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Trifluoromethylthiolative 1,2-difunctionalization of alkenes with diselenides and $AgSCF_3$†

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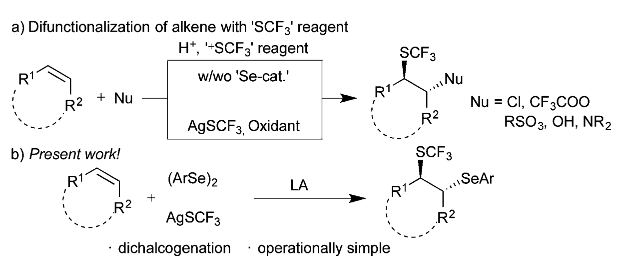
An efficient regioselective difunctionalization of alkenes *via* trifluoromethylthiolation has been accomplished employing diaryl diselenide and $AgSCF_3$ in the presence of $BF_3{\cdot}OEt_2$. Various substituted 1,2-dichalcogenated products having the SCF_3 moiety were synthesized in good to excellent yields under mild conditions. The preliminary mechanistic investigation revealed the possible reaction pathway and unique combination of diselenide and $AgSCF_3$ for successful transformation.

Fluorinated molecules have found widespread application in various fields. Notably, a significant number of drugs in pharmaceuticals and agrochemicals contain at least one fluorine atom/group in the form of –F, $–CF_3$, $–SCF_3$, or $–SOCF_3$.[1] Recently, trifluoromethylthio ($–SCF_3$) containing organic molecules gained significant attention, due to their unique properties such as high lipophilicity, bioavailability, and metabolic stability. The representative examples of $–SCF_3$ containing drug molecules include toltrazuril, cefazaflur, and fipronil. Thus, the development of an elegant strategy for the construction of trifluoromethylthiolated molecules has been of continuing interest in organic synthesis and other fields.[2] Consequently, enormous efforts have been dedicated towards the development of various strategies for the construction of trifluoromethylthiolated compounds such as F-exchange[3] and direct introduction of $–CF_3$[4] and $–SCF_3$[5] groups. Among them, direct trifluoromethylthiolation, using electrophilic or nucleophilic 'SCF_3' reagents, is the most efficient and viable strategy in the synthesis of trifluoromethyl sulfides *via* the direct construction of C–SCF_3 bonds.

On the other hand, difunctionalization of readily accessible substituted alkenes with electrophiles and nucleophiles is an efficient multi-component approach for the synthesis of structurally complex frameworks.[6] In this context, the incorporation of the trifluoromethylthio ($–SCF_3$) group along with other functional groups, such as amines, amides, and acids,[7] is a useful concept for the synthesis of trifluoromethylthiolated molecules, which could provide the excellent opportunity for medicinal chemists in the drug evolution. Billard and co-workers reported for the first time trifluoromethylthiolative functionalization of alkenes using electrophilic trifluoromethylthiolating reagents.[8] Subsequently, numerous methods[9] employing electrophilic trifluoromethylthiolating reagents have been documented (Scheme 1a). However, use of nucleophilic trifluoromethylthiolating reagents is rather limited.[10] For instance, the groups of Wang[10a] and Qing[10d] utilized $AgSCF_3$ in combination with superstoichiometric amounts of persulfate for the difunctionalization of alkenes. Wang and co-workers[10b] utilized a substoichiometric amount of copper acetate and $AgSCF_3$. On the other hand, the combination of $AgSCF_3$ and trichloroisocyanuric acid was exploited by Yang and co-workers.[10c] However, to the best of our knowledge, difunctionalization of alkenes with nucleophilic $AgSCF_3$ in the absence of a metal catalyst or oxidant was not documented in the literature. Thus, we envisioned an arylselenative trifluoromethylthiolation of alkenes with diaryl diselenide and nucleophilic $AgSCF_3$ for the synthesis of 1,2-dichalcogenated compounds, where the potential intermediate $ArSeSCF_3$ might afford the expected product in the presence of Lewis acids (Scheme 1b). We herein disclose an elegant arylselenative trifluoromethylthiolation of substituted alkenes.

