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Recent trends in dehydroxylative trifluoromethylation, -methoxylation, -methylthiolation, and -methylselenylation of alcohols

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Owing to the prevalence of hydroxyl groups on molecules, much attention has been paid to the synthesis of functionalized organic compounds by dehydroxylative functionalization of parent alcohols. In this context, dehydroxylative trifluoromethylation, trifluoromethoxylation, trifluoromethylthiolation, and trifluoromethylselenylation of readily available alcohols have recently emerged as intriguing protocols for the single-step construction of diverse structures bearing C–CF_3, C–OCF_3, C–SCF_3, and C–$SeCF_3$ bonds, respectively. This Mini-Review aims to summarize the major progress and advances in this appealing research area with special emphasis on the mechanistic features of the reaction pathways.

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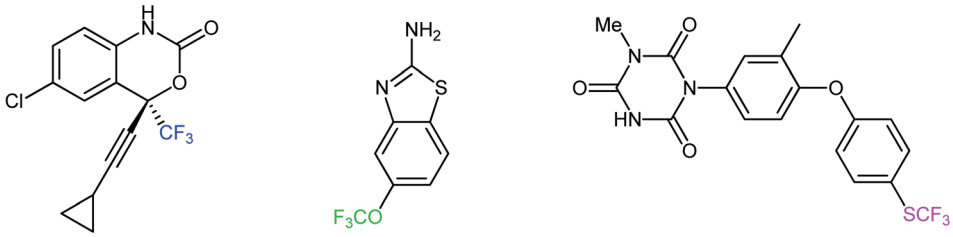

Efavirenz (anti-HIV drug) Riluzole (anti-glutamate drug) Toltrazuril (anti-coccidial drug)

Scheme 1 Selected examples of CF_3/OCF_3/SCF_3-based drugs.

1. Introduction

The incorporation of fluorinated moieties and particularly the trifluoromethyl (CF_3), trifluoromethoxy (OCF_3), trifluoromethylthio (SCF_3), and trifluoromethylseleno ($SeCF_3$) groups into organic molecules such as pharmaceuticals and agrochemicals can often substantially improve their physical, chemical, and biological properties because of the electronic properties, unique size, lipophilicity, and metabolic stability of these groups.[1,2] There are different examples of commercially available human and veterinary drugs that contain a CF_3, OCF_3, or SCF_3 moiety in their structures (Scheme 1).[3] However, there are no analogous CF_3Se-containing drugs, which is likely due to the limited synthetic options for their preparation.[4] Compounds containing the titled functionalities are versatile synthetic intermediates and can function as suitable building blocks for the preparation of many valuable functional materials.[5] Considering the widespread biological activities and synthetic usefulness of CF_3/OCF_3/SCF_3/$SeCF_3$-containing compounds, it has been of great synthetic interest to develop new, efficient, and practical methods for the introduction of these privileged moieties into organic molecules.[6–9]

In recent years, direct dehydroxylative functionalization of alcohols has become one of the hottest research topics in organic chemistry because it is a powerful and general strategy for the construction of various valuable functionalized organic compounds from inexpensive and abundantly available alcohols without isolation of intermediates.[10] In this regard, dehydroxylative trifluoro-methylation, -methoxylation, -methylthiolation, and -methylselenylation of alcohols have captured the imagination of the organic chemical community and have become promising synthetic methods for constructing C–CF_3, C–OCF_3, C–SCF_3, and C–$SeCF_3$ bonds, respectively. These synthetic processes are advantageous because the starting materials possess high selectivity and stability, are abundant and inexpensive, with low toxicity, and there is no need for isolation of intermediates. In continuation of our interest in organofluorine chemistry[11] and modern organic synthesis,[12–18] in this Mini-Review, we will highlight the most important advances and progress in the arena of dehydroxylative trifluoro-methylation, -methoxylation, -methylthiolation, and -methylselenylation of alcohols (Scheme 2), with a particular emphasis on the mechanistic aspects of the reaction pathways.

2. Dehydroxylative trifluoromethylation

After their seminal work on the conversion of allylic alcohols to trifluoromethanes through a two-step esterification/decarboxylative trifluoromethylation procedure,[19] Altman and

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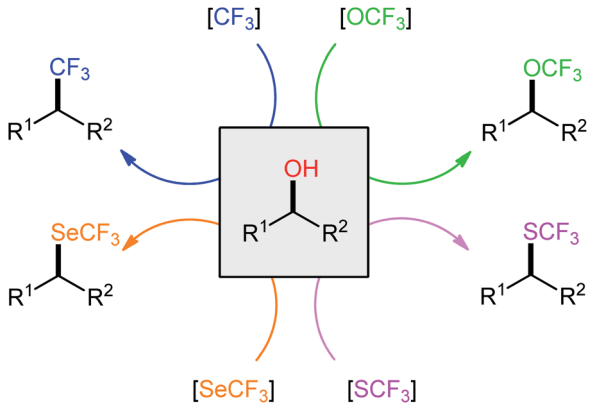
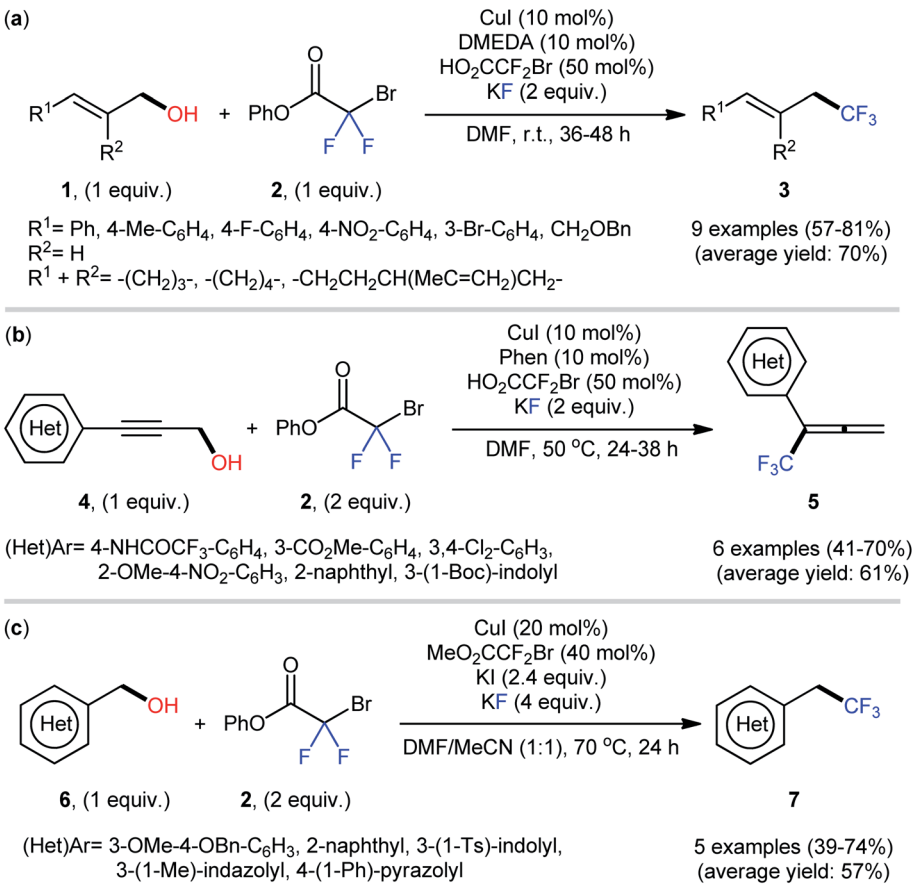
Esmail Vessally was born in Sharabiyan, Sarab, Iran, in 1973. He received his B.S. degree in pure chemistry from the University of Tabriz, Tabriz, Iran, and his M.S. degree in organic chemistry from Tehran University, Tehran, Iran, in 1999 under the supervision of Prof. H. Pirelahi. He completed his PhD degree in 2005 under the supervision of Prof. M. Z. Kassaee. Now he is employed at Payame Noor University as a Professor of organic chemistry. His research interests include theoretical organic chemistry, new methodologies in organic synthesis, and spectral studies of organic compounds.

