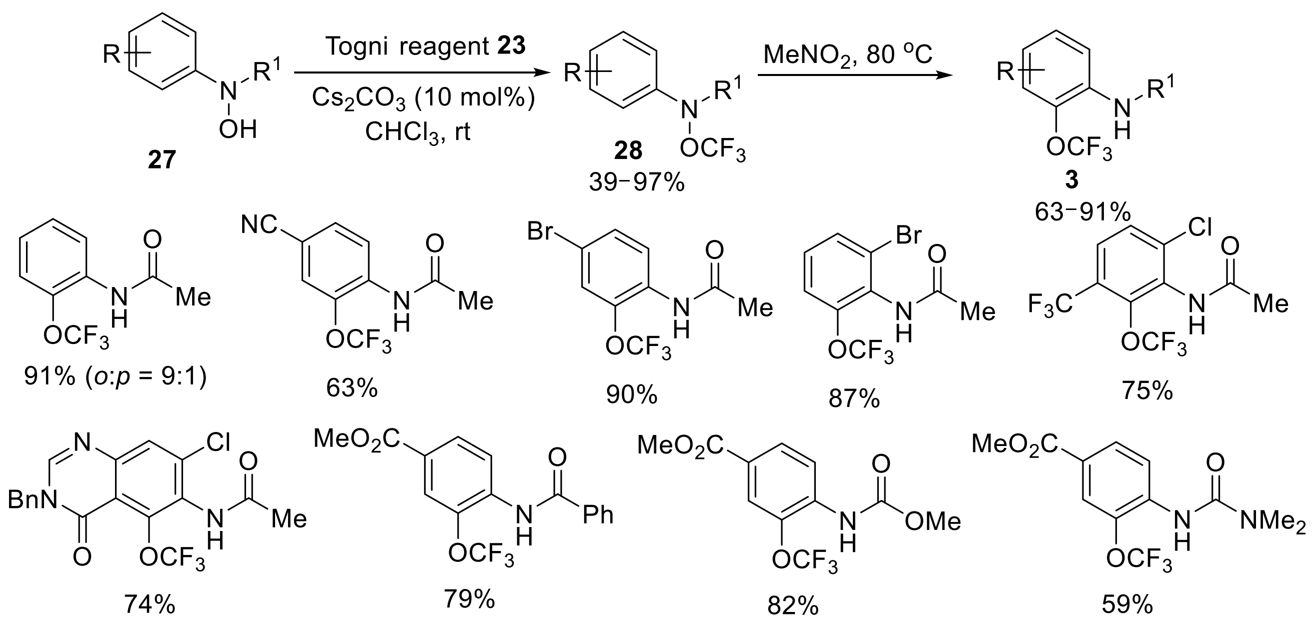


Scheme 20. Silver-mediated trifluoromethylation of aliphatic alcohols.

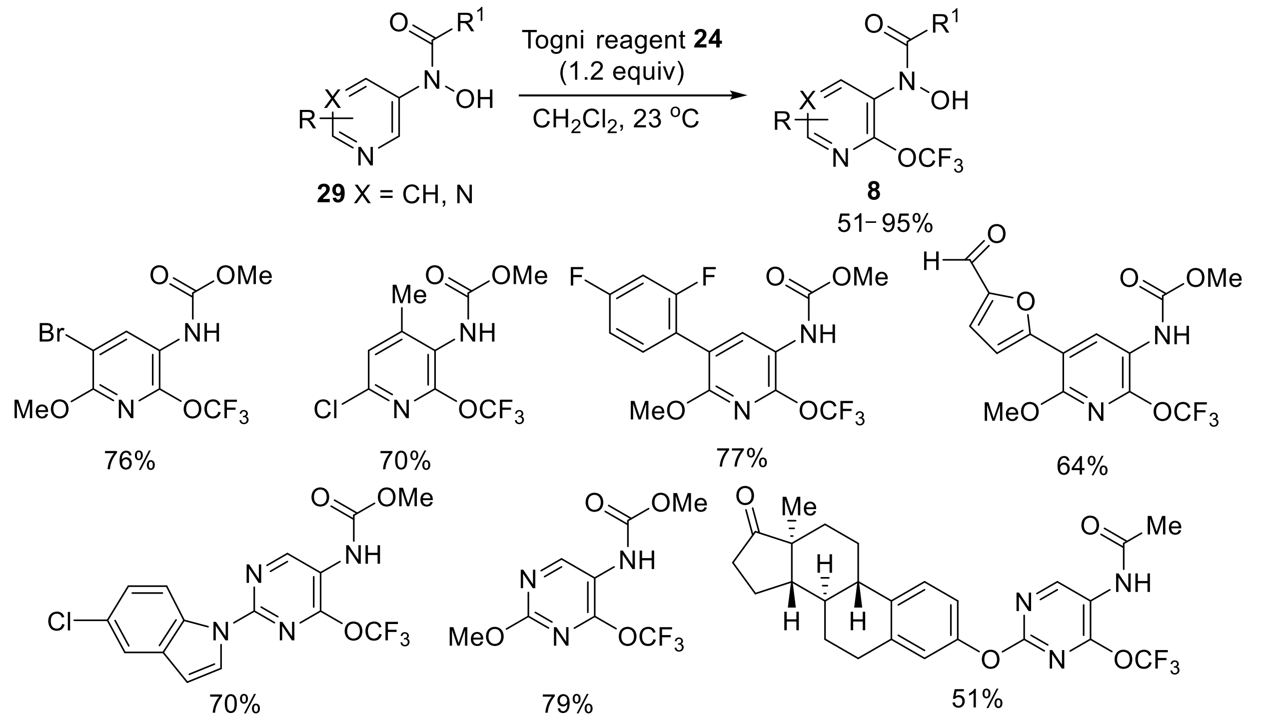
2.3.3. Radical O-Trifluoromethylation

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 Cs_2CO_3 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 OCF_3 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 OCF_3 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*-OCF_3 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 OCF_3 migration step and rearrangement proceeded at room or below temperature. Electron-deficient heteroaromatic substrates **29** required heating to perform rearrangement stage.

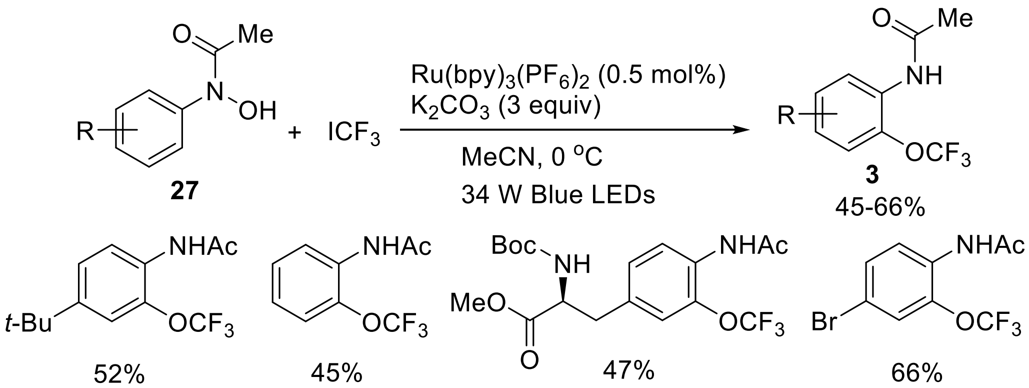


Scheme 21. O-Trifluoromethylation/OCF$_3$-migration of protected *N*-aryl-*N*-hydroxylamines.



Scheme 22. *O*-Trifluoromethylation/OCF$_3$-migration reaction of protected *N*-heteroaryl-*N*-hydroxylamines.

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, Ru(bpy)$_3$(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 *tert*-butyl, bromo, esters and carbamates with yield ranging from 45% to 66%.



Scheme 23. Photocatalytic radical coupling reaction of *N*-aryl-*N*-hydroxylamides with trifluoromethyl iodide.

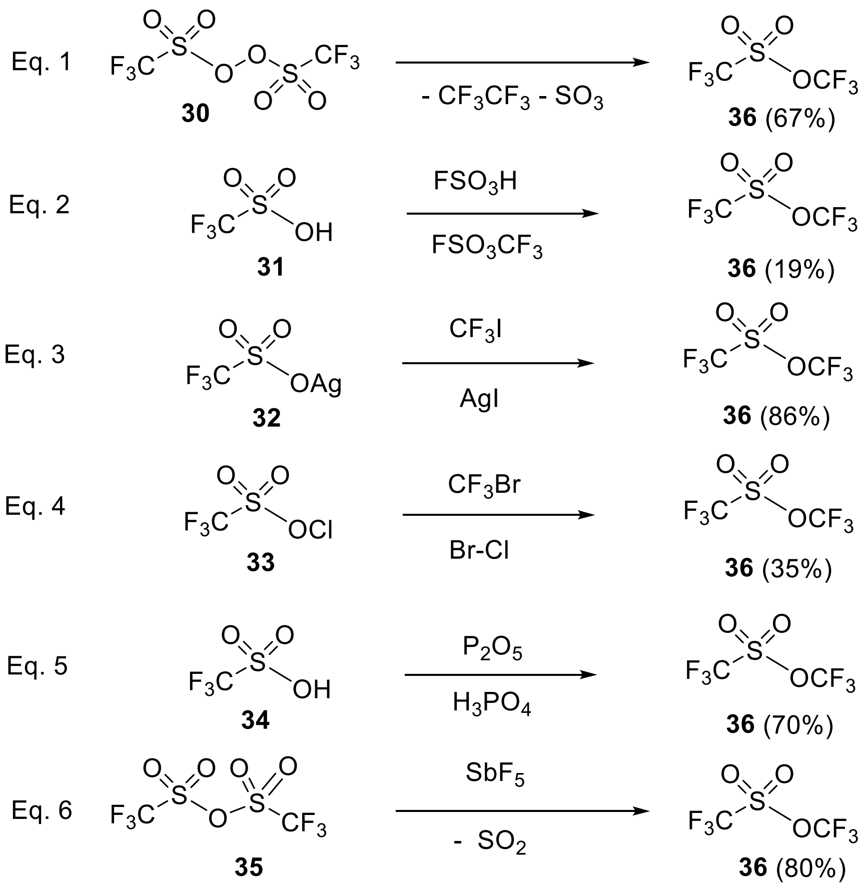
The regioselective trifluoromethoxylation of functionalized anilines, pyridines and pyrimidines is operationally simple and displayed high levels of functional group tolerance. However, this method is limited by preparation of protected *N*-(hetero)aryl-*N*-hydroxylamines precursors. Besides the products 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 applicationis expensive. Further development of the photocatalytic radical strategy using *N*-aryl-*N*-hydroxylamides 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

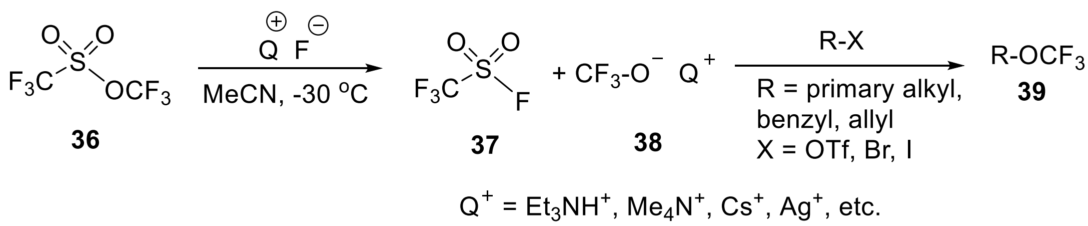
3.1.1. Trifluoromethyl Trifluoromethanesulfonate (TFMT)

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_2O [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].