Initially, the difunctionalization of styrene **1a** with diphenyl diselenide **2a** and $AgSCF_3$ was chosen as a model reaction.



Scheme 1 Trifluoromethylthiolative difunctionalization of alkenes.

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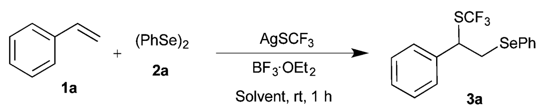
Table 1 Difunctionalization of styrene **1a** with diphenyl diselenide **2a** and $AgSCF_3$: optimization[a]



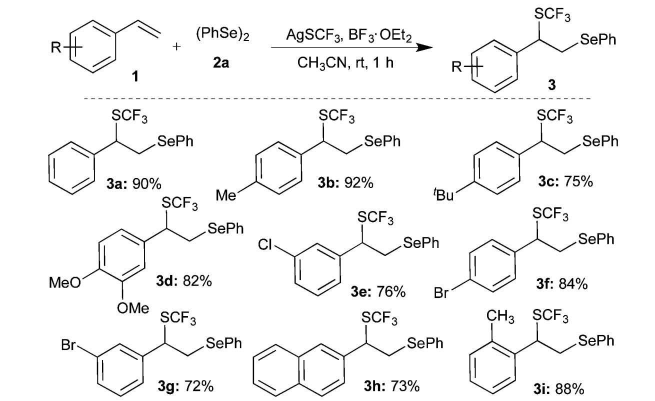
Entry	$BF_3 \cdot OEt_2$ (equiv.)	Solvent	Yield[b] (%)
1	1.0	CH_3CN	44
2	1.0	DCE	<5
3	1.0	DCM	20
4	1.0	THF	20
5	1.0	DMF	<5
6	2.0	CH_3CN	40
7	0.5	CH_3CN	26
8	0.2	CH_3CN	24
9[c]	1.0	CH_3CN	48
10[d]	1.0	CH_3CN	20
11[e]	1.0	CH_3CN	96

[a] Reaction conditions: styrene **1a** (0.24 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.0 equiv.), $AgSCF_3$ (0.24 mmol, 1.0 equiv.), $BF_3 \cdot OEt_2$, solvent (0.24 M), rt, 1 h. [b] Isolated yield. [c] At 50 °C. [d] 0.5 equiv. of styrene. [e] 2.0 equiv. of styrene.

Initial screening of Lewis acids suggested that $BF_3 \cdot Et_2O$ was the most suitable promoter of the expected difunctionalization (see the ESI†). Thus, the reaction of 1 equiv. of **1a** with 1 equiv. of both **2a** and $AgSCF_3$ in the presence of 1 equiv. of $BF_3 \cdot Et_2O$ in acetonitrile at room temperature afforded the expected product **3a** in 44% yield after 12 h. Having identified the formation of the expected product **3a**, various conditions were examined to improve the yield of **3a**. Thus, different solvents such as DCM, DCE, and CH_3CN were screened at room temperature to enhance the transformation (Table 1, entries 1–5). Among them, only acetonitrile showed a better yield.

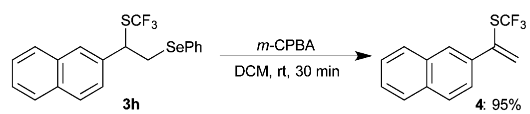
Next, increasing the $BF_3 \cdot OEt_2$ to 2.0 equivalents doesn't show much improvement in the yield, but decreasing the equivalents of $BF_3 \cdot OEt_2$ shows drastic reduction in the yield (Table 1, entries 6 and 7). Subsequently, the focus was directed to study the effect of temperature. Increasing the reaction temperature to 50 °C with one equivalent of $BF_3 \cdot OEt_2$ furnished product **3a** in only comparable yield (Table 1, entry 9). On the other hand, altering the equivalents of styrene showed a drastic change in the outcome (Table 1, entries 10 and 11). The best yield of 96% for the formation of **3a** was observed with 2.0 equivalents of styrene in the presence of one equivalent of **2a**, $AgSCF_3$ and $BF_3 \cdot OEt_2$ at room temperature after 1 h; the same conditions were used for further studies.