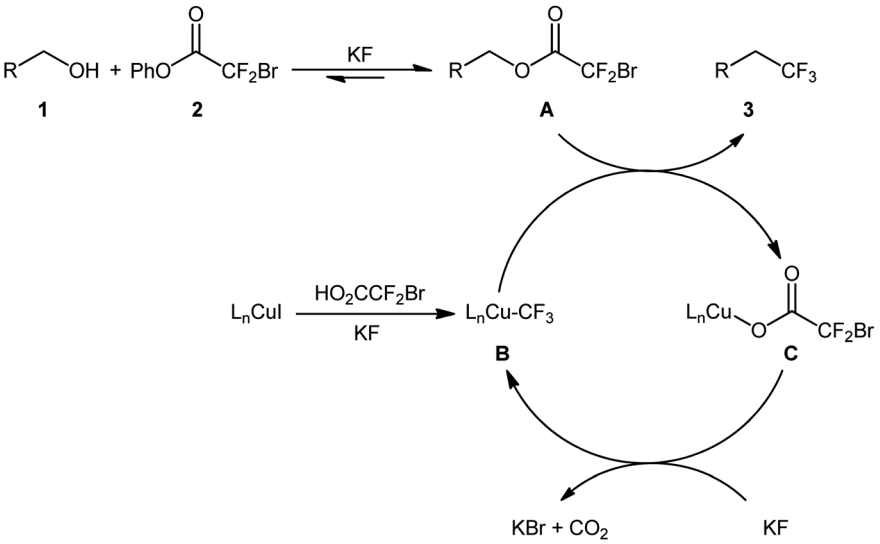


Scheme 2 Direct dehydroxylative trifluoro-methylation, -methoxylation, -methylthiolation, and -methylselenylation of alcohols.

colleagues developed bench-stable phenyl bromodifluoroacetate (PhO_2CCF_2Br) as a new nucleophilic trifluoromethylation reagent, which can directly convert alcohols to trifluoromethanes in a single operation without isolation of intermediates.[20] They showed that treatment of various allylic alcohols **1** with over-stoichiometric amounts of phenyl bromodifluoroacetate **2** in the presence of the CuI/DMEDA/HO_2CCF_2Br combination as a catalytic system in DMF at room temperature afforded the corresponding deoxytrifluoromethylated products **3** in good to high yields (Scheme 3a). The substrate scope was evaluated on nine terminally substituted allylic alcohols, which proved that various linear cinnamyl alcohols and endocyclic alkenols were compatible with this reaction. Moreover, this strategy was successfully applied for the direct deoxytrifluoromethylation of a series of propargylic alcohols **4** (by replacement of the DMEDA ligand with Phen) and (hetero)benzylic alcohols **6** (by employing MeO_2CCF_2Br reagent instead of HO_2CCF_2Br and using over-stoichiometric amounts of KI) (Scheme 3b and c). Of note, propargylic alcohols underwent rearrangement and resulted in allenylic structures. Furthermore, the synthetic utility of this procedure was highlighted by gram-scale synthesis of (4,4,4-trifluorobut-1-en-1-yl)benzene (75% yield on a 20 mmol scale). Finally, the synthetic potentiality of this strategy was showcased by preparing a fluorinated analogue of tebufenpyrad, an acaricide. Regrettably, the authors did not investigate the applicability of secondary and tertiary alcohols in their methodology. On the basis of several control experiments, a plausible mechanism was proposed by the authors for this trifluoromethylation protocol involving the following key steps (Scheme 4): (i) transesterification between phenyl

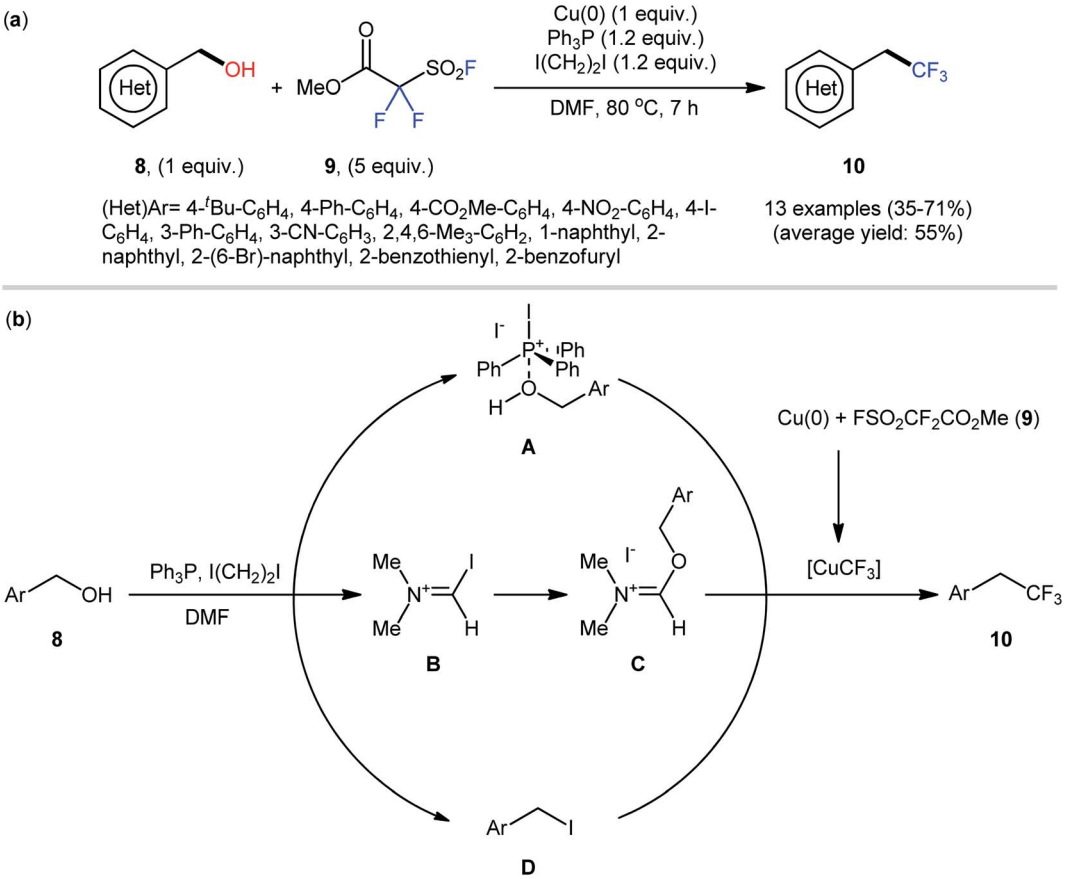


Scheme 3 Cu-catalyzed deoxytrifluoromethylation of (a) allylic alcohols **1**; (b) propargylic alcohols **4**; and (c) (hetero)benzylic alcohols **6** with phenyl bromodifluoroacetate **2** developed by Altman.

