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Alkoxysulfenylation of alkenes: development and recent advances

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Among the wide variety of synthetic transformations of inexpensive and abundant feedstock alkenes, vicinal difunctionalization of carbon–carbon double bonds represent one of the most powerful and effective strategies for the introduction of two distinct functional groups into target compounds in a one-pot process. In this context, the direct alkoxysulfenylation of alkenes has emerged as an elegant method to construct valuable β-alkoxy sulfides in an atom- and pot-economic manner utilizing readily accessible starting materials. Here, we review the available literature on this appealing research topic by hoping that it will be beneficial for eliciting further research and thinking in this domain.

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1. Introduction

Sulfides (thioethers; *R*–*S*–*R*′) are undoubtedly one of the most important subclasses of organosulfur compounds and play a significant role in the field of drug discovery and development due to their diversified biological activities such as anticancer, antipsychotic, anti-inflammatory, antiretroviral, anti-muscarinic, antiarrhythmic, and antiplatelet properties.[1,2] Intriguingly, more than thirty FDA-approved drugs contain one or more thioether motifs in their structures.[2] It is noteworthy to mention that this privileged moiety is also found in various agrochemicals, mainly in fungicides, herbicides and

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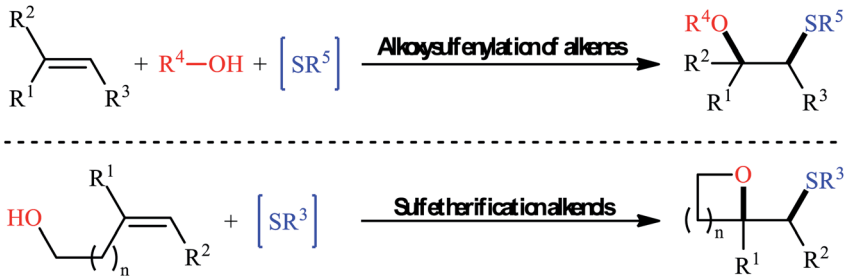

Fig. 1 Inter- and intramolecular alkoxysulfenylation of C–C double bonds.

insecticides.[3] In this family of compounds, β-alkoxy sulfides have recently attracted significant interest among chemists not only because of their interesting biological properties but also widespread synthetic applications.[4] Traditionally, these compounds are obtained through the reaction of β-alkoxy haloalkoxides with thiophenol sodium salts.[5] Another conventional approach is to react β-hydroxy thioethers with haloalkanes under alkaline conditions.[6] However, these methods suffer from certain disadvantages, such as limited substrate diversity and complicated multi-step operations. In order to bypass these limitations, the direct alkoxysulfenylation of widely available and inexpensive alkenes with alcohols and various sulfenylating agents (*e.g.*, thiols, disulfides, sulfonyl chlorides, sulfonyl hydrazides, sodium sulfinates) has emerged as a powerful and ideal strategy for the synthesis of the titled compounds which offer numerous advantages over the classical approaches such as simpler starting materials, shorter reaction steps, and higher atom economy. Since a number of remarkable discoveries and developments in this domain have taken place during the past few decades, seems it is an appropriate time to summarize those achievements. In continuation of our interest on organosulfur chemistry[7,8] and difunctionalization reactions,[9–16] in this review, we intend to highlight the literature reports on the alkoxysulfenylation of alkene substrates from 1981 till today. For clarity, the topic is divided into two major parts. The first section covers methods of intermolecular alkoxysulfenylation reactions, while the second focuses exclusively on the intramolecular reactions (Fig. 1).