Having achieved the suitable conditions for the tri-component difunctionalization of **1a** for the synthesis of the highly functionalized molecule, the scope and generality of the transformation were investigated. For example, 4-alkyl (methyl/*tert*-butyl) substituted styrenes gave products **3b** and **3c** in 92% and 75% yield, respectively (Scheme 2). Similarly, electron donating group (3,4-dimethoxy) and halogen (bromo/chloro) substituted styrenes were also well tolerated under the optimized conditions to afford the corresponding difunctionalized products **3d**, **3e**, **3f**, and **3g** in excellent yields. The reaction of 2-vinylnaphthalene also furnished a similar product, **3h**, in 73% yield. Also, sterically hindered 2-methylstyrene underwent smooth reaction to give **3i** in 88% yield. However, actively coordinating cyano and NMe_2 group substituted styrenes do not afford difunctionalized products.

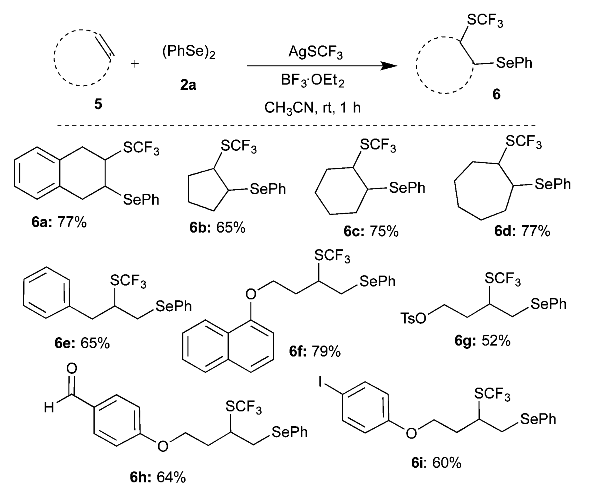


Scheme 2 Difunctionalization of substituted styrenes.

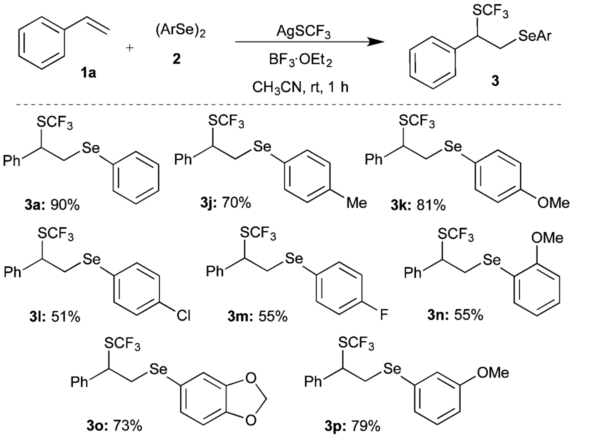
Further, to confirm the regioselectivity of the difunctionalized product, oxidative elimination of –SePh was envisioned. Thus, the isolated difunctionalized compound **3h** was treated with *m*-CPBA in DCM at room temperature. Interestingly, the formation of α-(trifluoromethylthio)vinylnaphthalene **4** was observed in 95% yield (eqn (1)). The formation of **4** further confirms that SCF_3 and SePh were attached at α-carbon and β-carbon, respectively.