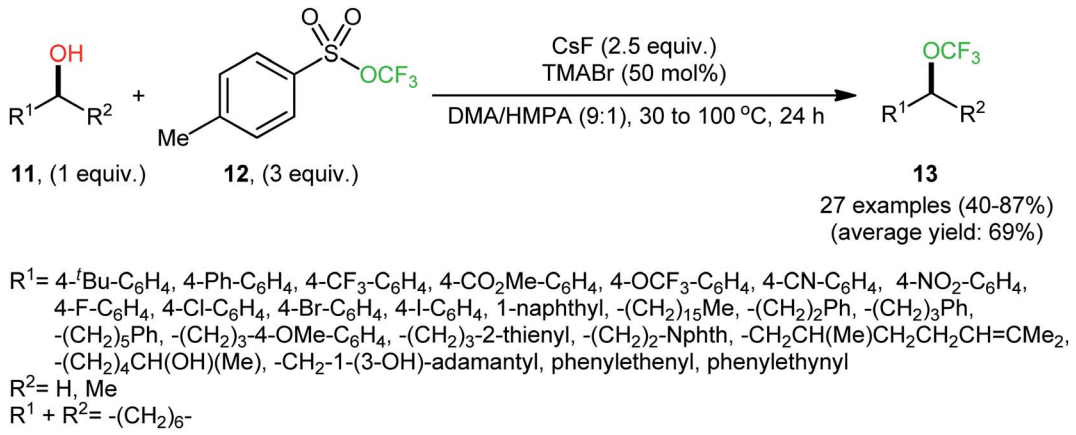


Scheme 4 The plausible mechanism for the reactions in Scheme 2.

bromodifluoroacetate **2** and the starting alcohol **1** to generate alkyl bromodifluoroacetate intermediate **A**; (ii) formation of the active Cu–CF_3 species **B** *via* interaction of the L_nCuI precatalyst with HO_2CCF_2Br; (iii) direct nucleophilic trifluoromethylation of intermediate **A** with Cu–CF_3 species **B** to give the desired product **3** and carboxylate-coordinated [Cu] complex **C**; and (iv) CO_2 liberation and halogen exchange to recover the active Cu–CF_3 species **B** and completion of the catalytic cycle.



Scheme 5 (a) Wu-Xiao's synthesis of (2,2,2-trifluoroethyl)arenes **10**. (b) The proposed pathways for the formation of (2,2,2-trifluoroethyl)arenes **10**.



Scheme 6 Metal-free direct dehydroxytrifluoromethoxylation of alcohols **11** with trifluoromethyl tosylate **12**.

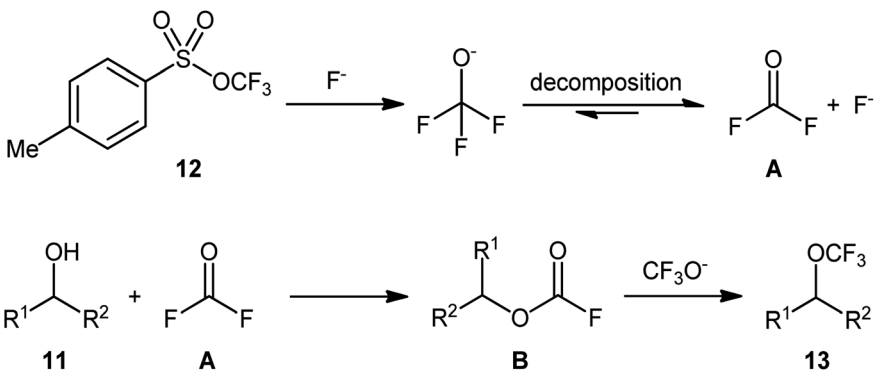
In another report, this research group also developed [1,1′-biphenyl]-4-yl-2-bromo-2,2-difluoroacetate (BBDFA) as an efficient trifluoromethylating reagent for Cu-catalyzed dehydroxylative trifluoromethylation of alcohols.[21] The reagent was synthetized on a 100 g scale in 93% yield *via* chlorination of commercially available bromodifluoroacetic acid with oxalyl chloride in the presence of a catalytic amount of DMF, followed by esterification of the resulting acid chloride with 4-phenylphenol, and it showed good thermal stability and high ability for trifluoromethylation of examined alcohols. However, the usefulness of this reagent was only demonstrated by deoxytrifluoromethylation of cinnamyl alcohol and 2-naphthalenemethanol, without any substrate scope exploration.

Drawing inspiration from these works, very recently, the Wu group, in collaboration with the Xiao group, described an interesting Cu(0)-catalyzed dehydroxylative trifluoromethylation of a library of (hetero)benzylic alcohols **8** with Chen's reagent (methyl fluorosulfonyldifluoroacetate; **9**) in the presence of the Ph_3P/ICH_2CH_2I system, which acted as the activator of the hydroxyl group.[22] The reactions were performed in DMF at 80 °C, tolerated a series of synthetically useful functionalities (*e.g.*, –Br, –I, $–CO_2Me$, –CN, $–NO_2$), and provided the desired (2,2,2-trifluoroethyl)arenes **10** in modest to good yields (Scheme 5a).

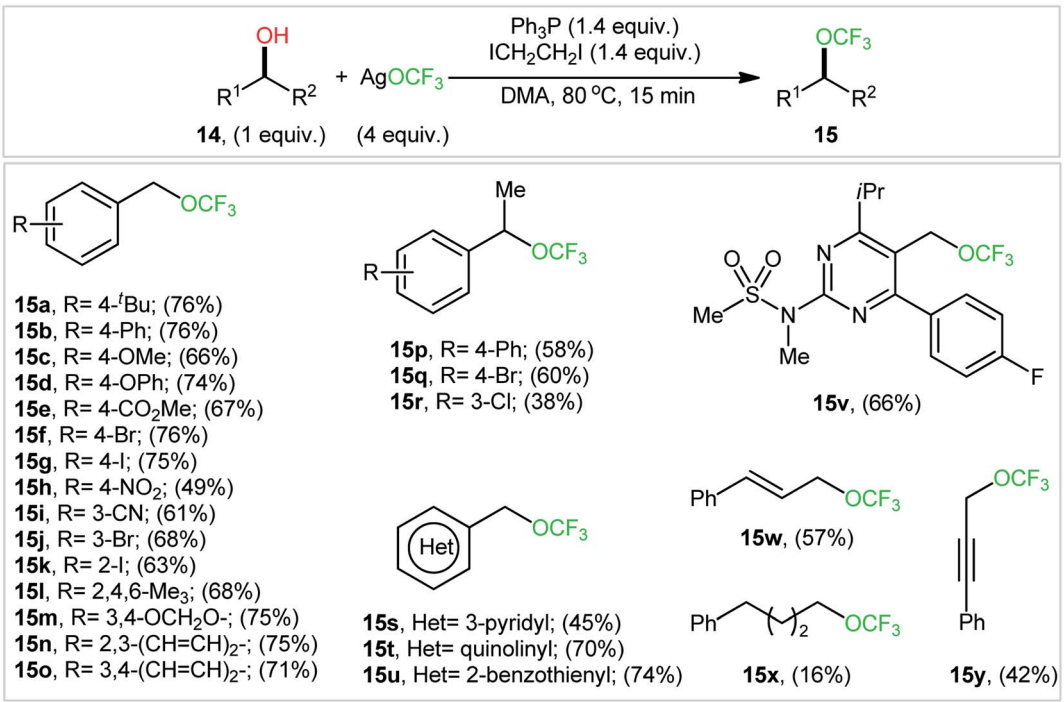
Regarding the influence of electronic effects of substituent groups in the phenyl ring periphery of benzylic alcohols, electron-rich substrates afforded higher yields compared to electron-poor ones. It is noteworthy that although aryl bromides remained intact under these conditions, undesired trifluoromethylation of C–I bonds was observed in the case of aryl iodides. Regrettably, alkyl alcohols did not exhibit reactivity under standard reaction conditions. It was noteworthy that under relatively similar conditions, dehydroxylative difluoromethylation and trifluoromethylthiolation of a diverse range of aliphatic alcohols with $TMSCF_2H$ and $AgSCF_3$, respectively, also effectively proceeded to afford the corresponding difluoromethylated and trifluoromethylthiolated compounds in reasonable yields. While the detailed mechanistic picture remains unclear, the authors speculated that phosphonium **A**, iminium **C**, or (hetero)benzyl halide **D** might be key intermediates for this trifluoromethylation reaction (Scheme 5b).