2. Intermolecular alkoxysulfenylation of C–C double bonds

After seminal works by the groups of Ogawa[17] and Franck[18] on trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed alkoxylative sulfenylation of a small library of glucal derivatives employing sulfenate esters as both alkoxylating and sulfenylating agents, the first general and practical methodology for intermolecular alkoxysulfenylation of alkenes was published by Tian and co-workers in 2014.[19] In this report they showed that the three-component reaction between terminal aromatic alkenes **1**, sulfonyl hydrazides **2**, and aliphatic alcohols **3** catalyzed by molecular iodine afforded β-alkoxy sulfides **4** in good to excellent yields and outstanding regioselectivity, in which sulfenyl group selectively attached to the terminal carbon atom of the C–C double bond (Scheme 1). However, when aliphatic terminal alkenes were used as the substrates, mixtures of both possible isomers were obtained. Interestingly, while acyclic 1,2-disubstituted alkenes (*e.g.*, stilbene) failed to participate in this reaction, cyclohexene (a cyclic alkene) served as a suitable substrate and the target product was obtained in good yield as

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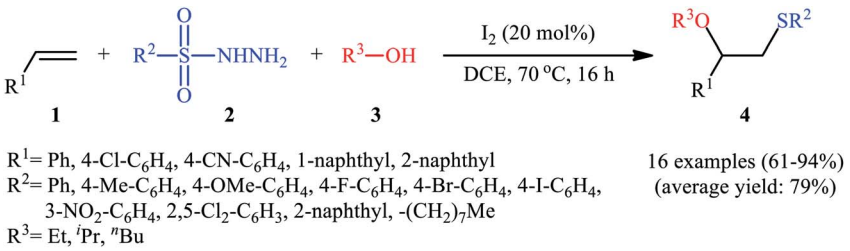
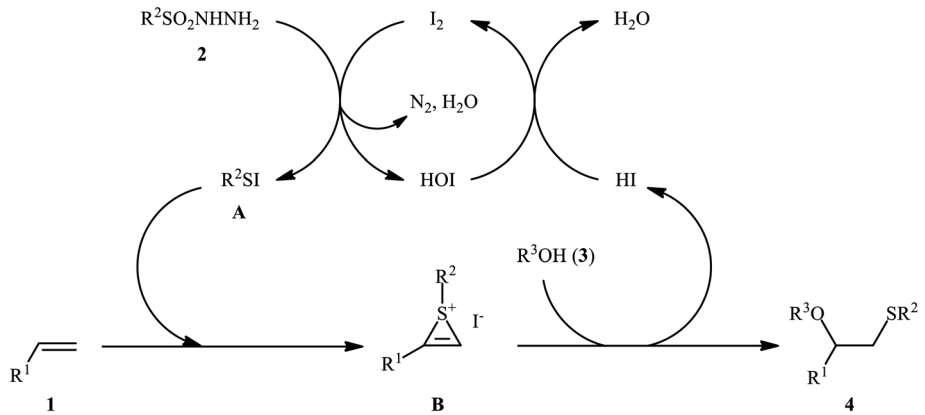


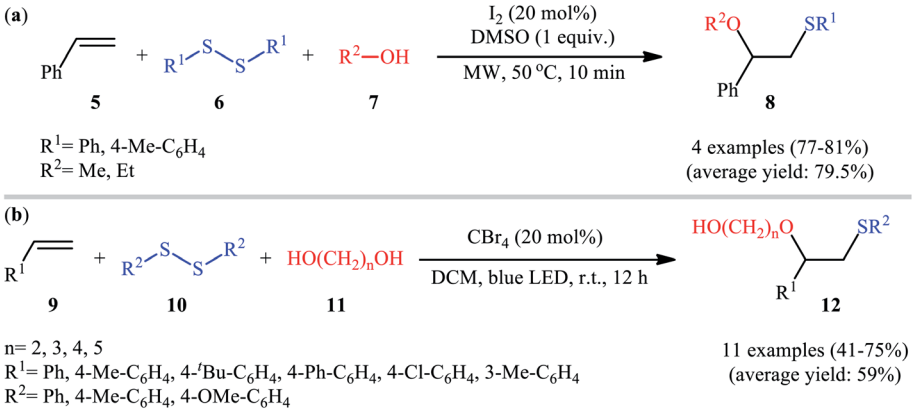
Scheme 1 Tian's synthesis of β-alkoxy sulfides **4**.

a single stereoisomer with *trans* configuration. Unfortunately, extension of the reaction to 1,1-disubstituted alkenes was not successful. Instead, in these cases, the corresponding vinyl thioethers were obtained in high yields. The following mechanism was proposed by the authors for this difunctionalization reaction: the sulfenyl iodide **A** formed from sulfonyl hydrazides **2** and I_2 is added to alkene **1** to form thiiranium intermediate **B**, then, the nucleophilic attack of alcohol **3** at the substituted carbon atom of thiiranium ion affords the expected ring-opening products **4** (Scheme 2).