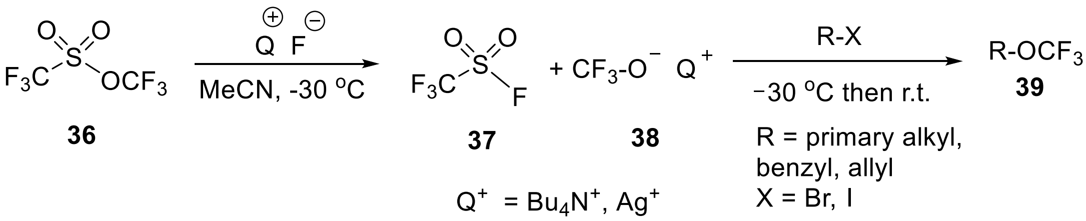
Scheme 24. Known methods for preparation of TFMT **36**.

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 **37** (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].



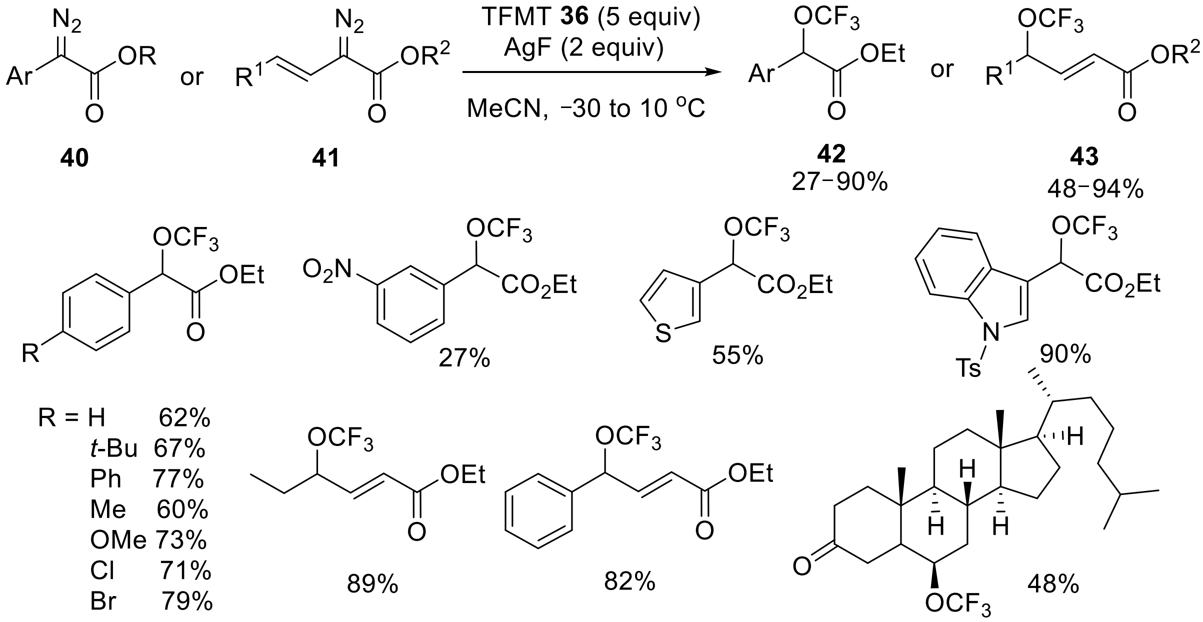
Scheme 25. Generation and reactivity of trifluoromethoxide salts **38**.

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 benzoyl 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.



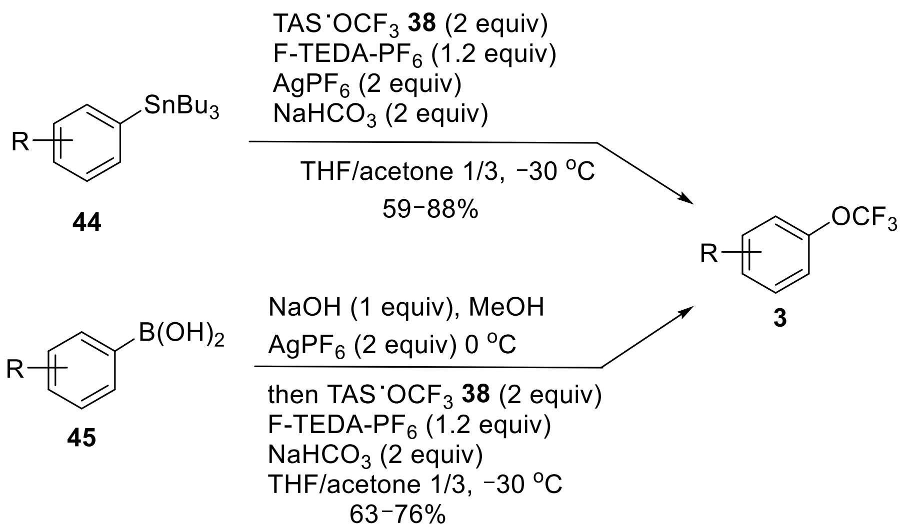
Scheme 26. Trifluoromethoxylation of alkyl bromides and iodides with trifluoromethoxide salts **38**.

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 resulted 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-trifluoromethoxyl 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 $AgOCF_3$. Interaction of Ag^+ ion with α-diazo esters generats the key alkyl–Ag^+ intermediate which could be further trifluoromethoxylated by CF_3O^- anion and the final products were obtained by quenching with water.



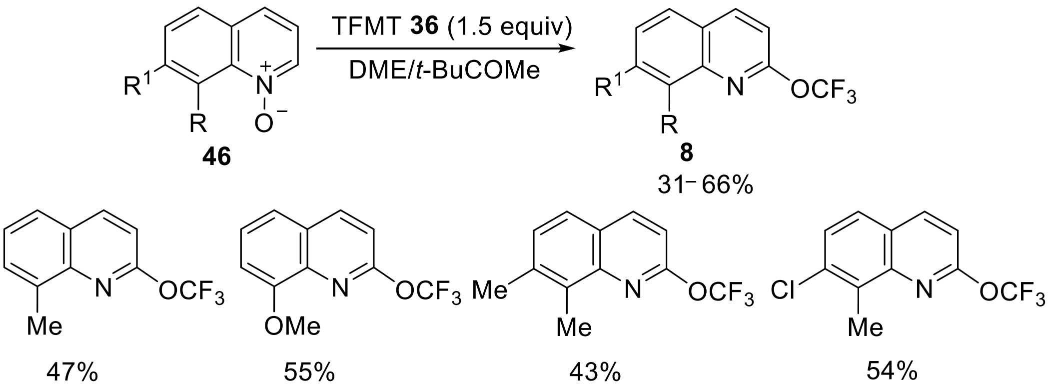
Scheme 27. Trifluoromethoxylation of α-diazo esters **40** and **41** with TFMT **36** and AgF.

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·OCF_3 **38** prepared in situ from TFMT **36** [115]. Treatment of aryl stannanes **44** with TAS·OCF_3 **38**, oxidant Selectfluor-PF_6, 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 $AgPF_6$ in methanol into corresponding aryl silver complexes which were treated with TAS·OCF_3 **38** and Selectfluor-PF_6 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 C_2-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**.

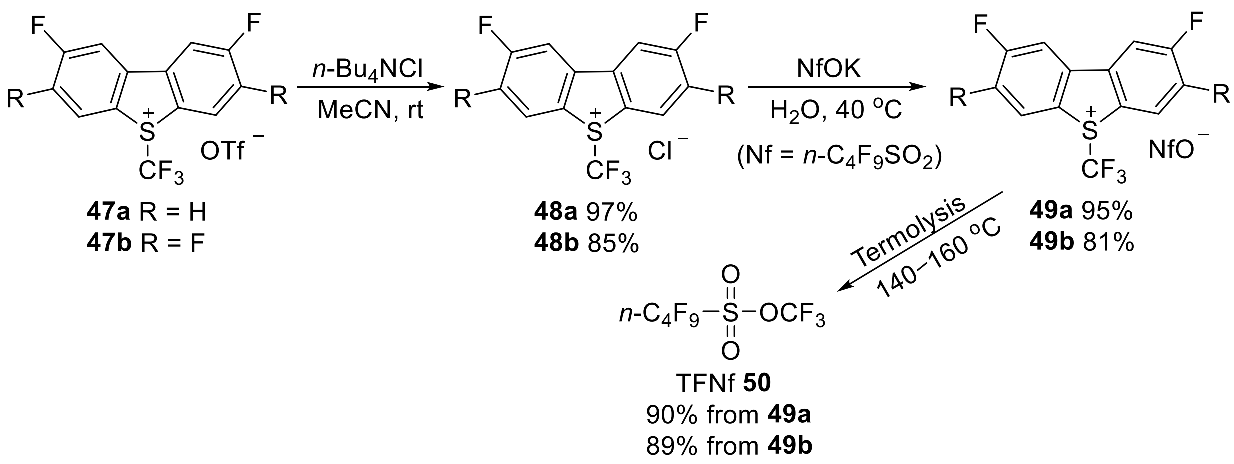


Scheme 29. Trifluoromethoxylation of quinoline *N*-oxides **46**.

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 trifluoromethoxylating reagents. However, the high volatility of TFMT (bp 19 °C) severely limits its synthetic application.

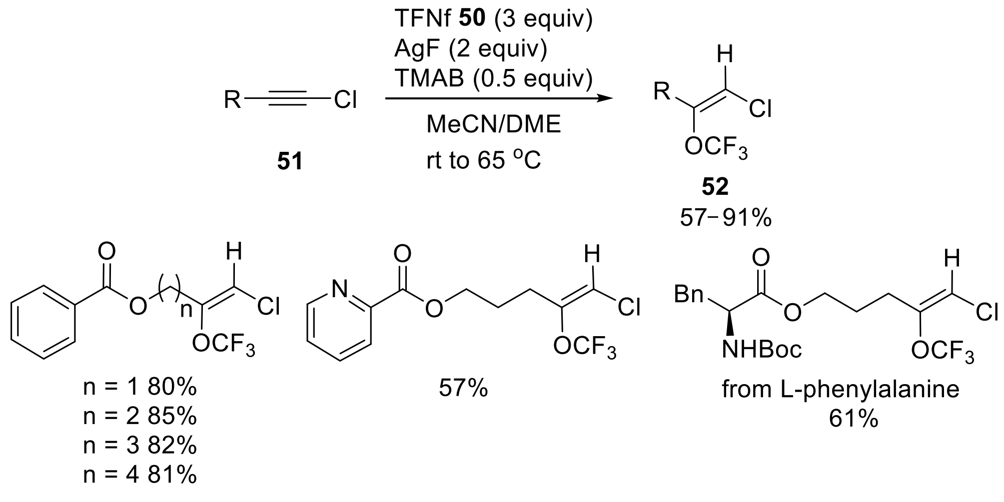
3.1.2. Trifluoromethyl Nonafluorobutanesulfonate (TFNf)

Recently, TFNf was developed as reactive and scalable nucleophilic trifluoromethoxylating 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 nonaflyl fluoride, which could easily be recovered after preparation of trifluoromethyl ethers and recycled.