3. Dehydroxylative trifluoromethoxylation

At the outset of 2018, Tang and colleagues discovered that a combination of nucleophilic trifluoromethoxylating reagent **12** (trifluoromethyl tosylate), quaternary ammonium salt



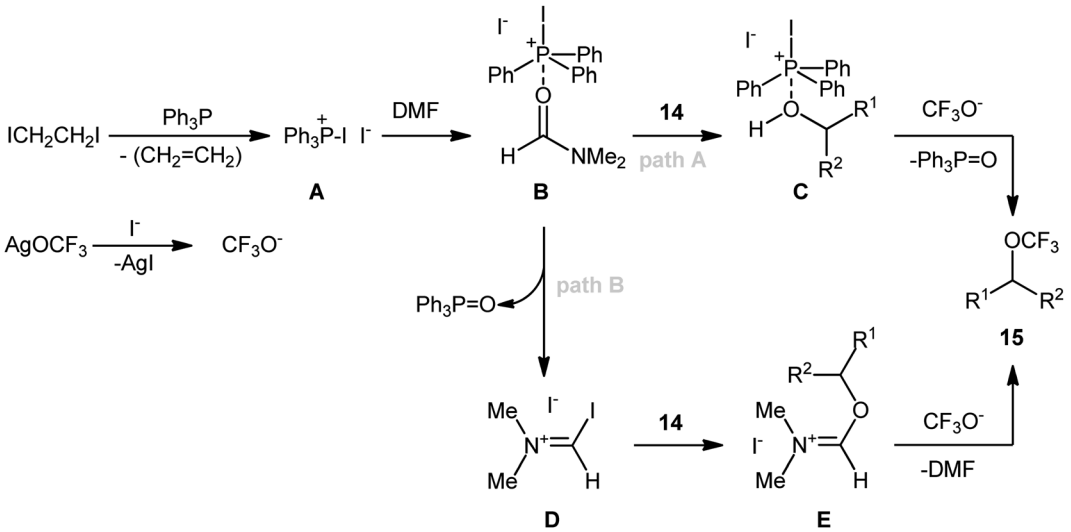
Scheme 7 Mechanism proposed to explain the formation of alkyl trifluoromethyl ethers **13**.



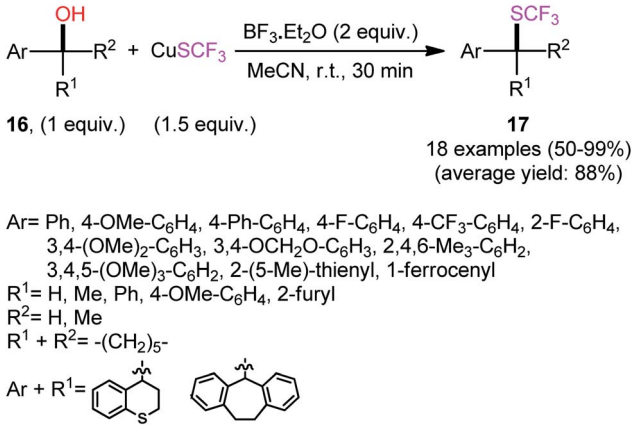
Scheme 8 Ph_3P/ICH_2CH_2I-promoted dehydroxylative trifluoromethoxylation of aliphatic alcohols **14** using $AgOCF_3$ as a nucleophilic trifluoromethoxylating reagent.

(tetramethylammonium bromide; TMABr), and fluoride source (CsF) enabled direct dehydroxylative trifluoromethoxylation of various primary and secondary alcohols **11**, giving the corresponding alkyl trifluoromethyl ethers **13** in moderate to high yields, ranging from 40% to 87% (Scheme 6).[23] The synthetic broad scope of the protocol was established using a library of various alkyl, benzyl, allyl, and propargyl alcohols. Significantly, the authors showcased the potentiality of this process by dehydroxytrifluoromethoxylation of complex bioactive molecules such as cholane-3,12,24-triol (a natural product) and pleuromutilin (an antibacterial drug). The reaction demonstrated a high degree of chemoselectivity, and in the presence of a secondary or tertiary alcohol, the reaction preferentially took place at the position of a primary alcohol.

Based on mechanistic studies (isotope labelling and ^{19}F NMR experiments), the author proposed a plausible mechanistic pathway for the above transformation, as depicted in Scheme 7.[24] The reaction begins with the release of trifluoromethoxide anion (CF_3O^-) from reagent **12** under the action of a fluoride salt. Subsequently, CF_3O^- undergoes



Scheme 9 Mechanistic proposal for the formation of trifluoromethyl ethers **15**.



Scheme 10 Lewis acid-mediated dehydroxylative trifluoromethylthiolation of benzylic alcohols **16** with $CuSCF_3$, as reported by Rueping.

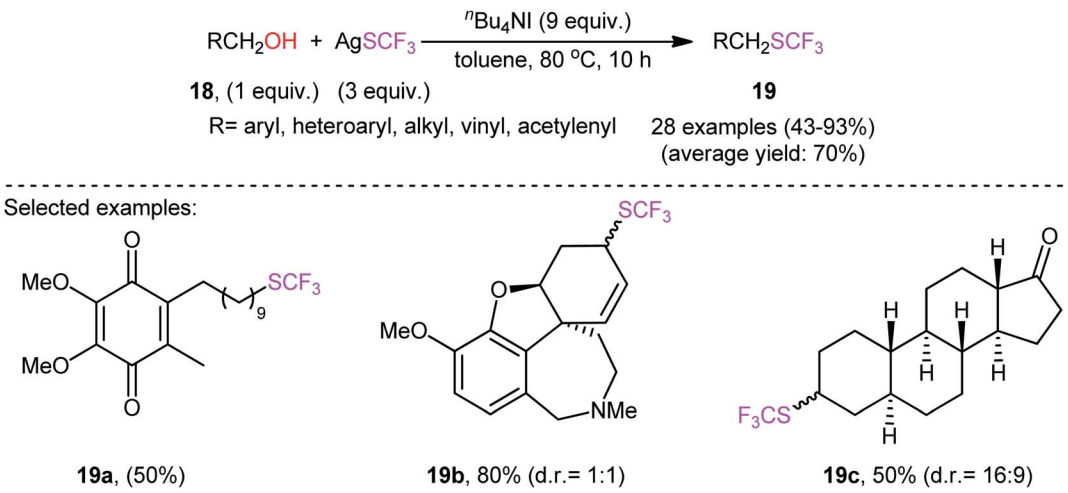
decomposition to produce carbonic difluoride **A** which, upon esterification with alcohol **11**, generates alkyl fluoroformate intermediate **B**. Finally, nucleophilic substitution reaction of activated species **B** with *in situ*-generated CF_3O^- affords the final product **13**. Of note, the studies indicated that the presence of TMABr in the reaction mixture is crucial for improving the nucleophilicity of OCF_3 anion, while in the absence of any quaternary ammonium salt, inferior results in terms of product yield were observed.

In an attempt to further demonstrate the strength of this novel and interesting alkyl trifluoromethyl ether synthesis, Lin and Xiao along with their co-workers documented an elegant Ph_3P/ICH_2CH_2I-promoted trifluoromethoxylation of aliphatic alcohols using $AgOCF_3$ as a nucleophilic trifluoromethoxylating reagent, which allowed very rapid access to the corresponding dehydroxytrifluoromethoxylated products.[25] Through exploration and optimization of this dehydroxylative functionalization, the authors identified that the reaction rate is highly dependent on the nature of solvent. Among several solvents tested (*e.g.*, DMSO, DMF, NMP, and toluene), DMF was found to be the most effective. Furthermore, the outcome of this transformation was also dramatically dependent on the reaction temperature. The best results were obtained by performing the process at 80 °C. A higher or lower temperature resulted in lower yields. With these optimized reaction conditions, 25 trifluoromethyl ethers **15** were synthesized in 16–76% yields from the corresponding aryl/benzyl/allyl/propargyl alcohols **14** (Scheme 8). Notably, a diverse range of functional groups such as fluoro, chloro, bromo, iodo, cyano, nitro, ester, and ether functionalities were demonstrated to be well-tolerated by this protocol. However, the major drawback of this synthetic protocol was its very low efficiency for functionalization of alkyl alcohols. Intriguingly, the authors nicely solved this problem by replacing Ph_3P with $Ph_2PCH{=}CH_2$ and performing the process at 100 °C. However, the only reported case of a secondary alkyl alcohol led to a mediocre yield.