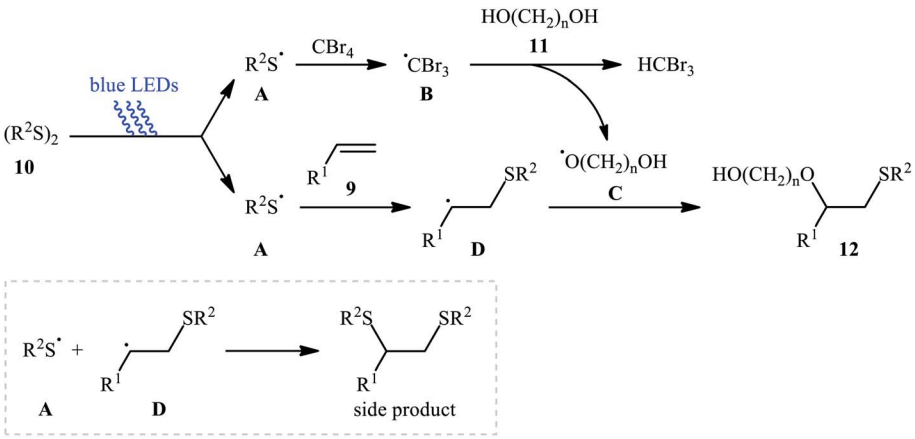
Subsequently, Braga and colleagues demonstrated that the same transformation could be achieved by using disulfides as sulfur sources.[20] Thus, in the presence of 20 mol% of I_2 as a catalyst and 1.0 equiv. of DMSO as an oxidant under microwave irradiation, alkoxysulfenylation of styrene **5** with a small series of aromatic disulfides **6** and aliphatic alcohols **7** furnished the corresponding β-alkoxy sulfides **8** in high yields and regioselectivities (Scheme 3a). Of note, in this reaction alcohols not only were served as substrates but also as solvents. Intriguingly, when disulfides were replaced with diselenides, the respective β-alkoxy selenide products were obtained in fair to excellent yields. The authors proposed a mechanistic course analogous to that of Tian and co-workers for the alkoxysulfenylation with sulfonyl hydrazides. Recently, Meng and Wang along with their co-workers demonstrated the similar alkoxysulfenylation under visible light irradiation and photocatalyst-free conditions.[21] The transformation was performed in DCM at room temperature by using the combination of blue LED and carbon tetrabromide (CBr_4). Under these conditions several styrene derivatives **9** carrying various substituents were slowly converted to the corresponding β-alkoxy sulfides **12** in moderate to good yields by treatment with diaryl disulfides **10** and diols **11** (Scheme 3b). The results proved that the lengths of carbon chain in diols had a notable impact on the rate of reaction. Generally, shorter chain diols were found to be more reactive than the longer chain alternatives. The authors attributed this observation to the interaction of the intermolecular hydroxyl groups. It is worth noting that when H_2O was used in place of diols under the identical conditions, the hydroxysulfenylated products were obtained in modest to high yields. However, no product was observed when aliphatic alkene or aliphatic disulfide were used as one of the substrates. Furthermore, the process is not viable for gram-scale due to the drastic reduction in the yield (from 69% in the 0.6 mmol scale, to 40% in the 5.0 mmol scale). Several control experiments were implemented to probe the mechanism of this reaction; no reaction was observed in the absence of CBr_4 or a light source. Additionally, no reaction could be observed when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction mixture. On this basis, the authors proposed a plausible mechanistic pathway in which the S–S bond in disulfide **10** undergoes hemolytic cleavage under the irradiation of blue LED to generate thiyl radical **A**, which after reaction with CBr_4 affords a tribromomethyl radical **B**. Next, abstraction of a hydrogen by the newly formed radical **B** from diol **11** leads to alkoxyl radical **C** and $HCBr_3$. Conversely, the addition of another molecule of thiyl radical **A** to alkene **9** provides carbon-



Scheme 2 I_2-catalyzed alkoxylative sulfenylation of alkenes **1** with sulfonyl hydrazides **2** and alcohols **3**.