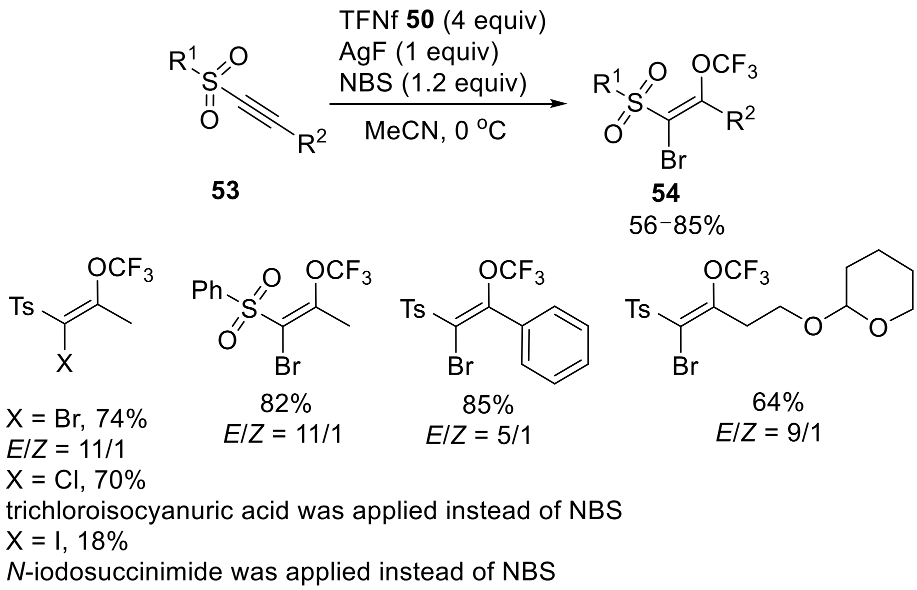
Scheme 30. Preparation of TFNf **50**.

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 CF_3-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.



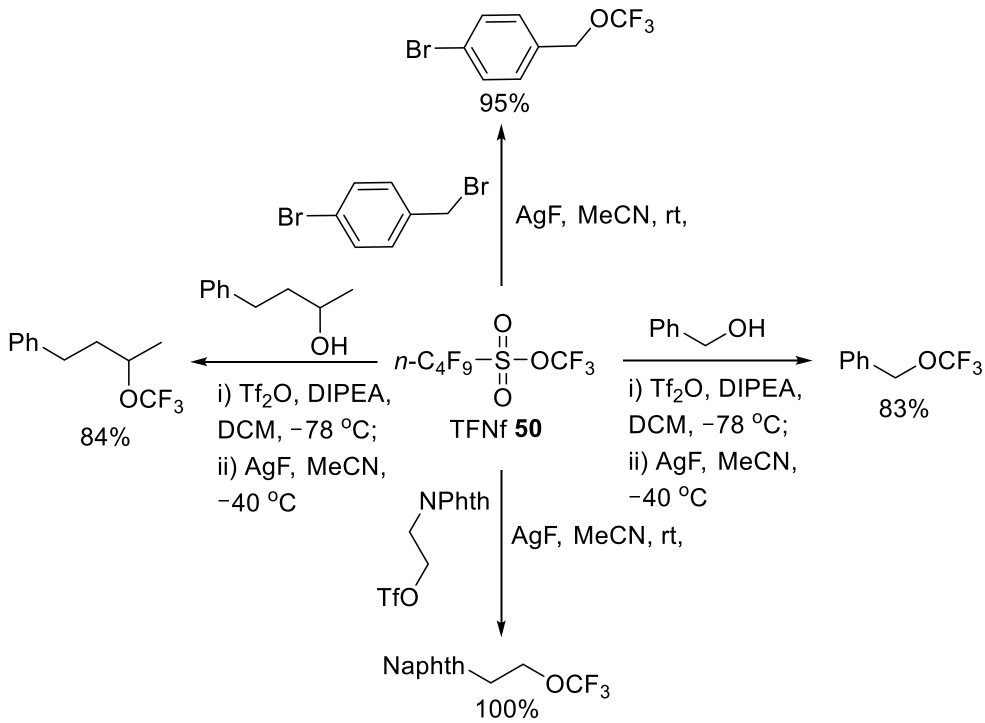
Scheme 31. Hydrotrifluoromethoxylation of 1-chloroalkynes **51**.

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 *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**.

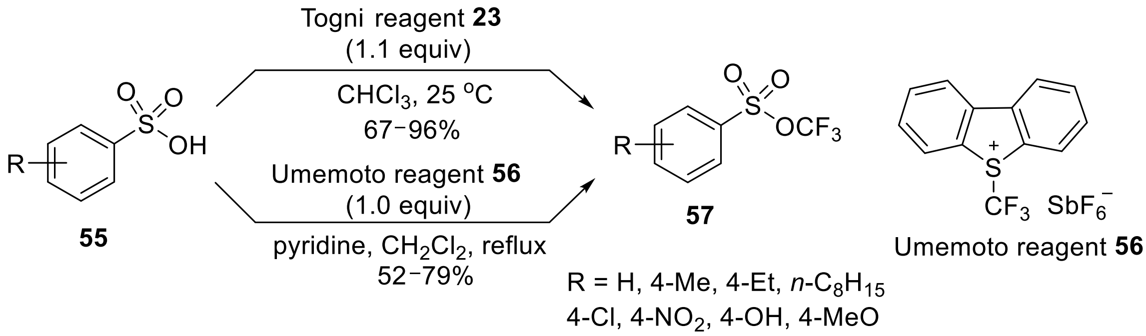
TFNf **50** (Scheme 33) under AgF-activation was found to be effective reagent for convertion of benzyl bromide and alkyl triflate to the alkyl trifluoromethyl ethers in excellent yields [125]. Furthermore, TFNf **50** could act as a nucleophilic trifluoromethoxylating reagent to perform one-pot synthesis of alkyl trifluoromethyl ethers from primary and secondary alcohols via triflates in high yields.



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

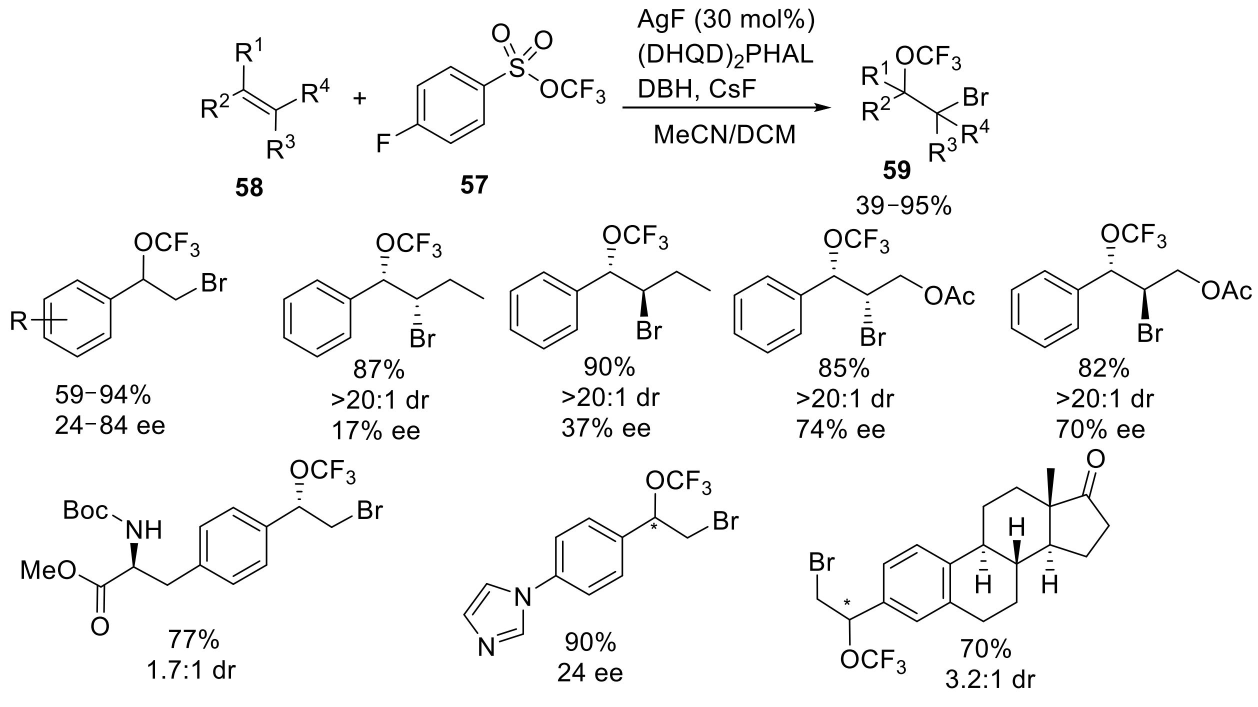
3.1.3. Trifluoromethyl Arylsulfonates (TFMS)

TFMSs are structural analogs of trifluoromethyl triflate that release the trifluoromethoxide anion due to the cleavage of the S-OCF_3 bond. The aryl group in TFMSs decreases their volatility and reactivity in comparison with TFMT. Synthesis of TFMS **57** (Scheme 34) was based on the electrophilic trifluoromethylation of aryl sulfonic acids **55** with both hypervalent iodine 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].



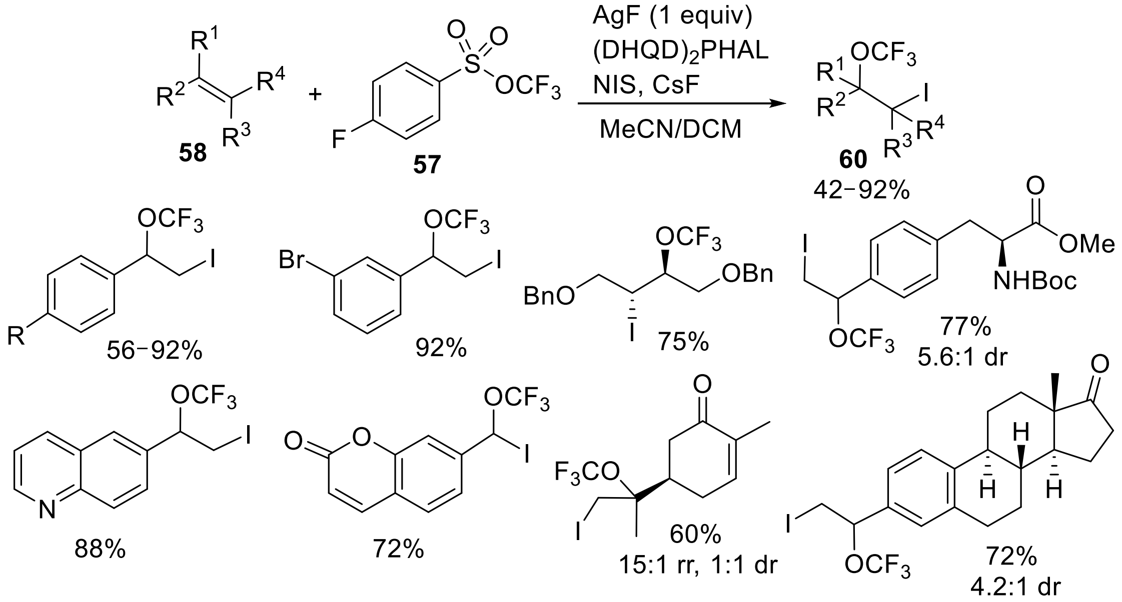
Scheme 34. Trifluoromethylation of arylsulfonic acids **55** using Togni reagent **23** and Umemoto reagent **56**.

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.