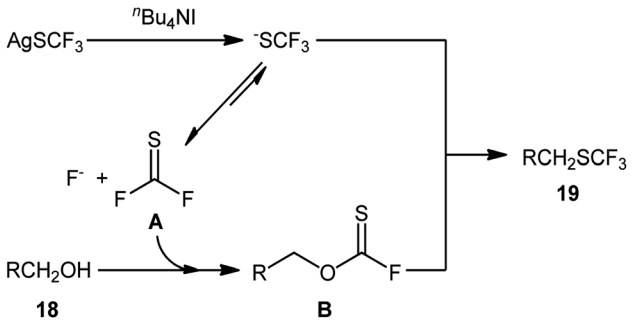
Mechanistically (Scheme 9), the reaction may be initiated by the reaction of Ph_3P with ICH_2CH_2I to give diiodophosphonium salt **A**, which upon coordination with the reaction solvent DMF, furnishes complex **B**. Subsequently, substitution of an alcohol **14** with a DMF molecule in complex **B** yields complex **C**, and after nucleophilic attack by trifluoromethoxy anion, generated from $AgOCF_3$ by precipitating AgI, affords the observed alkyl trifluoromethyl ether **15**. In another possibility, a sequential P–O bond formation and C–O bond cleavage process converts complex **B** into a triphenylphosphine oxide ($Ph_3P{=}O$) and the Vilsmeier–Haack-type intermediate **D**. Later, nucleophilic substitution of alcohol **14** with intermediate **D** leads to the formation of intermediate **E**, which after nucleophilic trifluoromethoxylation with CF_3O^-, provides the final product **15**.

4. Dehydroxylative trifluoromethylthiolation

The first report of the direct dehydroxylative trifluoromethylthiolation of alcohols was published by Rueping



Scheme 11 Qing's synthesis of trifluoromethylthioethers **19**.

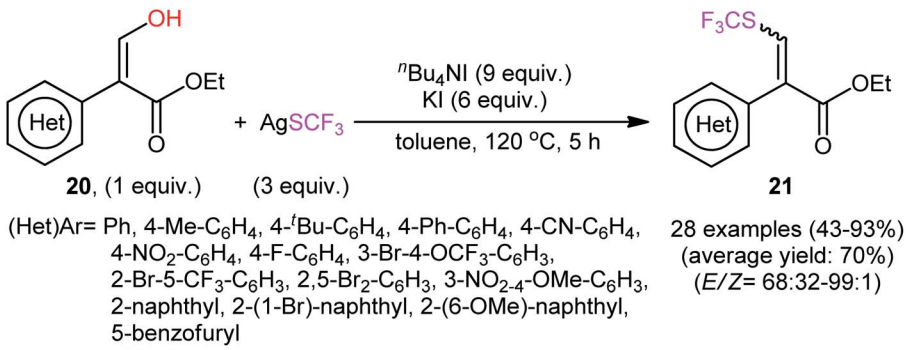


Scheme 12 Proposed reaction mechanism for the synthesis of trifluoromethylthioethers **19** starting from alcohols **18** with $AgSCF_3$.

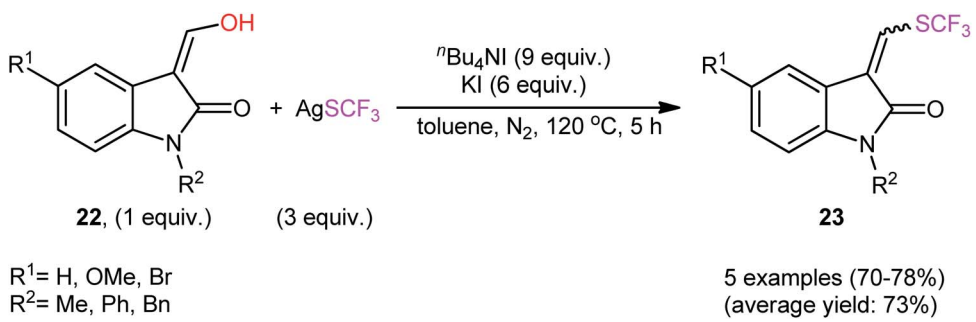
and co-workers in 2014,[26] who disclosed that the treatment of benzylic alcohols **16** with $CuSCF_3$ as a stable and readily available SCF_3 source and $BF_3 \cdot Et_2O$ as a Lewis acid additive under an air atmosphere resulted in the formation trifluoromethylthioethers **17** in moderate to quantitative yields within 30 min (Scheme 10). All three types of alcohols (primary, secondary, and tertiary) were applicable to this reaction, and in all cases, the corresponding trifluoromethylthioethers were selectively obtained. However, due to the strong acidic conditions, poor functional group tolerance occurs with this method. It should be mentioned that the presence of $BF_3 \cdot Et_2O$ was essential for the success of this C–S bond formation reaction. No product was detected with the lack of this additive, even at elevated temperatures.

Other Brønsted or Lewis acids such as MsOH, TsOH, TFA, $Sc(OTf)_3$, $Bi(OTf)_3$, and $In(OTf)_3$ were also tested and proved to be completely ineffective. The identical reaction conditions were also applied for trifluoromethylthiolation of allylic alcohols to give the corresponding allylic trifluoromethyl thioethers in good to excellent yields (9 examples, 73–96% yield) and high regioselectivities, in which regardless of the substitution pattern, conjugated aryl/olefin products were predominantly formed in the case of aryl-substituted allyl alcohols. Mechanistic investigations indicated that the reaction may occur *via* an S_N1-type process, as evidenced by the formation of racemic products from enantiopure alcohols.

Immediately after, Qing and collaborators developed a similar dehydroxytrifluoromethylthiolation of alkyl alcohols **18** with $AgSCF_3$, employing a large excess of the mild reagent *n*-Bu_4NI as activator and toluene as solvent (Scheme 11).[27] The reaction was shown to be quite general, and a diverse range of primary aliphatic, benzylic, allylic, and propargylic alcohols participated in the trifluoromethylthiolation. Moreover, secondary alcohols also accomplished production of the corresponding products albeit the addition of a very large amount of another activator, KI (8 equiv.), and elevated reaction temperature (120 °C) were needed to prevent the competitive elimination reaction. However, tertiary alcohols were not suitable substrates for this transformation.



Scheme 13 Qing's synthesis of α-aryl-β-(trifluoromethylthio)acrylates **21**.

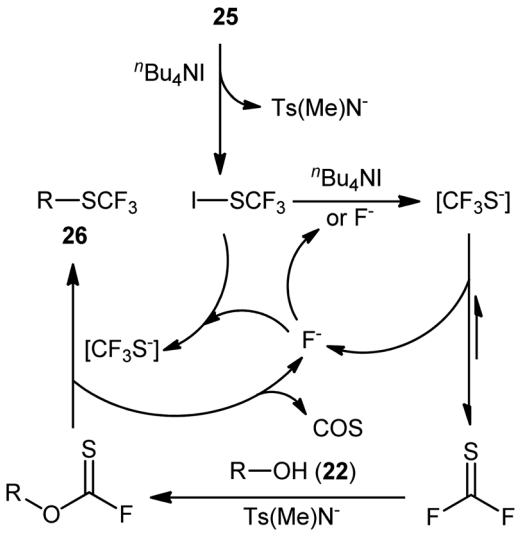


Scheme 14 Synthesis of 3-(((trifluoromethyl)thio)methylene)indolin-2-ones **23** *via* $^nBu_4NI$-mediated dehydroxytrifluoromethylthiolation of 3-(hydroxymethylene)indolin-2-one derivatives **22** with $AgSCF_3$.