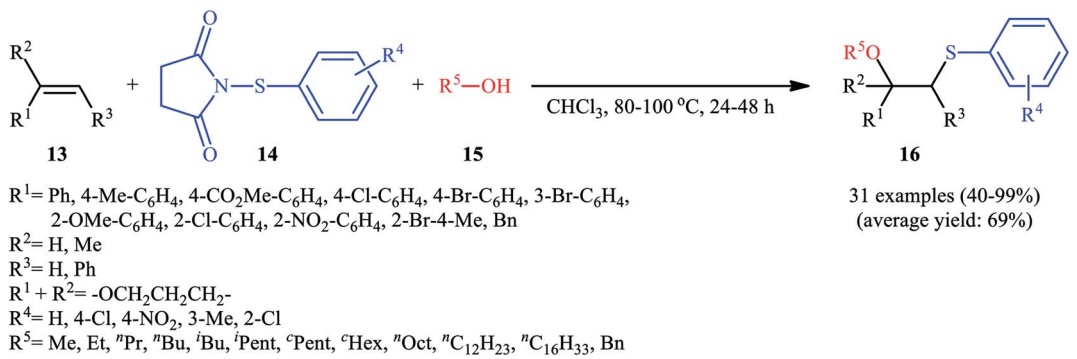
Scheme 3 (a) I_2-catalyzed alkoxysulfenylation of styrene **5** with aromatic disulfides **6** and aliphatic alcohols **7** developed by Braga; (b) visible-light-induced alkoxysulfenylation of alkenes **9** with disulfides **10** and diols **11**.



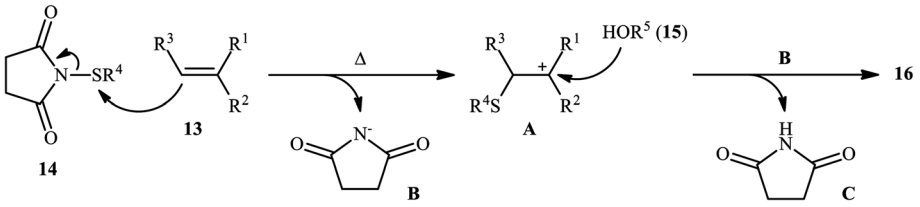
Scheme 4 Possible mechanism for the formation of β-alkoxy sulfides **12**.

centered radical **D**. Finally, coupling of alkoxyl radical **C** with intermediate **C** gives the desired product **12** (Scheme 4).

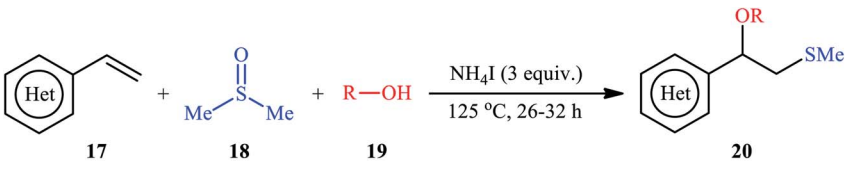
In 2015, Fu's research team disclosed the use of easily available 1-(arylthio)pyrrolidine-2,5-diones as an alternative sulfenylating reagent in oxysulfenylation reactions.[22] In this investigation, thirty one β-alkoxy sulfides **16** were synthesized in moderate to quantitative yields by direct reaction of various mono-, 1,1-di-, and 1,2-di-substituted alkenes **13** with functionalized 1-(arylthio)pyrrolidine-2,5-diones **14** and aryl/benzyl alcohols **15** in $CHCl_3$ under catalyst- and additive-free conditions (Scheme 5). Noteworthy, in this transformation, the terminal alkenes were more reactive than the internal ones, and aliphatic alkenes were also tolerated, although the products were obtained in lower yields. Regarding the reaction



Scheme 5 Catalyst-free oxysulfenylation of alkenes **13** with 1-(arylthio)pyrrolidine-2,5-diones **14** and alcohols **15**.



