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Trifluoromethylthiolative 1,2-Difunctionalization of Alkenes with Diselenides and $AgSCF_3$

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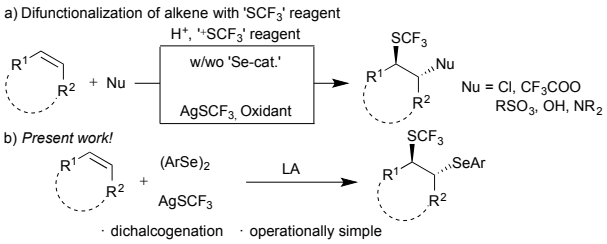
An efficient regioselective difunctionalization of alkenes via trifluoromethylthiolation have been accomplished employing diaryl diselenide and $AgSCF_3$ in the presence of $BF_3{\cdot}OEt_2$. Various substituted 1,2-dichalcogenated products having SCF3 moiety were synthesized in good to excellent yield 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, significant number of drugs in the pharmaceuticals and agrochemicals contain at least one fluorine atom/group in the form of -F, $-CF_3$, $-SCF_3$, and $-SOCF_3$.[1] Recently, trifluoromethylthio ($-SCF_3$) containing organic molecules gained significant attention, due to its unique properties such as high lipophilicity, bioavailability, and metabolic stability. The representative examples of $-SCF_3$ containing drug molecules include toltrazuril, cefazaflur, fipronil, and etc. Thus, the development of an elegant strategy for the construction of trifluoromethylthiolated molecules has been continuing interest in organic synthesis and other fields.[2] Consequently, enormous efforts have been dedicated to 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 bond.

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 trifluoromethylthio ($-SCF_3$) group along with other functional groups, such as amine, amide, acid, etc.,[7] is a useful concept to 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] were documented employing electrophilic trifluoromethylthiolating reagents (Scheme 1a). However, use of nucleophilic trifluoromethylthiolating reagents is rather limited.[10] For instance, the group of Wang[10a] and Qing[10d] utilized $AgSCF_3$ in combination with superstiochiometric amount of persulfate for the difunctionalization of alkenes. Wang and co-workers[10b] utilized the 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 the alkene with nucleophilic $AgSCF_3$ in the absence of 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.



Scheme 1. Trifluoromethylthiolative difunctionalization of alkenes.

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

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Initial screening of Lewis acids suggested that $BF_3{\cdot}Et_2O$ was the most suitable promoter of the expected difunctionalization (see Supporting Information). 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 expected product **3a**, various conditions were examined to improve the yield of **3a**. Thus, different solvents such as DCM, DCE, CH_3CN, etc. were screened at room temperature to enhance the transformation (Table 1, entries 1-5). Among them, acetonitrile only showed better yield.

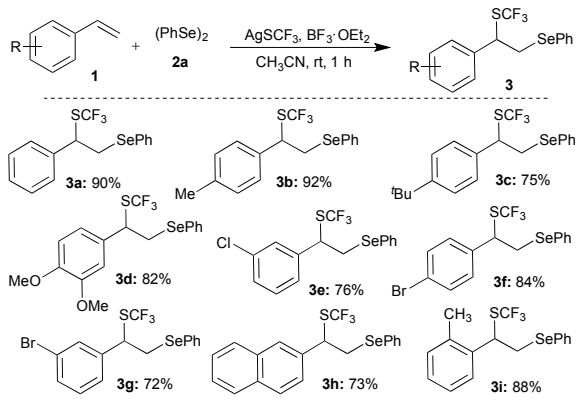
Table 1. Difunctionalization of styrene 1a with diphenyldiselenide 2a and $AgSCF_3$: Optimization[a]

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.

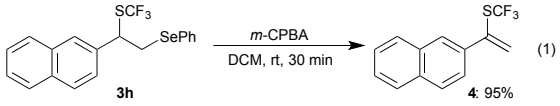
Next, increasing the $BF_3{\cdot}OEt_2$ to 2.0 equivalents doesn't show much improvement in the yield, but decreasing the equivalents of $BF_3{\cdot}OEt_2$ shows drastic reduction in the yield (Table 1, entries 6 and 7). Subsequently, the focus was directed to study the effect of temperature. Increasing the reaction temperature to 50 °C with one equivalent of $BF_3{\cdot}OEt_2$ furnished the 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, entry 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 condition was used for the 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 was investigated. For example, 4-alkyl (methyl/tert-butyl) substituted styrenes gave the product **3b** and **3c** in 92% and 75% yield, respectively (Scheme 2). Similarly, electron donating group (3,4-dimethoxy) and halogen (bromo/chloro) substituted styrene was also well tolerated under the optimized conditions to afford the corresponding difunctionalized product **3d**, **3e**, **3f**, and **3g** in excellent yields. The reaction of 2-vinylnaphthalene also furnished the 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.



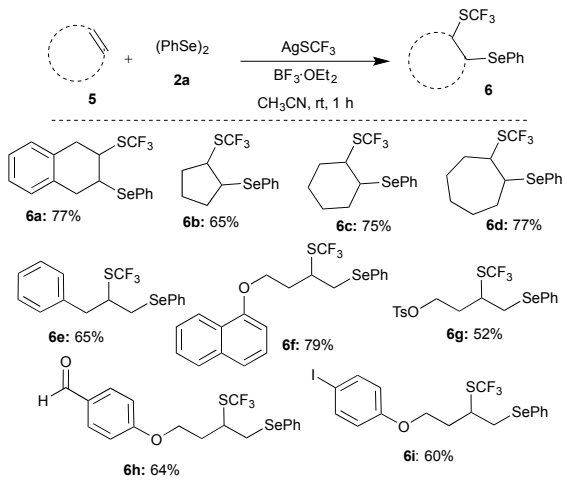
Scheme 2. Difunctionalization of substituted styrenes

Further to confirm the regioselectivity of 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 (eq 1). Formation of **4** further confirms that SCF_3 and SePh were attached at α-carbon and β-carbon, respectively.