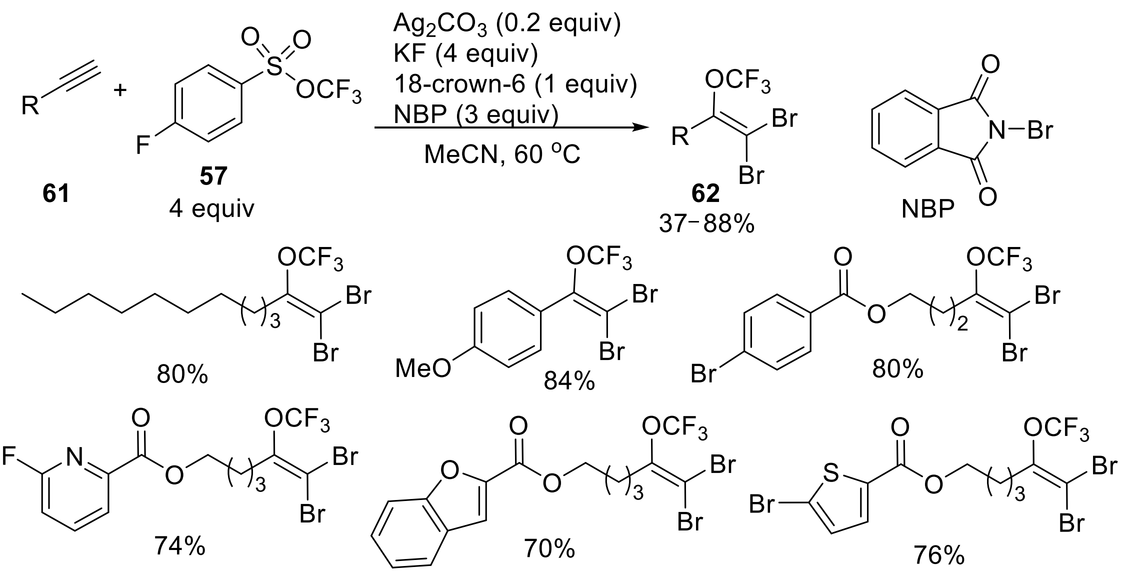
Scheme 35. Asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes **58**.

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.



Scheme 36. Silver-mediated intermolecular iodotrifluoromethoxylation of alkenes **58**.

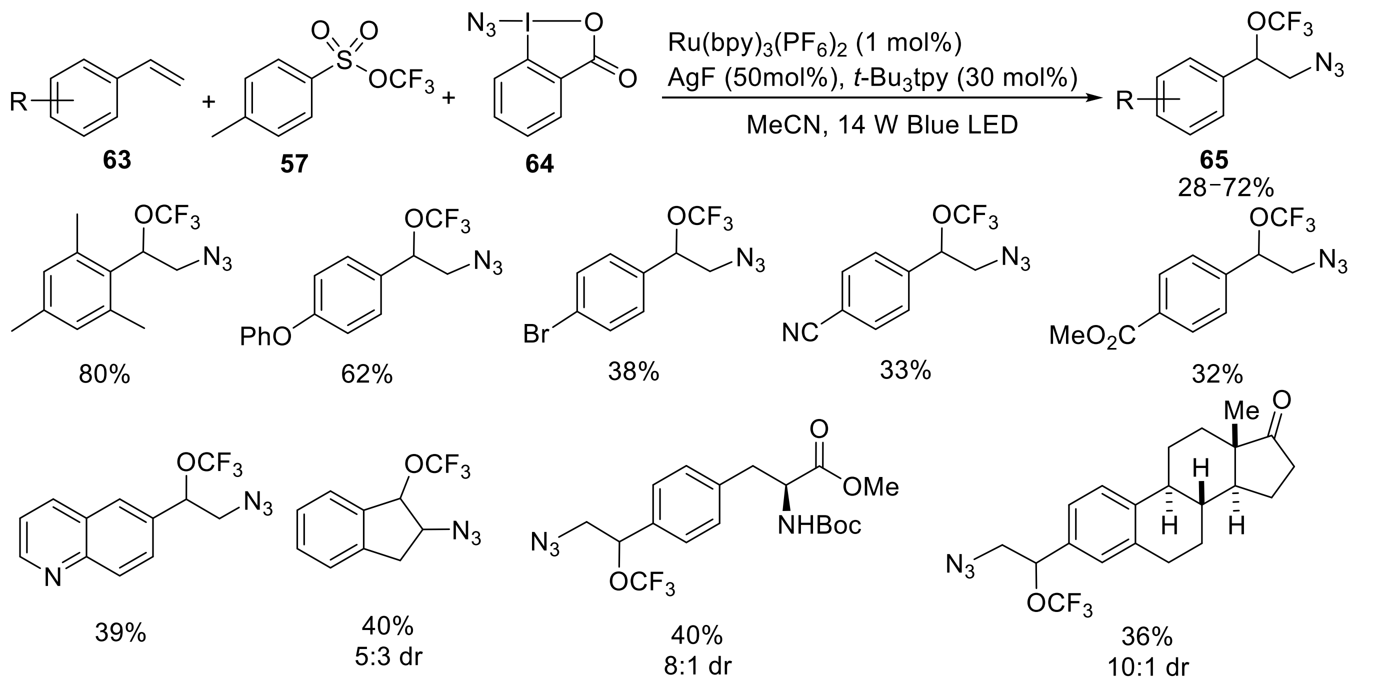
The reactivity of TFMS **57** (Scheme 37) with the range of terminal alkynes **61** was further explored [131]. The dibromotrifluoromethoxylated products **62** were obtained in the presence of KF, electrophilic bromination reagent and silver salt (Ag_2CO_3 or AgF) at low loadings (0.2 equiv), which 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.



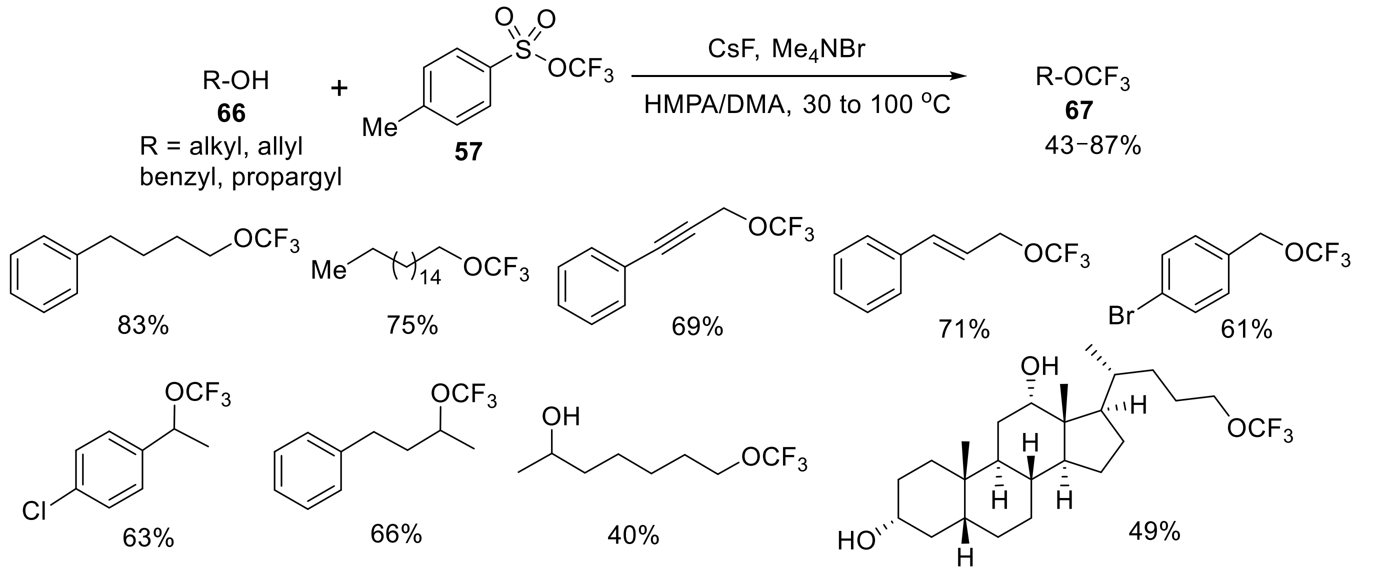
Scheme 37. Silver-catalyzed dibromotrifluoromethoxylation of terminal alkynes.

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.

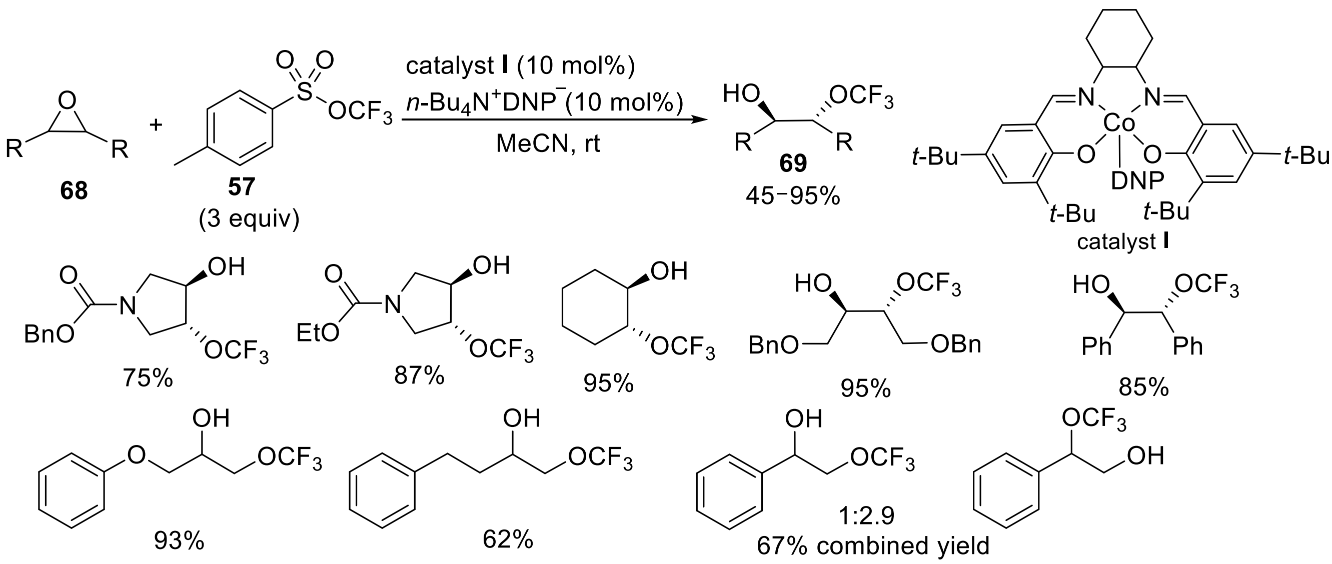


Scheme 38. Ag/Ru-catalyzed azidotrifluoromethoxylation of styrenes **63**.



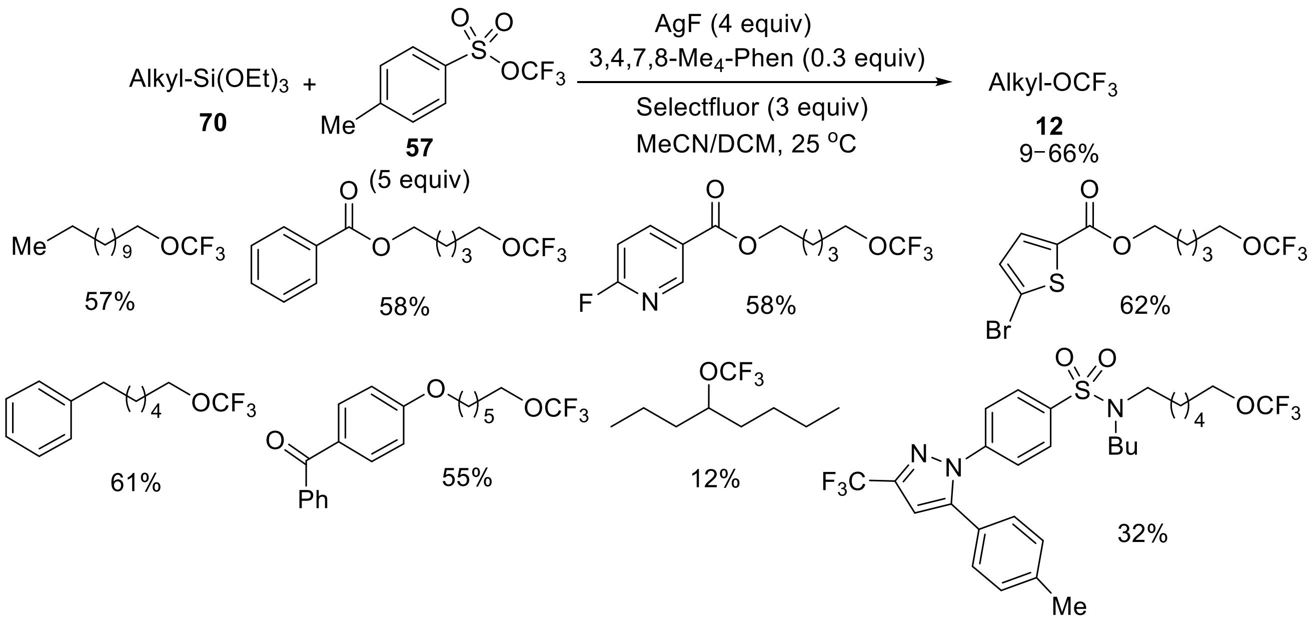
Scheme 39. Dehydroxytrifluoromethoxylation of alcohols **66**.