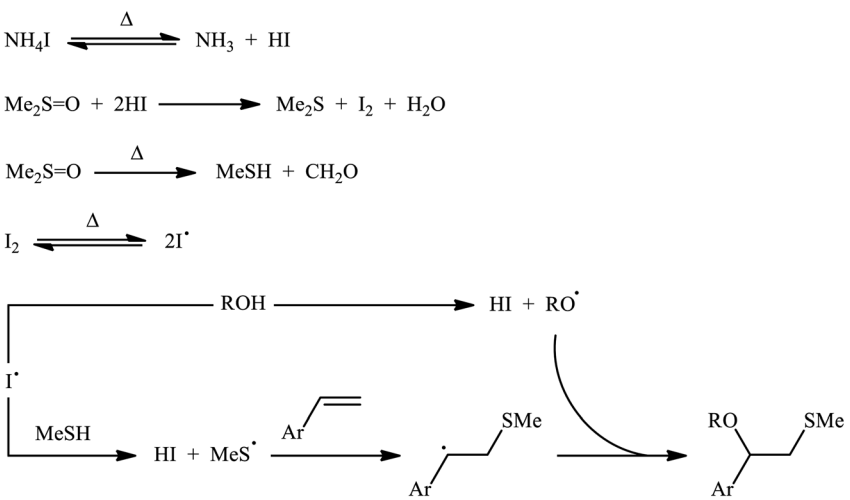
Scheme 6 The plausible mechanistic pathway for the reaction in Scheme 5.



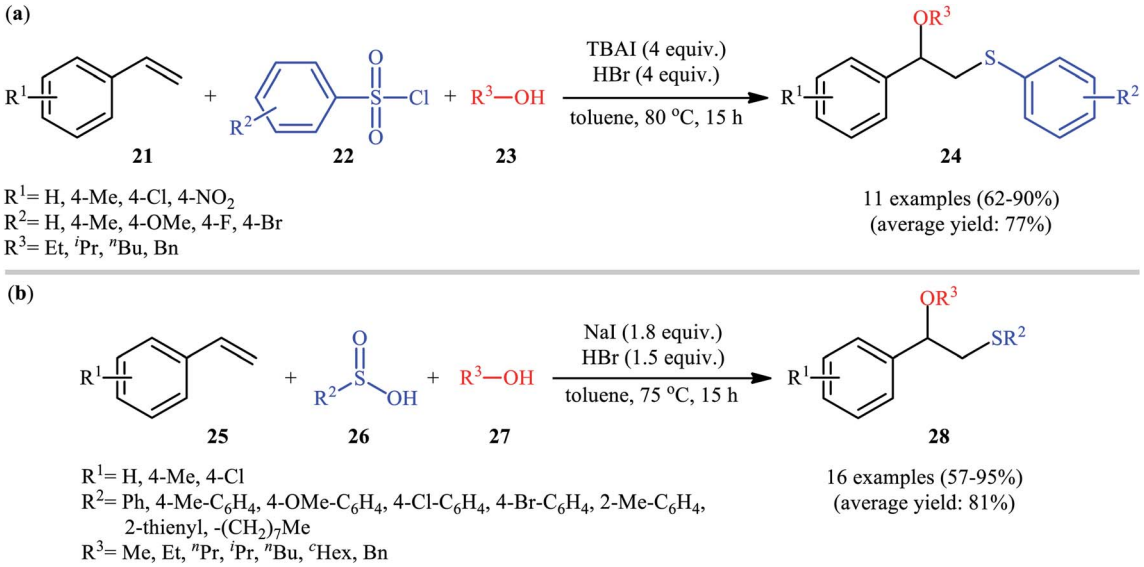
Scheme 7 Synthesis of β-alkoxy methyl sulfides **20** through the NH_4I-mediated three-component coupling alkenes **17**, dimethyl sulfoxide **18** and alcohols **19**.