 (1)

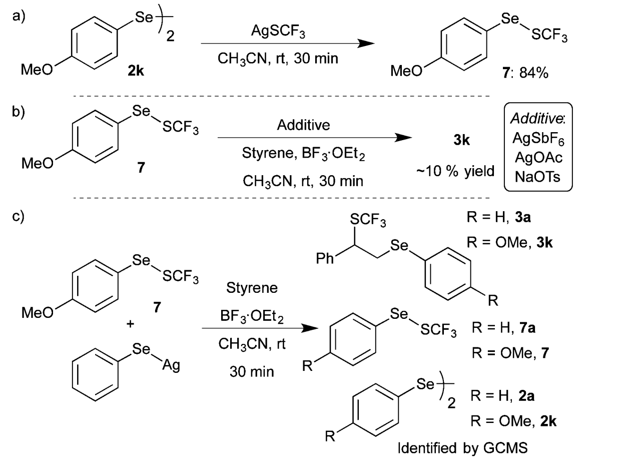
After the successful demonstration of the generality of substituted styrenes, the scope and limitations of other substituted alkenes were examined. Gratifyingly, replacement of styrene with 1,4-dihydronaphthalene under the optimized conditions afforded the difunctionalized product **6a** in 77% yield (Scheme 3). Similarly, other cyclic alkenes such as cyclopentene, cyclohexene, and cycloheptene also underwent smooth



Scheme 3 Difunctionalization of substituted alkenes.



Scheme 4 Difunctionalization of styrene with diaryl diselenide **2** and $AgSCF_3$.



Scheme 5 Control experiments.

reaction to afford the corresponding difunctionalized products **6b**, **6c**, and **6d** in 65, 75 and 77% yield, respectively. Also, difunctionalization of simple terminal alkenes such as allylbenzene was achieved in good yield. Consequently, various substituted homoallylic ethers were tolerated under the optimized conditions to afford difunctionalized products **6f–6i** in good to excellent yields. It is important to note that reactive functional groups such as formyl, sulfenyl and iodo moieties were well tolerated under the optimized conditions.

Subsequently, various substituted diaryl diselenides[11] were subjected to the difunctionalization of styrene under the optimized conditions. Methyl, methoxy, and halogen substituted diaryl diselenides gave the corresponding difunctionalized products **3j**, **3k**, **3l**, **3m** and **3p** in 70, 81, 51, 55 and 79% yields, respectively (Scheme 4).

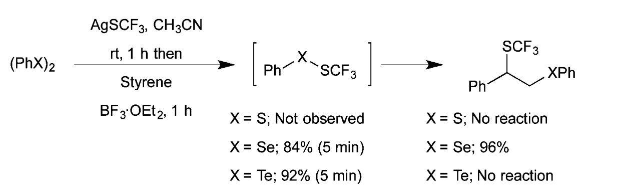
Interestingly, sterically hindered *o*-methoxy substituted diaryl diselenide furnished the corresponding product **3n** in good yield. Acid-sensitive acetal containing difunctionalized product **3o** was synthesized in 73% yield from the corresponding diaryl diselenide.

After the successful demonstration of $BF_3{\cdot}OEt_2$ induced difunctionalization of styrenes and alkenes with diaryl diselenides and $AgSCF_3$, the formation of potential intermediates and the plausible reaction mechanism of the developed transformation were investigated. ^{19}F NMR analysis of the optimized reactions showed an additional singlet at δ −45.3 along with $AgSCF_3$ and difunctionalized product **3a**. Subsequently, GCMS analysis revealed the formation of possible intermediate (phenylselanyl)-(trifluoromethyl)sulfane ($PhSeSCF_3$) from the corresponding diaryl diselenide and $AgSCF_3$. Consequently, ((4-methoxyphenyl)-selanyl)-(trifluoromethyl)sulfane **7** was synthesized from bis(4-methoxyphenyl)diselenide **2k** and $AgSCF_3$ in acetonitrile in 84% yield (Scheme 5a).[12] After the successful synthesis of **7**, the reactivity of **7** with styrene was investigated under the optimized conditions. The initial reaction of styrene **1a** with **7** in the presence of $BF_3{\cdot}OEt_2$ in CH_3CN didn't afford the expected product. A detectable amount of difunctionalized product **3k** was observed in ^{19}F NMR upon addition of an additive such as silver salt or NaOTs (Scheme 5b).