Cobalt-catalyzed trifluoromethoxylation of epoxides **68** was achieved by activation of TFMS **57** (Scheme 40) with 2,4-dinitrophenates [134]. The use of n-$Bu_4N^+DNP^-$ instead of fluorides to activate TFMS **57** enhanced nucleophilicity and stability of trifluoromethoxy anion as well as avoided formation of fluorinated byproducts. Under optimized conditions with TFMS **57**, catalyst **I**, n-$Bu_4N^+DNP^-$ 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.



Scheme 40. Cobalt-catalyzed trifluoromethoxylation of epoxides.

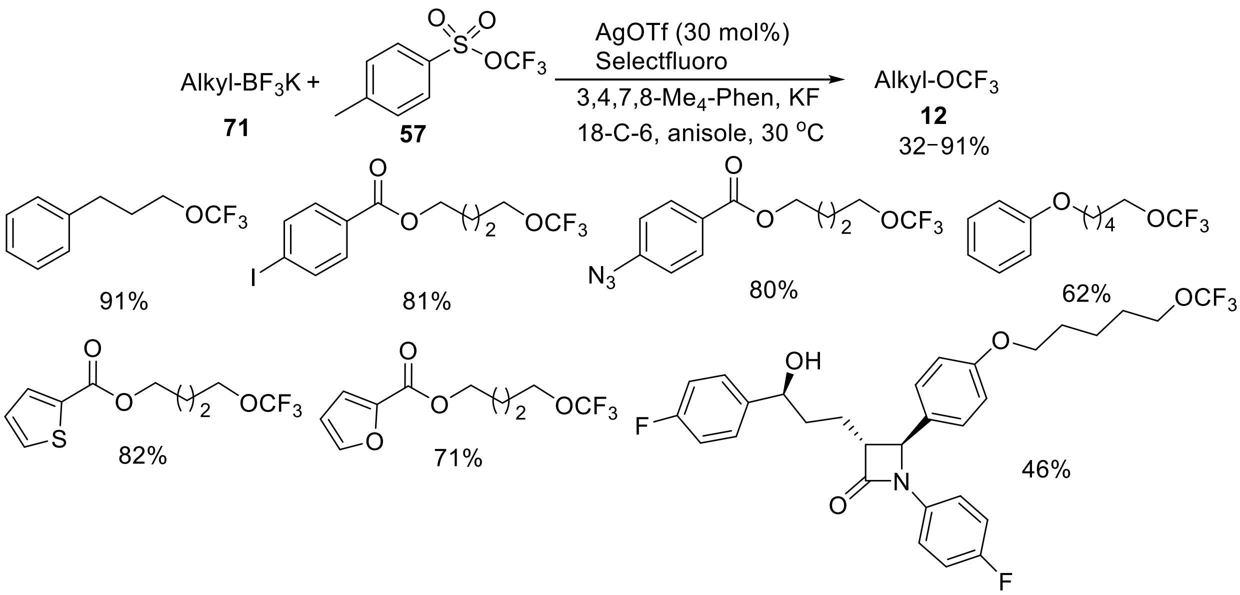
Trifluoromethoxylation of alkylsilanes **70** (Scheme 41) by TFMS **57** could be performed in the presence of a strong oxidant Selectfluor and silver fluoride as mediator as well as fluoride source [135]. The desired trifuoromethoxylated products **12** were obtained in good, isolated yields from primary 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.



Scheme 41. Silver-mediated oxidative trifluoromethoxylation of alkylsilanes **70**.

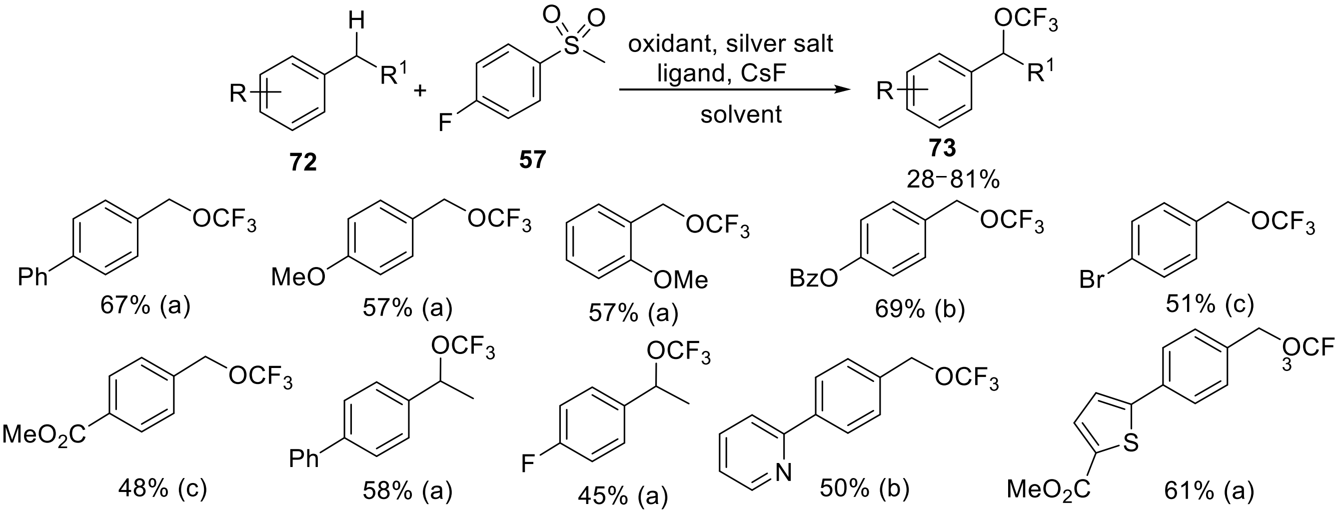
Analogous trifluoromethoxylation of alkyl trifluoroborates **71** (Scheme 42) by TFMS **57** was achieved under silver-catalyzed conditions [136]. This reaction was performed in the presence of AgOTf (30 mol %) and Selectfluor in anisole at 30 °C. Optimization experiments revealed that phenanthroline 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)OCF_3. This complex reacted with alkylborates to give alkyl radical and Ag(II)OCF_3 via single-electron oxidation. Finally, an alkyl radical was involved in a reaction with Ag(II)OCF_3 to form the desired trifluoromethyl ethers and regeneration of Ag(I).



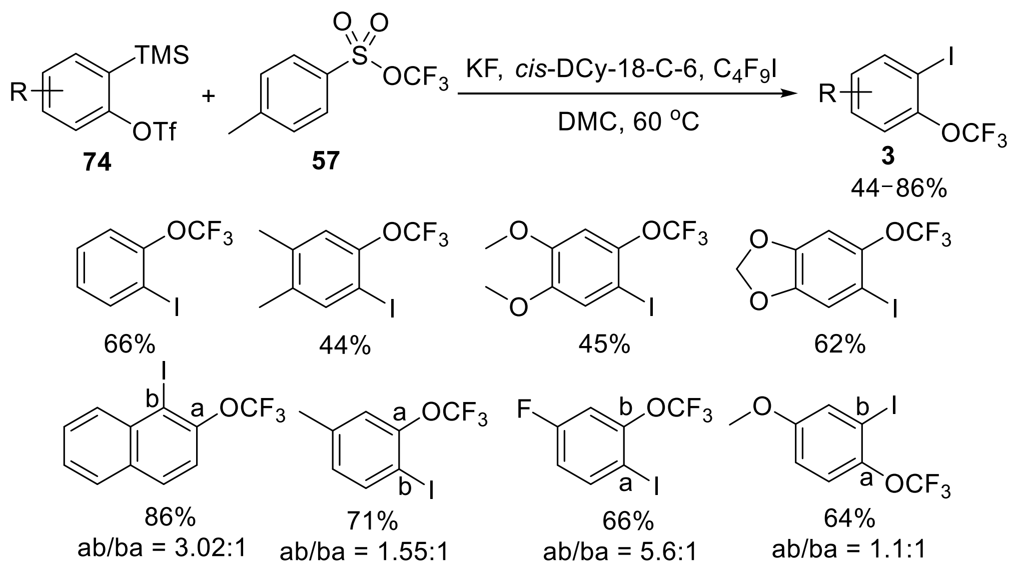
Scheme 42. Silver-catalyzed trifluoromethoxylation of alkyl trifluoroborates **71**.

TFMS were also employed in silver-promoted oxidative trifluoromethoxylation of benzylic C-H bond. Utilizing AgOTf as catalyst, various substrates **72** containing electron-donating and electron-withdrawing groups underwent trifluoromethoxylation of benzylic C-H bonds with trifluoromethyl TFMS **57** (Scheme 43) in the presence of such oxidants as $K_2S_2O_8$, F-TEDA-OTf or AgF_2 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 trifluoromethoxylation 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 OCF_3 anion could explain the results of the process.