mechanism, the authors proposed the formation of a carbonium ion intermediate **A** *via* the reaction of alkene **13** with 1-(arylthio)pyrrolidine-2,5-dione **14** followed by electrophilic attack of the alcohol **15** on the carbocation center (Scheme 6). Recently, Liang and Zhao applied this chemistry in highly enantiselective synthesis of a library of thiolated 1,3-aminoalcohols using a chiral selenide catalyst.[23]

A promising contribution to this field was reported by Yuan, Li, and co-workers in 2015,[24] when various terminal aromatic and heteroaromatic alkenes **17** were converted to the corresponding β-alkoxy methyl sulfides **20** through the NH_4I-mediated alkoxysulfenylation with dimethyl sulfoxide (DMSO; **18**) and alcohols **19** under metal-free conditions. As shown in Scheme 7, this reaction tolerated various primary and secondary alcohols and both electron-rich and electron-poor alkenes, and gave the final products in moderate to high yields and excellent regioselectivities. Two α-substituted styrenes have also been tested and afforded the expected products in good yields. Notably, β-substituted styrenes were also tolerated under the reaction conditions, however, the diastereoselectivity of products was modest at best. The proposed mechanism for this transformation is shown in Scheme 8 which is based on a radical process. First, molecular iodine (I_2) and methanethiol (MeSH) are formed from NH_4I and DMSO through a series of reactions. Next, I_2 is decomposed under the thermal condition to form iodine radical ($I^{\bullet}$), which is later reacted with precursor



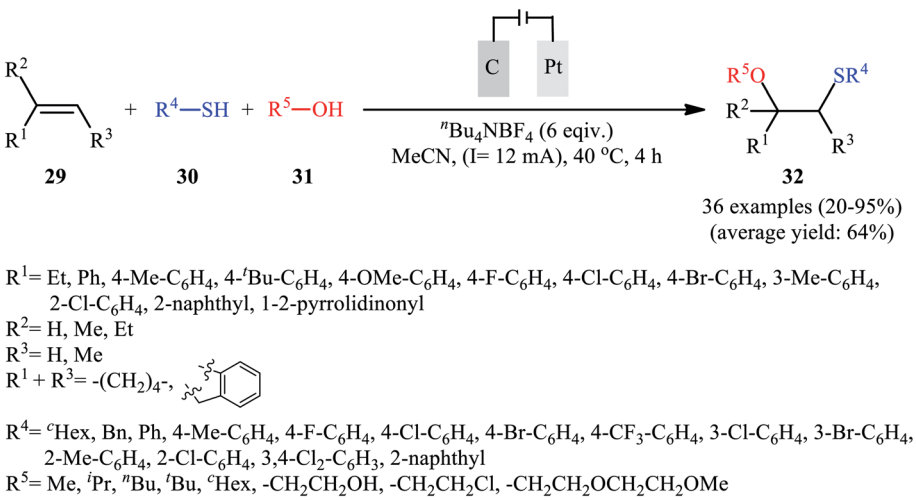
Scheme 8 Possible mechanism for the formation of β-alkoxy methyl sulfides **20**.



Scheme 9 (a) TBAI-mediated synthesis of β-alkoxy sulfides **24** reported by Lin and Guo; (b) NaI/HBr-mediated three-component alkoxysulfenylation reaction of alkenes **25** with sulfinic acids **26** and alcohols **27**.

MeSH resulting in a methylthiyl radical (MeSC˙) and concurrently abstracted a hydrogen atom from alcohols to afford alkoxy radical (ROC˙). Subsequently, addition of the methylthiyl radical to the C=C double bond of alkene leads to an alkyl radical intermediate. Finally, the rapid combination of alkoxy radical and the newly formed carbon-centered radical delivers the desired product. Recently, Liu *et al.* extended the substrate scope of this reaction to aliphatic (terminal and internal) alkenes by performing the process in the presence of $(COCl)_2$ in MeCN.[25] Noteworthy, cycloalkenes selectively afforded *trans*-adducts under these conditions. Besides alcohols, carboxylic acids also could be applied as suitable *O*-nucleophiles under the identical conditions.