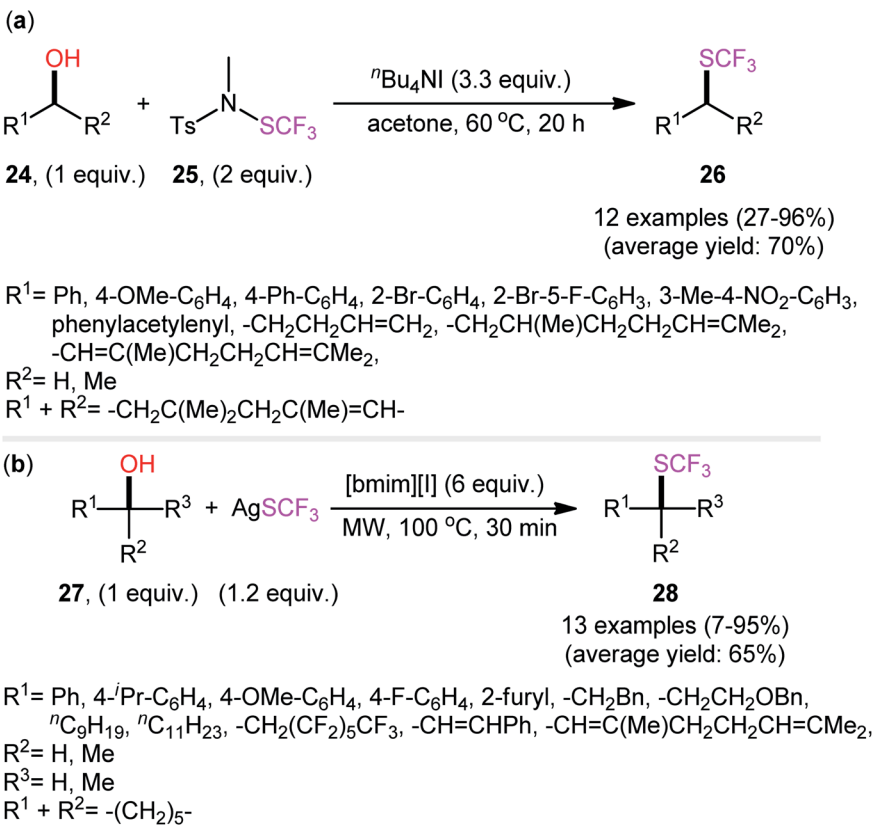
Interestingly, several biologically active alcohols such as idebenone **18a** (an anti-Alzheimer's drug), galantamine **18b** (an anti-Alzheimer's and anti-dementia drug), and epiandrosterone **18c** (a steroid hormone) also responded to the reaction. Notably, the authors observed that changing the ratio of $AgSCF_3$/*n*-Bu_4NI from 1 : 3 to 1 : 1 led to the selective formation of alkyl fluorides instead of the expected alkyl trifluoromethylthioethers. A plausible mechanism based on previous studies is outlined in Scheme 12.

In their subsequent studies, this research group extended the scope of their methodology to enols.[28] Thus, a library of (*Z*)-ethyl 2-(aryl)-3-hydroxyacrylates **20** were reacted with $AgSCF_3$, *n*-Bu_4NI, and KI in toluene at 120 °C leading to the respective α-aryl-β-(trifluoromethylthio)acrylates **21** in moderate to excellent yields and satisfactory stereoselectivities in favor of the (*E*)-products (Scheme 13). Under the same conditions, they also executed the direct dehydroxytrifluoromethylthiolation of a small series of 3-(hydroxymethylene)indolin-2-one derivatives **22**, offering a decent yield of the desired 3-(((trifluoromethyl)thio)methylene)indolin-2-ones **23** (Scheme 14). Interestingly, two electron-deficient phenols were also tested and gave products in satisfactory yields. To the best of our knowledge, this is the first and only reported example of dehydroxylative trifluoromethylthiolation of $C(sp^2)$–OH bonds.

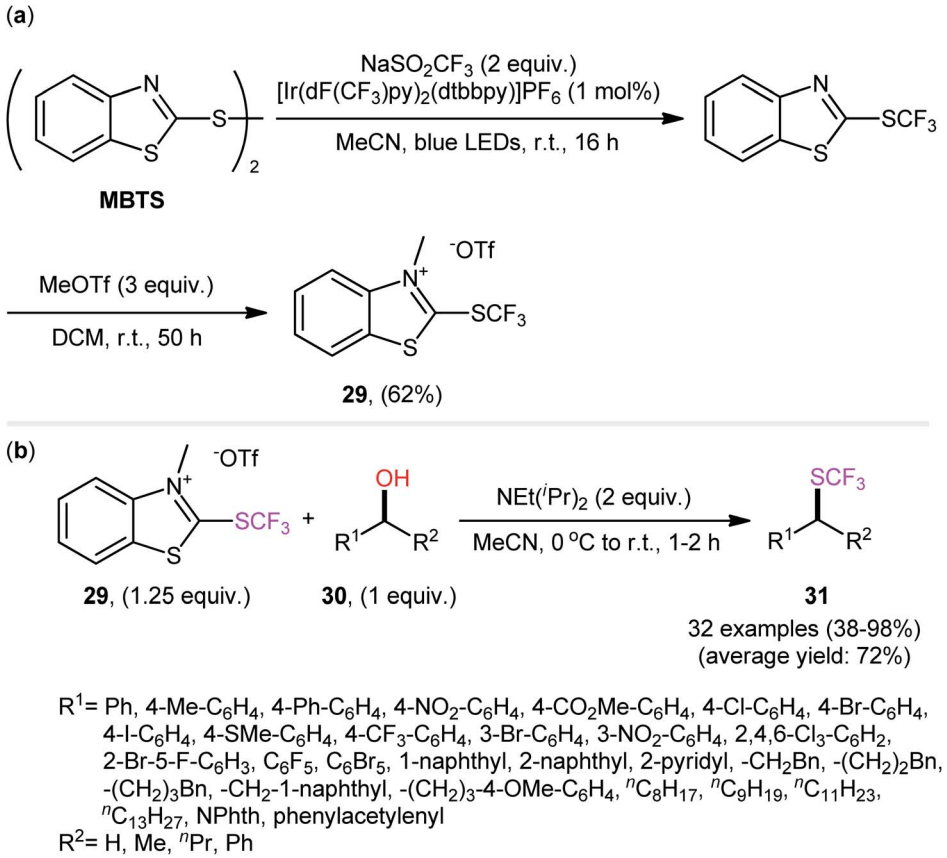
At the outset of 2016, Billard's research group devised an elegant metal-free method for dehydroxylative trifluoromethylthiolation of alkyl alcohols **24** using the second-generation trifluoromethanesulfenamide reagent **25** as an SCF_3 source and *n*-Bu_4NI as an activator in refluxing acetone to afford the corresponding alkyl trifluoromethylthioethers **26** in an efficient manner (Scheme 15a).[29] The experiments



Scheme 16 Proposed pathway of alkyl trifluoromethylthioethers **25** formation.



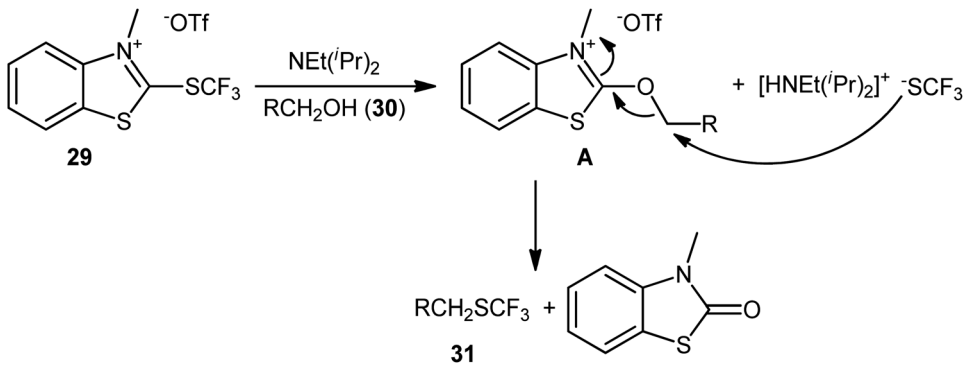
Scheme 15 (a) Metal-free dehydroxylative trifluoromethylthiolation of alkyl alcohols **24** with trifluoromethanesulfenamide **25**; (b) solvent-free microwave-assisted synthesis of alkyl trifluoromethylthioethers **28** from alkyl alcohols **27** and $AgSCF_3$.