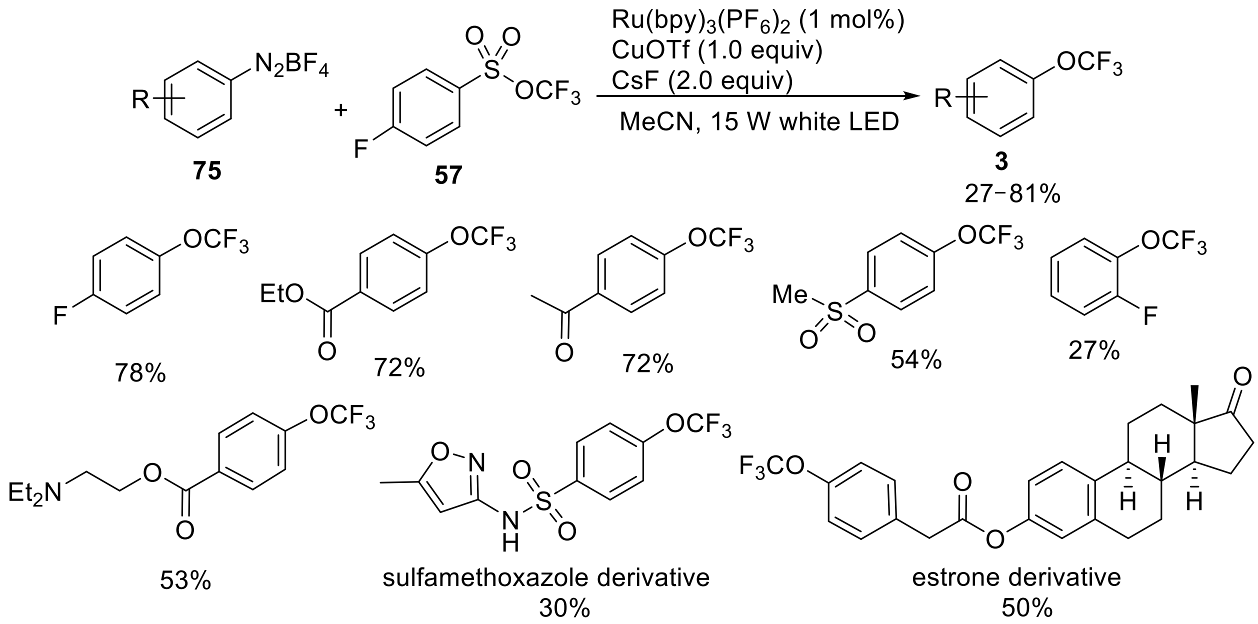
Scheme 43. Silver-promoted benzylic C-H trifluoromethoxylation (a: **57** (5.0 equiv), $K_2S_2O_8$ (3.0 equiv), AgOTf (30 mol%), 1,10-phenanthroline-5,6-dione (5 mol%), CsF (4.0 equiv), 50 °C, DMC, N_2. b: **57** (3.0 equiv), F-TEDA-OTf (3.0 equiv), AgOTf (30 mol%), 1,10-phenanthroline-5,6-dione (5 mol%), 4,7-diphenyl-1,10-phenanthroline (5 mol%), CsF (4.0 equiv), 25 °C, DMC, N_2. c: **57** (4.0 equiv), AgF_2 (6.0 equiv), 4,4′-dimethoxy-2,2′-bipyridine (10 mol%), di(2-pyridinyl)methanone (10 mol%), 25 °C, MeCN, N_2).

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 *o*-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 *o*-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.



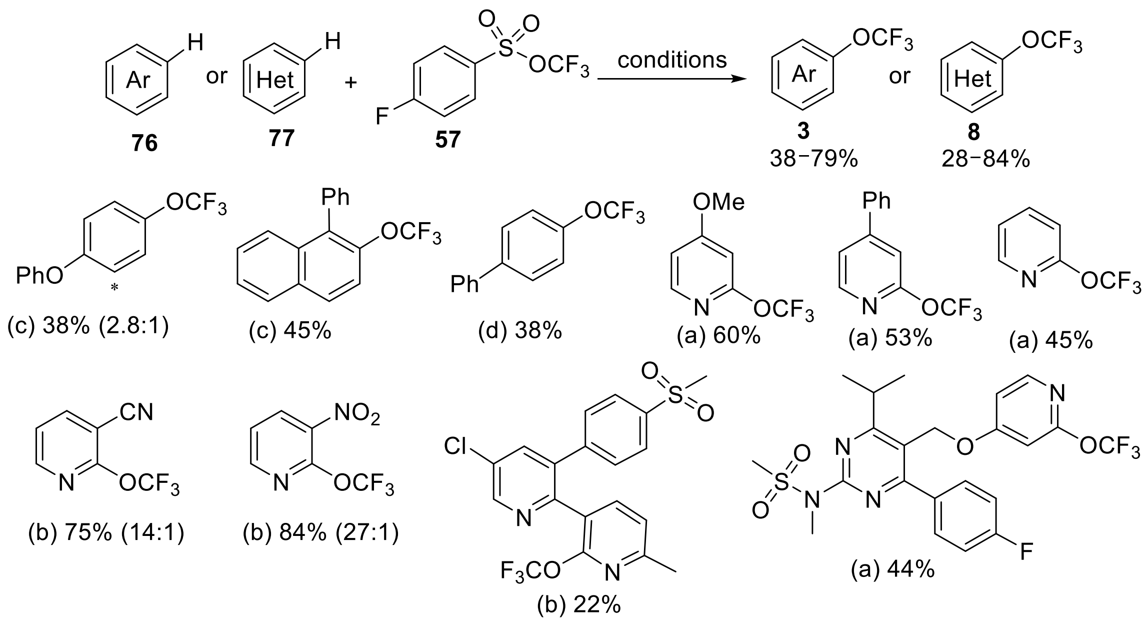
Scheme 44. One pot synthesis of *o*-trifluoromethoxylated iodoarene **3**.

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 aryldiazonium salts **75**, trifluoromethyl 4-fluorobenzenesulfonate **57**, CuOTf (1.0 equiv), CsF, and $[Ru(bpy)_3](PF_6)_2$ afforded the desired aryl trifluoromethyl ethers **3** with yields ranging from 27% to 81%. Electron-rich and electron-poor substrates **75** were efficiently trifluoromethoxylated, 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 trifluoromethoxylated products under the reaction conditions. The mechanistic study indicated that $Cu(II)(OCF_3)_2$ complex generated from trifluoromethyl arylsulfonate, CsF and CuOTf reacted with aryl radical generated from the excited state of photocatalyst and aryldiazonium salt to provide the aryl trifluoromethyl ether and regenerate Cu(I).



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 CF_3O-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 $Ag(II)OCF_3$ obtained by the combination of AgF_2 as the silver salt, Selectfluor as the oxidant, and TFMS **57** [140]. In addition, CsF was used as fluoride source for generation of CF_3O^- 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*-trifluoromethoxylated products **8** in good yields. This method could be also extended to pyridines **77** with electron-withdrawing substituents using AgF_2 as the oxidant and fluoride source. Thus, electron-deficient pyridines were selectively *ortho*-trifluoromethylated in moderated yields. The method tolerated a large range of functional groups, and several pharmaceutical and natural products could be directly trifluoromethylated to achieve the corresponding trifluoromethoxylated products.

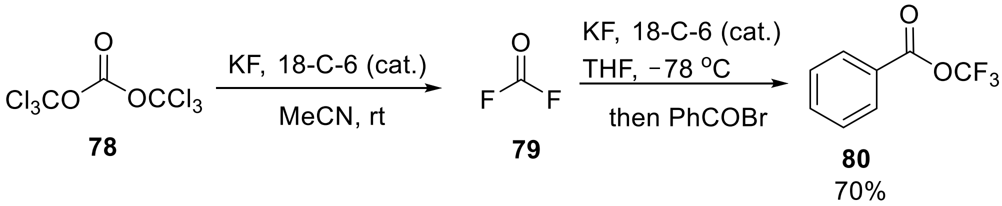


Scheme 46. Direct C-H trifluoromethoxylation of arenes and heteroarenes ((**a**): AgF_2 (1.0 equiv), **57** (3.0 equiv), Selectfluor (2.0 equiv), CsF (3.0 equiv), DMC, 35 °C; (**b**): AgF_2 (4.0 equiv), **57** (4.0 equiv), MeCN, 10 °C; (**c**): AgF_2 (1.0 equiv), **57** (4.0 equiv), Selectfluor (2.0 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_2 (4.0 equiv), **57** (4.0 equiv), di(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 trifluoromethoxylation 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.

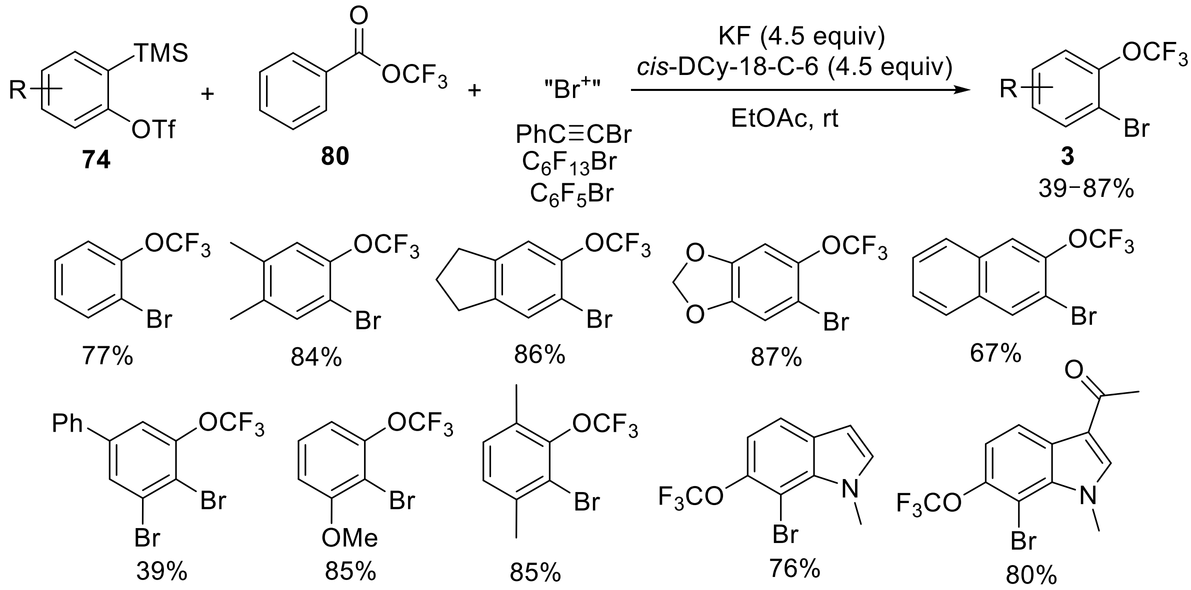
3.1.4. Trifluoromethyl Benzoate (TFBz)

TFBz **80** (Scheme 47) is a thermally stable liquid, which can be easily activated by fluoride anion to release CF_3O 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 benzoyl 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.



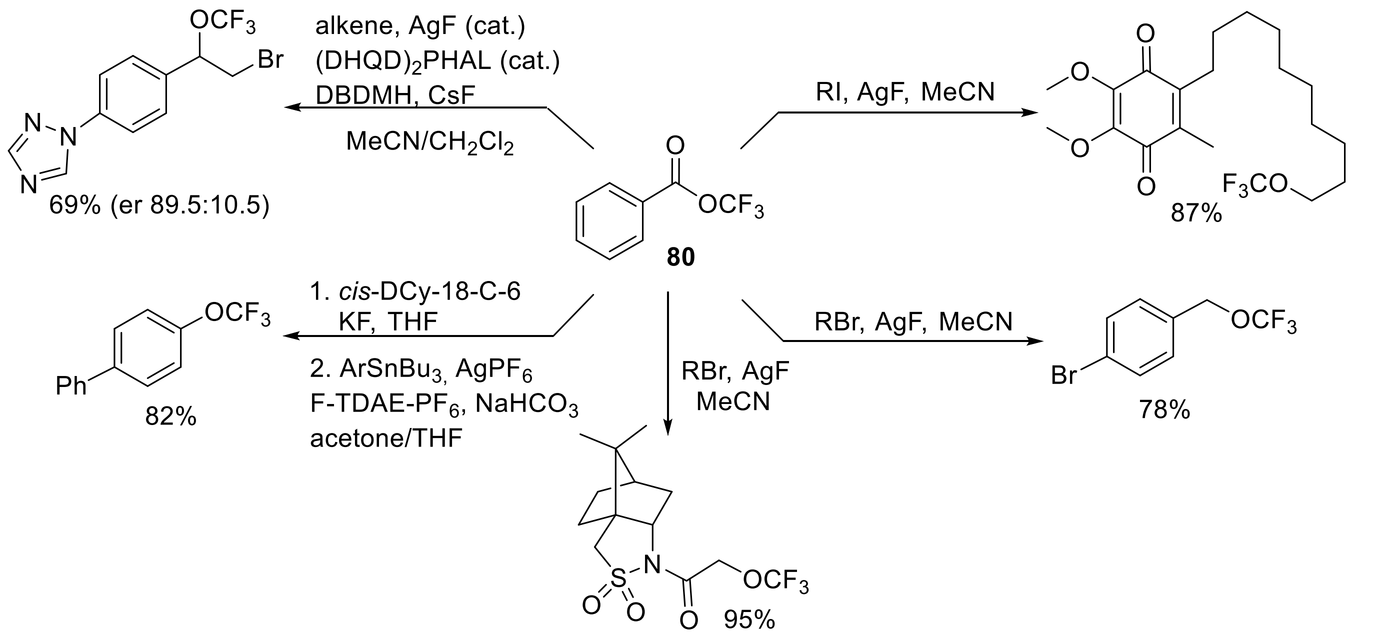
Scheme 47. Preparation of TFBz **80**.