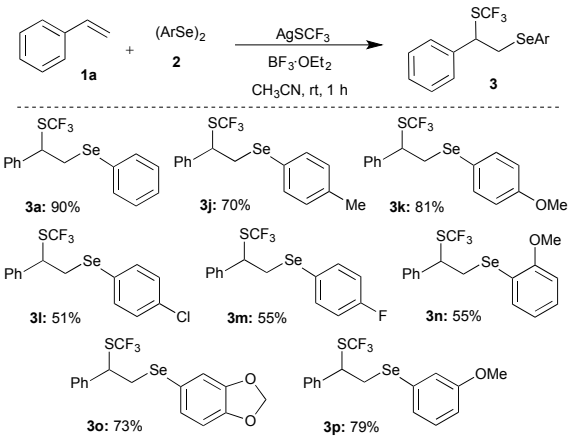
After the successful demonstration of the generality of substituted styrenes, scope and limitations of other substituted alkenes were examined. Gratifyingly, replacement of styrene with 1,4-dihydronaphthalene under the optimized conditions afforded the difunctionalized product **6a** in 77% yield (Scheme 3). Similarly, other cyclic alkenes such as cyclopentene, cyclohexene, and cycloheptene also underwent smooth reaction to afford corresponding difunctionalized product **6b**, **6c**, and **6d** in 65, 75 and 77% yield, respectively. Also, difunctionalization of simple terminal alkene such as allylbenzene was achieved in good yield. Consequently, various substituted homoallylic ethers were subjected under the optimized conditions to afford difunctionalized product **6f**-**6i** in good to excellent yield. 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 for 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).



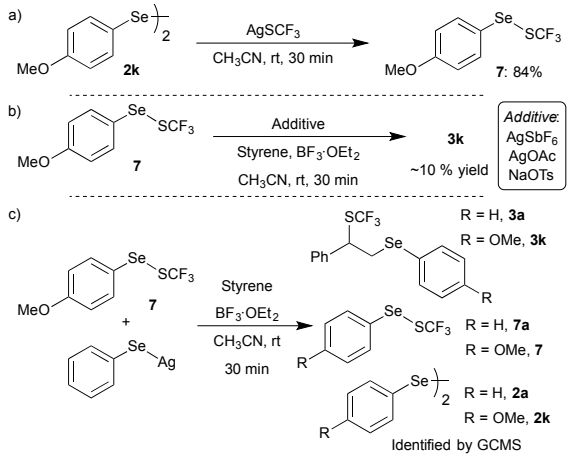
Scheme 3. Difunctionalization of substituted alkenes

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.



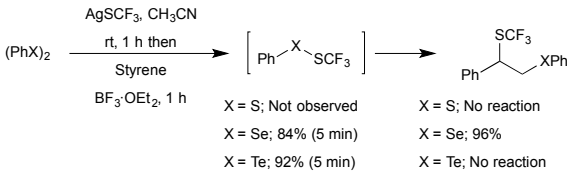
Scheme 4. Difunctionalization of styrene with diaryl diselenides 2 and $AgSCF_3$

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 intermediate and plausible reaction mechanism of the developed transformation was investigated. ^{19}F NMR analysis of optimized reactions showed an additional singlet at δ –45.3 along with $AgSCF_3$ and difunctionalized product **3a**. Subsequent, 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 and NaOTs (Scheme 5b).



Scheme 5. Control experiments

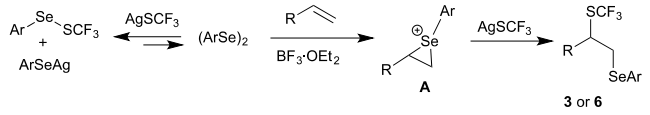
However, the formation of **7**, via treatment of diselenide and $AgSCF_3$ in CH_3CN in the presence of $BF_3{\cdot}OEt_2$, followed by the addition of styrene afforded the expected difunctionalized product **3k** in good yield. These studies suggested that $ArSeSCF_3$ might not be the intermediate of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



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

Furthermore, the difunctionalization was performed with other dichalcogenides in place of diselenide. 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 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 electrophilic -SeAr source and nucleophilic –SCF_3 source, respectively.

Based on the mechanistic study, the possible pathway for the difunctionalization of alkene was proposed as shown in Scheme 9. Initially, diphenyl diselenide **2a** and $AgSCF_3$ will 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**. Subsequent, regioselective ring opening of episelenonium ion **A** with $AgSCF_3$ would furnish the difunctionalized product **3**. Even though the concentration of $AgSCF_3$ is less at equilibrium but the overall reaction yield was satisfactory, because of the reversible reaction between $AgSCF_3$ and diphenyl diselenide.



Scheme 9. Plausible mechanism

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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Graphical Abstract

Trifluoromethylthiolative 1,2-Difunctionalization of Alkenes with Diselenides and $AgSCF_3$

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