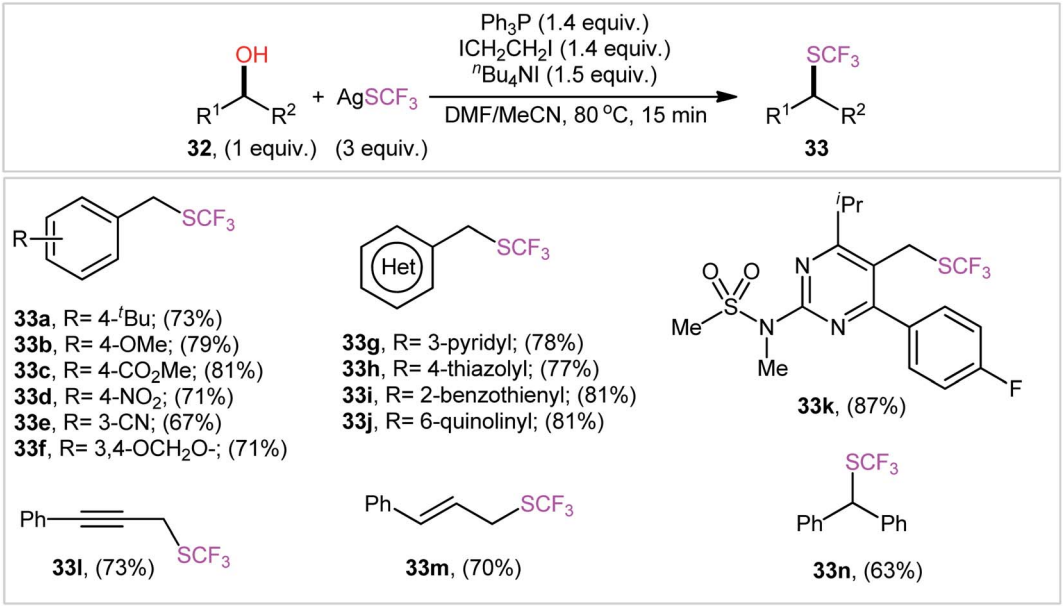
Scheme 17 Hünig's base-mediated dehydroxylative trifluoromethylthiolation of alkyl/benzyl/propargyl alcohols **30** with benzothiazolium reagent **29**.

demonstrated that the outcome of this reaction was not highly sensitive to the electronic nature of substrates, and therefore benzylic alcohols with either neutral, electron-donating, or electron-withdrawing substituents gave the trifluoromethylthiolated products in relatively similar yields. However, the steric effect was very strong (92% yield for benzyl alcohol to 46% for α-methylbenzyl alcohol). Unfortunately, the applicability of tertiary alcohols as starting materials was not explored in this study.

A presumptive mechanism for this dehydroxylative trifluoromethylthiolation reaction is represented in Scheme 16. Subsequently, a straightforward and greener approach for the synthesis of alkyl trifluoromethylthioethers **28** by the reaction between alkyl alcohols **27** and 1-*n*-butyl-3-methylimidazolium trifluoromethylthiolate ([bmim][SCF_3]) generated *in situ* from [bmim][I] and $AgSCF_3$ was reported by Pégot, Magnier, and co-workers.[30] The reactions were implemented under microwave irradiation and solvent-free conditions, tolerated primary, secondary, as well as tertiary alcohols, and rapidly provided the desired products in poor to excellent yields (Scheme 15b). Recycling tests indicated that the ionic liquid can be reused in



Scheme 18 Mechanism proposed to explain the formation of trifluoromethylthioethers **31**.



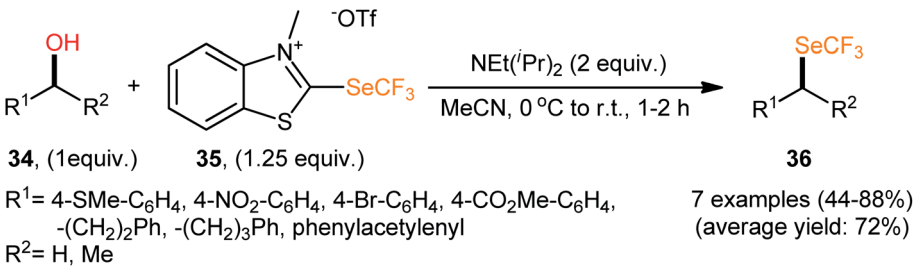
Scheme 19 Ph_3P/ICH_2CH_2I/n-Bu_4NI-mediated direct conversion of alcohols **32** into the corresponding trifluoromethyl thioethers **33** using $AgSCF_3$.

several consecutive trials without significant loss of its activity (from 96% in the first run to 96% in the fifth run).

In 2019, Hopkinson and co-workers designed and synthesized a new bench-stable 2-trifluoromethylthio-substituted benzothiazolium salt (BT-SCF_3; **29**) through visible-light-induced, Ir-catalyzed trifluoromethylthiolation of inexpensive 2-mercaptobenzothiazole disulfide (MBTS) with the Langlois reagent ($NaSO_2CF_3$) and subsequent reaction of the generated 2-SCF_3-substituted benzothiazole with MeOTf in DCM at room temperature (Scheme 17a).[31] The activity of this purely organic trifluoromethylthiolating reagent has been evaluated in the dehydroxylative trifluoromethylthiolation of a broad set of alkyl/benzyl/propargyl alcohols **30** in the presence of Hünig's base ($NEt(^iPr)_2$) in MeCN. Moderate to almost quantitative yields of the target trifluoromethyl thioethers **31** were obtained within 1–2 h at room temperature (Scheme 17b). The reaction exhibited satisfactory tolerance for an array of catalytically reactive functional groups (*e.g.*, F, Cl, Br, I, CF_3, CO_2Me, SMe, NO_2), and thus, promised further elaboration of the end products. It is worthwhile to note that the authors nicely adapted this approach to the direct construction of $SeCF_3$-substituted compounds from alcohols by developing a similar trifluoromethylselenyl-substituted benzothiazolium salt (BT-$SeCF_3$).

As for the mechanism, the authors speculated that the reaction most likely proceeds through the formation of key electrophilic 2-alkoxybenzothiazolium species **A** *via* nucleophilic attack of the alcohol **30** in the presence of $NEt(^iPr)_2$ at the C2-position of the BT-SCF_3 reagent **29** and subsequent nucleophilic substitution reaction with *in situ* generated $-SCF_3$ anion (Scheme 18). Guided by the same principle, a similar dehydroxylative functionalization strategy was applied by the same research group towards the synthesis of various perfluoroalkyl thioethers[32] and thioesters.[33]

In a recent report, Wu, Xiao, and colleagues accomplished the direct conversion of alcohols **32** into the corresponding trifluoromethyl thioethers **33** using $AgSCF_3$ as a source of F_3CS group and the Ph_3P/ICH_2CH_2I/n-Bu_4NI combination as an activation system in a 2 : 1 mixture of DMF and MeCN.[22] The reaction was compatible with a variety of functionalized benzylic alcohols, as well as heterobenzylic alcohols such as hydroxymethyl pyridines, quinolines, thiazoles, benzothiols, even simple allylic and propargylic alcohols (Scheme 19). As



Scheme 20 Hopkinson's synthesis of trifluoromethylselenoalkanes **36**.