Synthesis of a series of *ortho*-bromoaryl trifluoromethyl ethers **3** (Scheme 48) involving aryne 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, $C_6F_{13}Br$ or C_6F_5Br 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 C_6F_5I and CCl_4 as halogenation reagents afforded *ortho*-trifluoromethoxylated iodo- and chloroarenes respectively while in the absence of a halogenation reagent trifluoromethoxylation–protonation products were formed in good yield.



Scheme 48. Trifluoromethoxylation—bromination of ortho-(trimethylsilyl)aryl triflates **74**.

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.

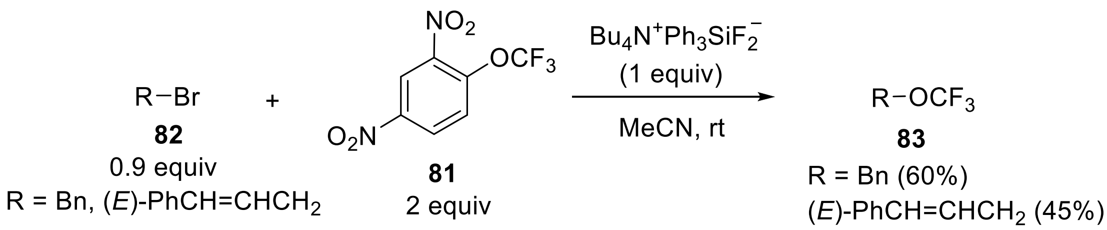


Scheme 49. Trifluoromethoxylations with TFBz **80**.

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.

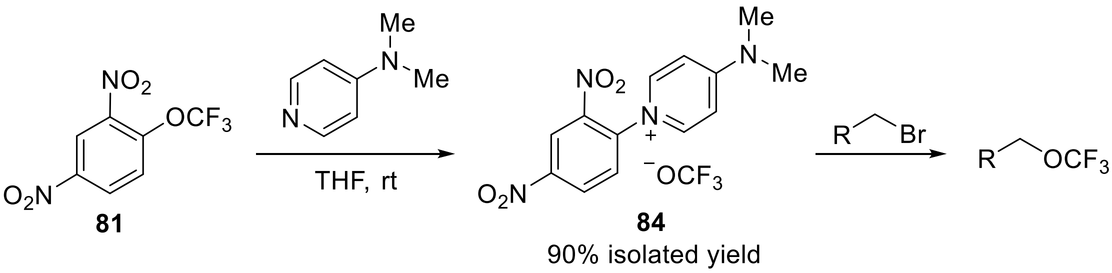
3.1.5. 2,4-Dinitro(Trifluoromethoxy)Benzene (DNTFB)

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 benzyl 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.



Scheme 50. Trifluoromethoxylation of benzyl and allylic bromides with DNTFB **81**.

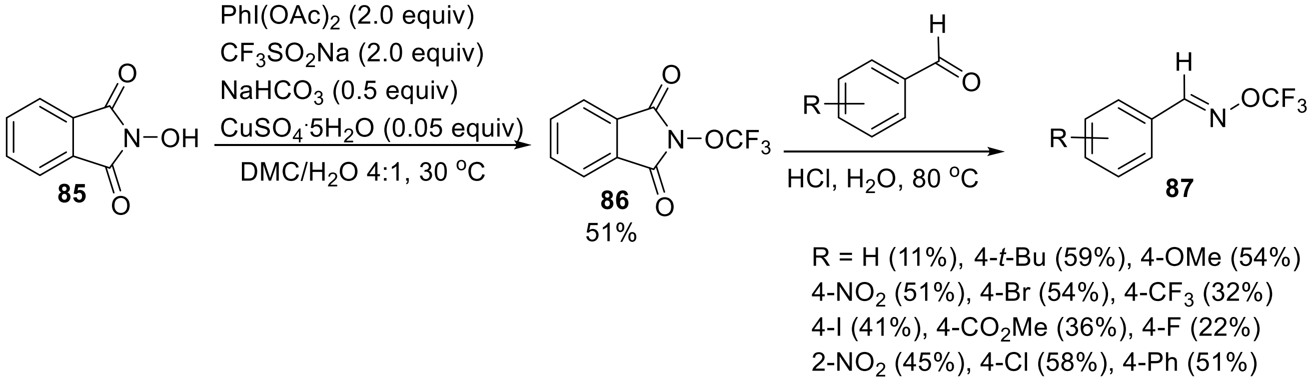
Thus, DNTFB showed low reactivity and very limited scope. Nevertheless, isolable pyridinium trifluoromethoxide salt **84** was easily prepared from the reaction of DNTFB **81** (Scheme 51) with 4-dimethylaminopyridine [143]. This salt was an effective trifluoromethoxide source for S_N2 reactions to form trifluoromethyl ethers.



Scheme 51. Preparation of pyridinium trifluoromethoxide salt **84**.

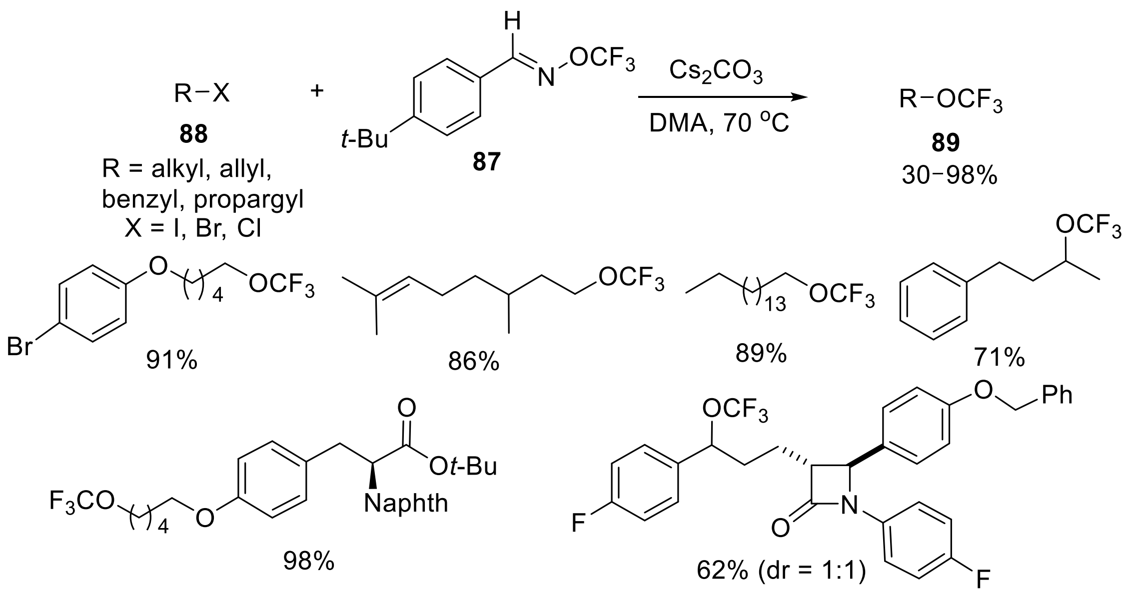
3.1.6. (E)-O-Trifluoromethylbenzaldoximes (TFBO)

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 CF_3 source and phenyliodine(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 Cs_2CO_3 as optimal base in DMA, followed by reaction of the resulting $CsOCF_3$, (detected by ^{19}F NMR) with unactivated alkyl iodides, bromide, and chloride **88** without any metal assistance allowed 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 then 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.

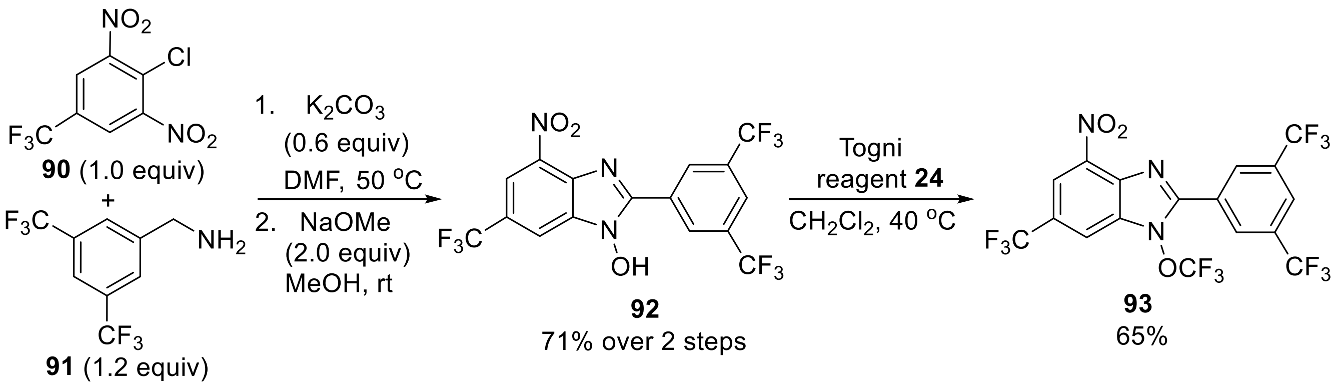


Scheme 53. Base-promoted trifluoromethoxylation of alkyl halides with TFBO **87**.

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*-OCF_3 bond providing •OCF_3 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 benzylamine **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 CH_2Cl_2 at 40 °C led to 1-trifluoromethoxybenzimidazole **93** in good yield.

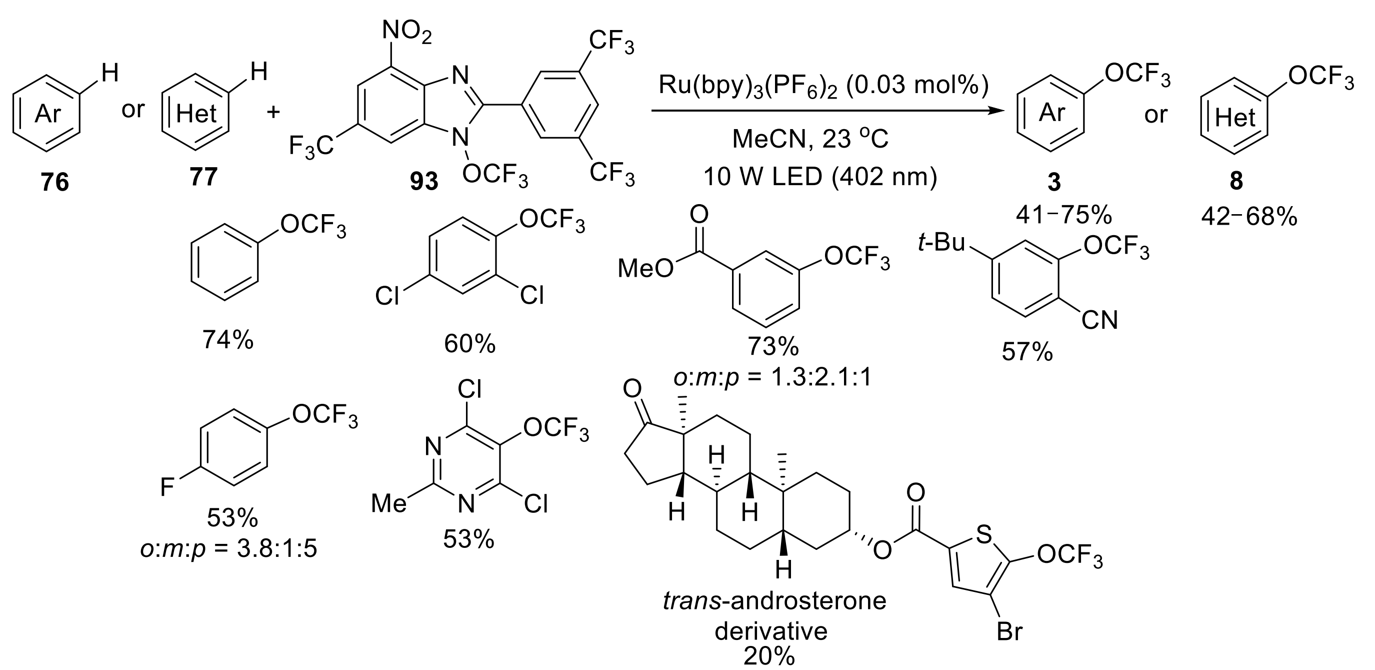


Scheme 54. Preparation of 1-trifluoromethoxybenzimidazole **57**.