In 2016, Lin and Guo realized the effectiveness of broadly available and bench-stable sulfonyl chlorides as sulfenylating agents in alkoxysulfenylation reactions of C–C double bonds.[26] In this study, they showed that treatment of aromatic terminal alkenes **21** with arylsulfonyl chlorides **22** and aliphatic alcohols **23** in the presence of excess amounts of tetrabutylammonium iodide (TBAI) as a promoter and HBr as an acidic additive in toluene furnished the corresponding β-alkoxy sulfides **24** in good to excellent yields, ranging from 62% to 90% (Scheme 9a). Internal aliphatic alkenes were also found to be suitable substrates for this protocol as exemplified by the formation of (2-ethoxycyclohexyl) (*p*-tolyl)sulfane by using cyclohexene as the substrate. However, just like previous works, aromatic alcohols were inert in this transformation. The mechanism proposed by the authors to explain this difunctionalization reaction is analogous to the one depicted for in Scheme 2. Along this line, the same research group also reported that in the presence of



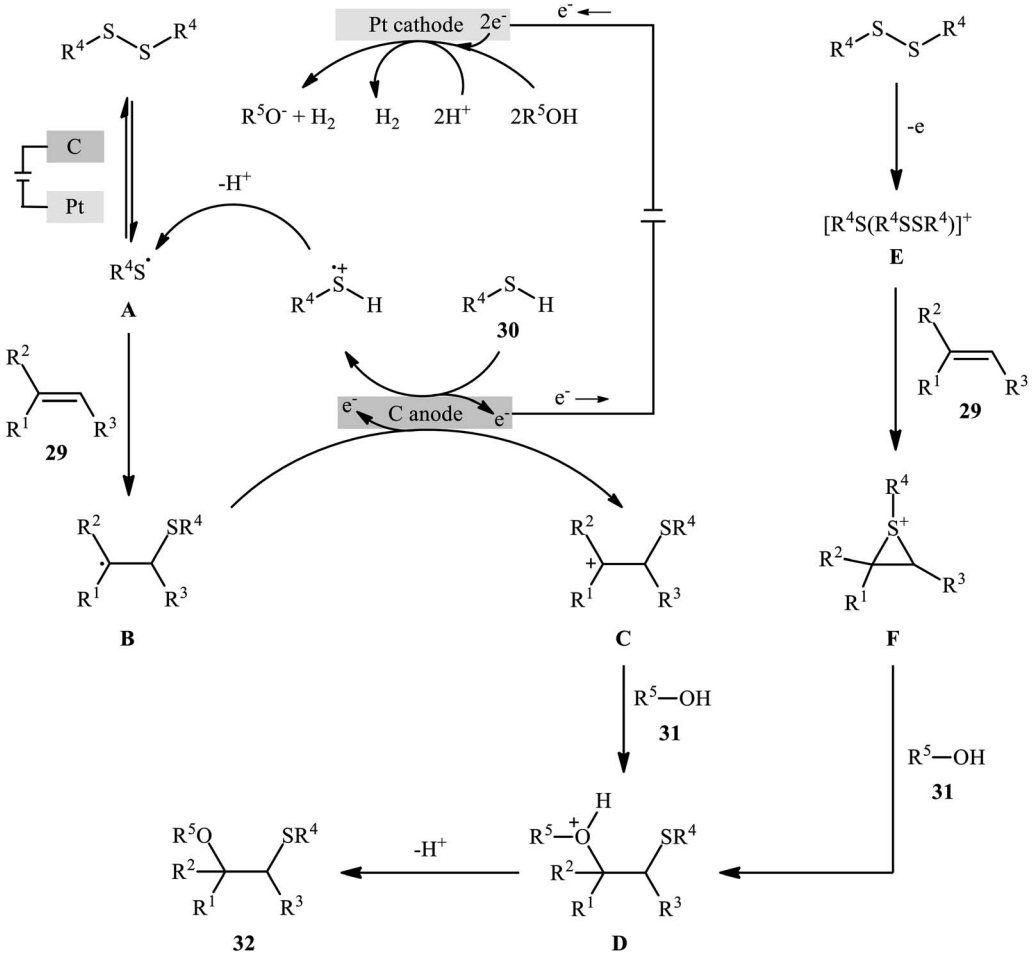
Scheme 10 Electrochemical alkoxysulfenylation of alkenes **29** with thiols **30** and alcohols **31**.