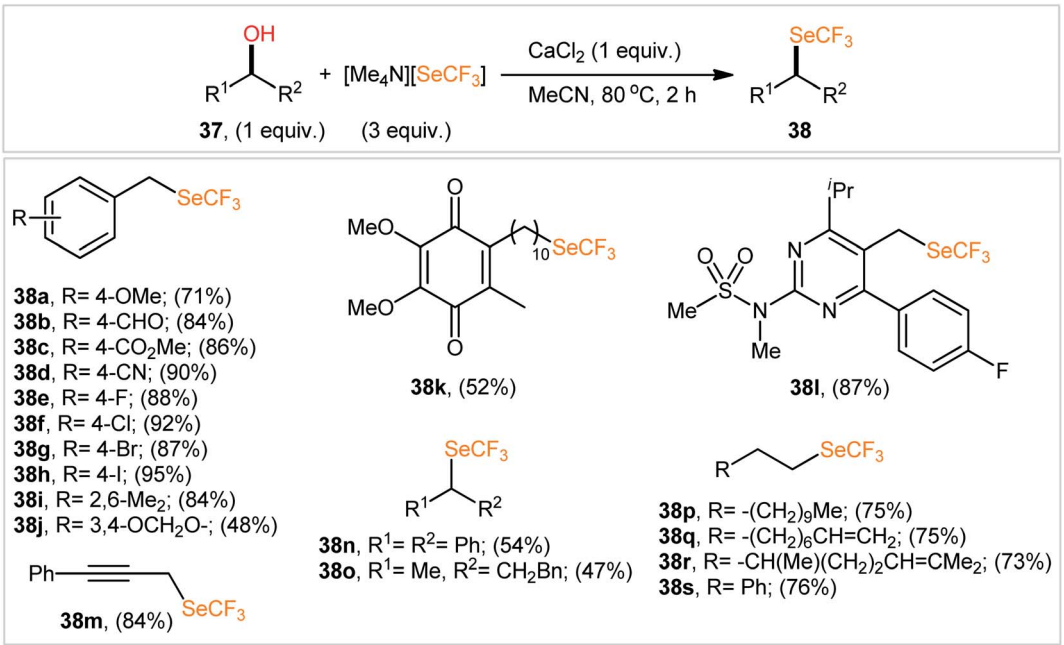
for alkyl alcohols, the corresponding products were obtained in poor yields. In this case, when $Ph_2PCH{=}CH_2$ was used instead of Ph_3P, the product yields were significantly increased. The plausible mechanism for this transformation is analogous to the one depicted in Scheme 5. It should be mentioned that this mechanism is tentative and lacks experimental evidence.

5. Dehydroxylative trifluoromethylselenylation

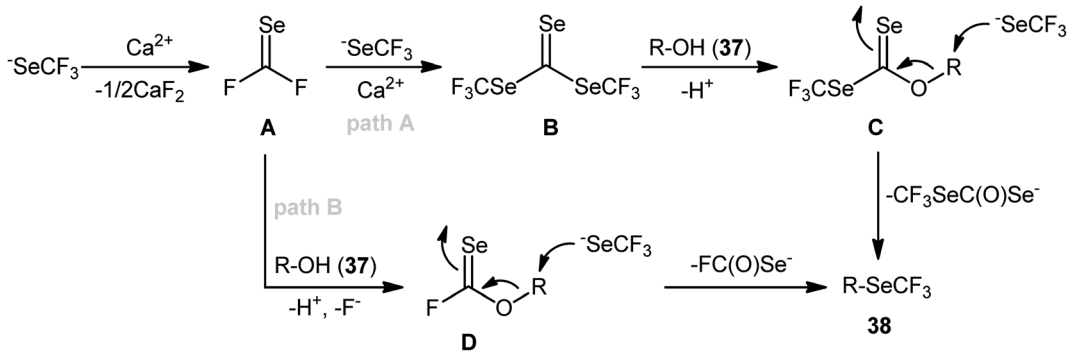
Compared to trifluoromethylation, trifluoromethoxylation, and trifluoromethylthiolation, the direct trifluoromethylselenylation of alcohols is relatively less explored, although there has been much recent attention on the development of novel and efficient methodologies for the synthesis of $SeCF_3$-substituted compounds.[34] In 2019, in the same study describing the deoxytrifluoromethylthiolation of alcohols with the benzothiazolium salt BT-SCF_3, Hopkinson's research team reported the successful $NEt(^iPr)_2$-promoted preparation of trifluoromethylselenoalkanes **36** from the respective alcohols **34** employing 2-trifluoromethylseleno-substituted benzothiazolium salt (BT-$SeCF_3$; **35**) (Scheme 20).[31] Notably, BT-$SeCF_3$ was synthesized *via* the same general strategy used to prepare BT-SCF_3.

In 2020, using $[Me_4N][SeCF_3]$ salt as a stable, non-volatile, and readily accessible source of nucleophilic $SeCF_3$, Zhang and colleagues engineered the direct dehydroxylative trifluoromethylselenylation of alcohols **37** for the synthesis of valuable alkyl trifluoromethyl selenoethers **38** under catalyst-free conditions.[35] By employing 3-phenylpropyl alcohol as the model reactant, several additives such as CaF_2, $CaCl_2$, $CaBr_2$, $Ca(OTf)_2$, $Ca(C_2O_4)$, $CaSO_4$, HCl, and LiI were carefully screened. Among them, excellent results were obtained for this transformation with $CaCl_2$, whereas MeCN was found to be the most effective solvent among the other common organic solvents tested (DMA, DMF, NMP, DMSO, MeCN, DCM, toluene, and 1,4-dioxane).[36] Evaluation of the substrate scope clearly demonstrated that the reaction was tolerant to a variety of primary and secondary aliphatic alcohols (Scheme 21). However, tertiary alcohols provided complicated mixtures. In order to elucidate the mechanism of the reaction, the authors performed several control experiments, such as GC-MS analyses, ^{19}F NMR studies, and others.[37]

From these results, the authors proposed two possible pathways for this transformation. The first pathway (Scheme 22, path A) starts with the formation of carbonoselenoic difluoride intermediate **A** through the decomposition of $^-SeCF_3$ with $CaCl_2$ as a fluoride scavenger, which after reaction with another two equivalents of $^-SeCF_3$ in the presence of Ca^{2+} cations provides bis(trifluoromethyl)-carbonotriselenoate **B** (this intermediate was detected by ^{19}F NMR and GC-MS analyses). Subsequently, the nucleophilic substitution of key intermediate **B** by alcohol **37** leads to a carbonoselenoate **C**. Finally, the nucleophilic attack of intermediate **C** with $^-SeCF_3$ anion provides the target trifluoromethylselenylated product **38**. The key steps of the second possible route (Scheme 22, path B) are the generation of *O*-alkyl carbonofluoridoselenoate **D** *via* straightforward reaction of intermediate **A** with alcohol **37** and its nucleophilic substitution by $^-SeCF_3$ to form the observed product **38**. According to the authors, pathway B is not likely the major process in the Ca-mediated dehydroxy trifluoromethylselenylation,[38] especially when using a large excess of $[Me_4N][SeCF_3]$.



Scheme 21 Selected examples of $CaCl_2$-promoted dehydroxylative trifluoromethylselenylation of alcohols **37** with $[Me_4N][SeCF_3]$.



Scheme 22 Mechanistic proposal for the reaction in Scheme 21.

6. Conclusion

Because of their unique physicochemical and biological properties, there has been broad interest in fluorinated compounds in various research fields such as pharmaceuticals, medical imaging, agrochemicals, and materials science. Among all fluorine-containing functionalities, the trifluoromethyl (CF_3), trifluoromethoxyl (OCF_3), trifluoromethylthiol (SCF_3), and trifluoromethylselenyl ($SeCF_3$) groups are becoming increasingly prominent in new drugs due to their strong electron-withdrawing nature and high lipophilic properties. Therefore, the high demand for biologically active compounds has stimulated significant efforts to develop efficient methods for the installation of these groups into organic molecules. As shown in this Mini-Review, recently direct dehydroxylative trifluoromethylation, trifluoromethoxylation, trifluoromethylthiolation, and trifluoromethylselenylation of alcohols have emerged as efficient new methods for the construction of CF_3/OCF_3/SCF_3/$SeCF_3$-functionalized compounds from inexpensive and readily available starting materials without the need for time-consuming pre-functionalization steps.

As illustrated, various aliphatic and benzylic alcohols were applicable in these reactions. However, aromatic alcohols were mainly unsuitable substrates. Therefore, many more studies are needed to develop efficient procedures that allow trifluoromethylation, -methoxylation, -methylthiolation, and -methylselenylation reactions of aromatic alcohols. Moreover, there are insufficient reported examples for some reactions such as trifluoromethylselenylations, and thus, additional study is necessary to determine the scope and limitations of these reactions.

Conflicts of interest

There are no conflicts to declare.

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