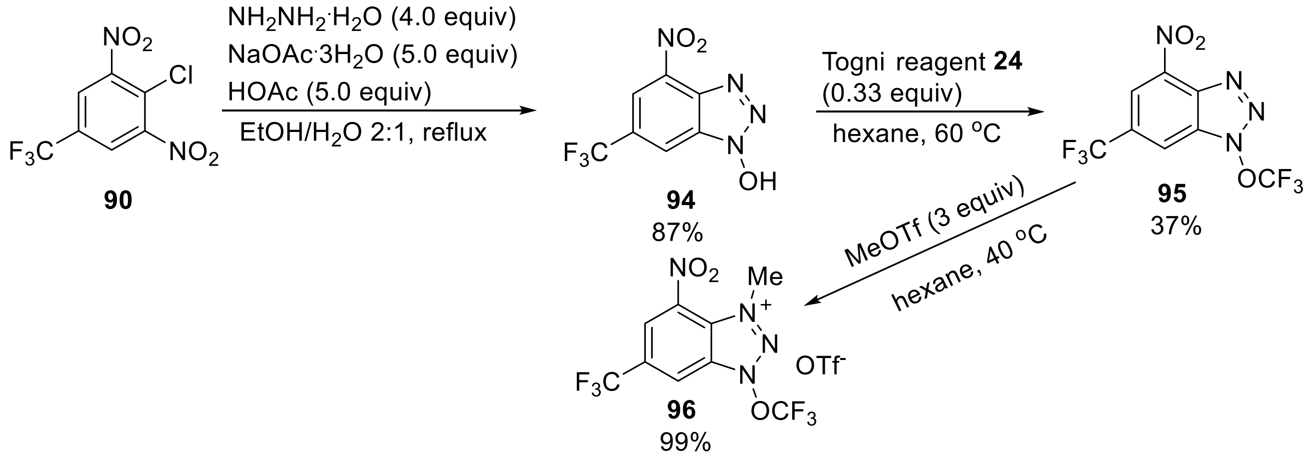
Reaction of 1-trifluoromethoxybenzimidazole **93** (Scheme 55) with arenes **76** in the presence of a redox-active catalyst under irradiation with violet LED light in MeCN at room temperature afforded aryl trifluoromethyl ethers **3** in moderate to good yields [59,60,144]. Use of the photocatalyst $[Ru(bpy)_3](PF_6)_2$ (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, nitrile, 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 OCF_3 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 photoexcitation of 1-trifluoromethoxybenzimidazole **93** followed by a homolytic cleavage of the *N*–OCF_3 bond to generate OCF_3 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 trifluoromethoxylation of arenes and heteroarenes demonstrated that 3-methyl-1-trifluoromethoxybenzotriazolium triflate **96** (Scheme 56) could generate OCF_3 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.

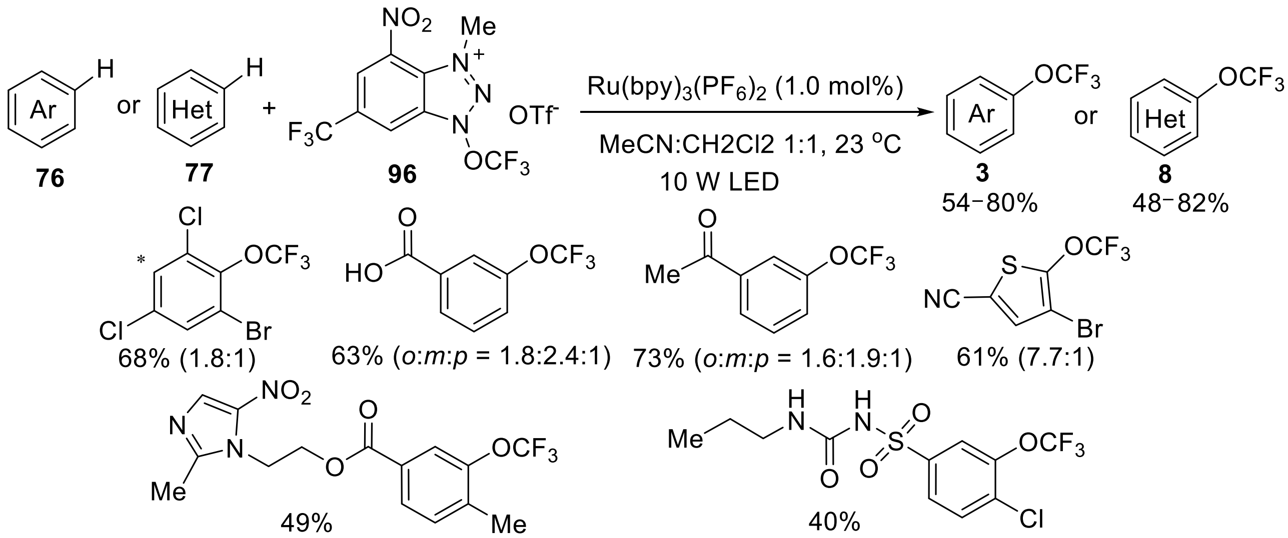


Scheme 55. C-H Trifluoromethoxylation of arenes and heteroarenes with reagent **93**.



Scheme 56. Preparation of 3-methyl-1-trifluoromethoxybenzotriazolium triflate **96**.

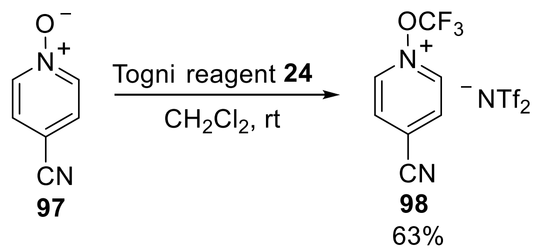
Investigation of various reaction parameters showed that irradiation with blue light of 1-trifluoromethoxybenzotriazolium triflate **96** (Scheme 57) and 10 equivalents of structurally diverse arenes **76** or heteroarenes **77** in the presence of photoredox catalysis $Ru(bpy)_3(PF_6)_2$ afforded the corresponding C-H trifluoromethoxylation products **3** or **8** in moderate to excellent isolated yields without any *N*-arylated side products [145]. 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 trifluoromethoxylated 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 **77** scope (pyridine, pyrimidine, and thiophene), including a number of examples of late-stage trifluoromethoxylation. 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 trifluoromethoxyl radical to arene forming the cyclohexadienyl radical followed by oxidation with $Ru(bpy)_3^{3+}$ and deprotonation afforded the trifluoromethoxylated product.



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

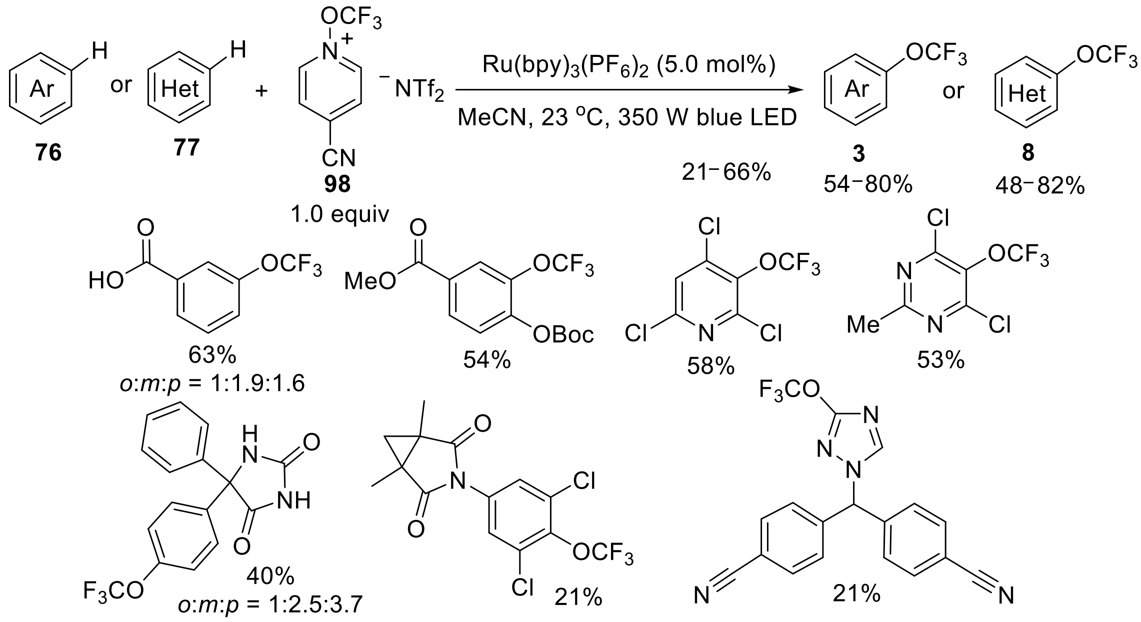
3.2.3. *N*-Trifluoromethoxypyridinium Salt **98**

4-Cyano substituted *N*-trifluoromethoxypyridinium 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 multigramgram scale by trifluoromethylation of 4-cyanopyridine *N*-oxide **97** using Togni reagent **24** [146]. Activation of Togni reagent **24** with *N*-trimethylsilylbis(trifluoromethanesulfonyl)imide allowed to be obtained 4-cyano-*N*-trifluoromethoxypyridinium salt **98** in 63% yield.



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

Reaction of arenes **76** or heteroarenes **77** (Scheme 59) with *N*-trifluoromethoxypyridinium 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*-trifluoromethoxypyridinium 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 $Ru(bpy)_3^{2+*}$ to $Ru(bpy)_3^{3+}$ 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 thrifluoromethoxy group. These include the reagents for nucleophilic as weel radical pathway for introduction of a CF_3-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 thrifluoromethoxylating reagents will be developed to overcome the current shortcoming.

Author Contributions: Conceptualization, J.H., A.E.S., V.A.S.; methodology, V.A.S.; literature revision, A.E.S., G.B., J.H. and V.A.S.; formal analysis, J.H., A.E.S., V.A.S.; writing—original draft preparation, Q.W., A.E.S., G.B., J.H. and V.A.S.; writing—review and editing, X.Z., J.H., A.E.S., G.B. and V.A.S.; visualization, J.H., V.A.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: V.A.S. gratefully acknowledges support from IKERBASQUE, the Basque Foundation for Science.

Conflicts of Interest: The authors declare no conflict of interest.

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