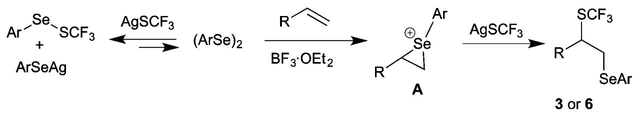
However, the formation of **7**, *via* treatment of diselenide and $AgSCF_3$ in CH_3CN in the presence of $BF_3{\cdot}OEt_2$, followed by the addition of styrene afforded the expected difunctionalized product **3k** in good yield. These studies suggested that $ArSeSCF_3$ might not be the intermediate of the developed transformation and the formed $ArSeSCF_3$ might exist in equilibrium with $AgSCF_3$ and diaryl diselenide. Further, to confirm the reversible formation of $ArSeSCF_3$ from $AgSCF_3$ and diselenides, compound **7** was treated with silver phenylselenate and styrene in the presence of $BF_3{\cdot}OEt_2$. Interestingly, a mixture of difunctionalized products **3a** and **3k** was observed along with $-SCF_3$ exchanged products **7** and **7a** and possible diselenides **2a** and **2k** in GCMS and ^{19}F NMR analysis (Scheme 5c). This $-SCF_3$ exchange could be explained *via* the initial formation of diselenides followed by reaction with $AgSCF_3$. All the above observations confirm the possible reversible reaction between diselenides and $AgSCF_3$.

Furthermore, difunctionalization was performed with other dichalcogenides in place of diselenides. Unfortunately, both diphenyl disulfide and diphenyl ditelluride did not afford the expected product (Scheme 6). Further analysis of the reaction mixture suggested the possible reasons that the disulfides failed to get activated due to the high bond energy of the S–S bond and no availability of ditelluride due to the rapid, irreversible formation of $PhTeSCF_3$. Thus, based on the observed regioselectivity and mechanistic investigation, in the present strategy diselenide and $AgSCF_3$ acted as an electrophilic –SeAr source and a nucleophilic $-SCF_3$ source, respectively.

Based on the mechanistic study, the possible pathway for the difunctionalization of alkenes was proposed as shown in Scheme 7.



Scheme 6 Reaction of styrene with different dichalcogenides and $AgSCF_3$.



Scheme 7 Plausible mechanism.

Initially, diphenyl diselenide **2a** and $AgSCF_3$ convert into **7a**, which exists in equilibrium with **2a** and $AgSCF_3$. The remaining diselenide on reaction with styrene in the presence of $BF_3 \cdot OEt_2$ would afford the episelenonium intermediate **A**. Subsequently, regioselective ring opening of episelenonium ion **A** with $AgSCF_3$ would furnish the difunctionalized product **3**. Even though the concentration of $AgSCF_3$ is lower at equilibrium, the overall reaction yield was satisfactory, because of the reversible reaction between $AgSCF_3$ and diphenyl diselenide.

In conclusion, we have developed an efficient regioselective difunctionalization of alkenes with diaryl diselenide and $AgSCF_3$ in the presence of $BF_3 \cdot OEt_2$ as an activator. The developed reaction tolerates various functional groups and allows the synthesis of diverse 1,2-dichalcogenated products having a trifluoromethylthio moiety in good to excellent yield. The preliminary mechanistic investigation revealed the possible reaction pathway and unique combination of diselenide and $AgSCF_3$ for successful transformation.

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Conflicts of interest

There are no conflicts to declare.

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