over-stoichiometric amounts of NaI and HBr, styrene derivatives **25** were similarly coupled with various aryl/alkyl-sulfinic acids **26** and alkyl/benzyl-alcohols **27** to obtain β-alkoxy sulfide products **28** with yields of up to 95% (Scheme 9b).[27]

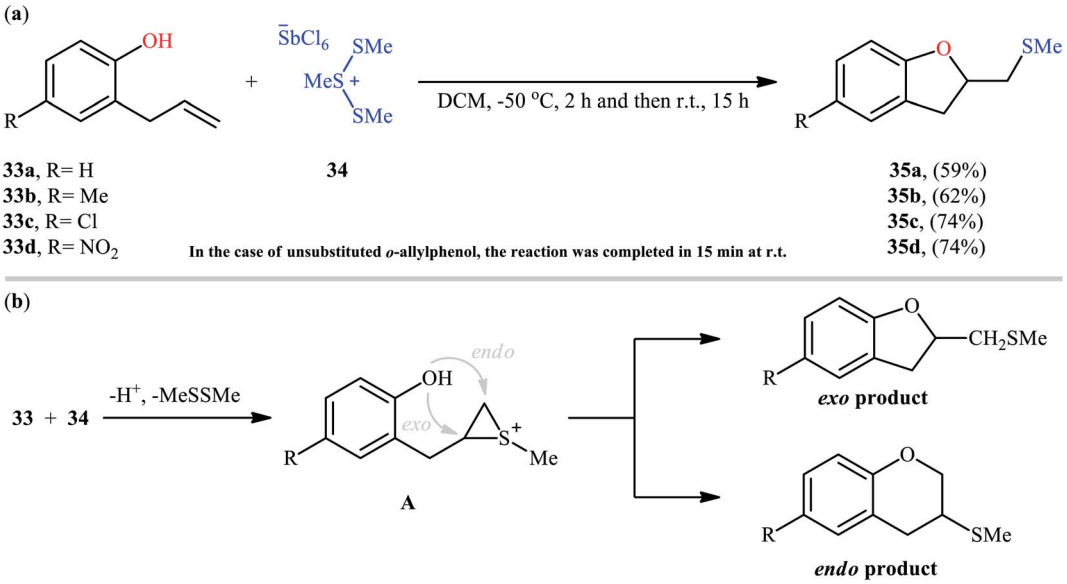
In 2018, Lei and co-workers developed an elegant electrochemical alkoxysulfenylation of alkenes **29** with thiols **30** and alcohols **31** under external oxidant-free conditions which exhibited better substrate scope compared to previously reported examples of this chemistry.[28] The reactions were conducted in an undivided cell under a constant current of 12 mA cm^{-2} with carbon anode and platinum plate cathode employing $^{n}Bu_4NBF_4$ as the electrolyte and MeCN as the solvent at 40 °C, which afforded the β-alkoxy sulfide products **32** in 20–95% yields (Scheme 10). Noteworthy, other nucleophiles such as amines, acetic acid and water were also developed as the coupling partners in this reaction. Some important information of this oxidative sulfenylation reaction are listed below: (i) although both aromatic and aliphatic thiols were compatible with this reaction, aliphatic thiols afforded significantly poorer yields compared to aromatic ones; (ii) like previous works, the scope of alcohols was restricted to the use of aliphatic and benzylic alcohols; and (iii) the protocol for difunctionalization of aliphatic and internal alkenes was considerably less efficient than aromatic and terminal alkenes. According to the authors proposed mechanism (Scheme 11), this reaction proceeds through a thiiranium ion intermediate.

3. Intramolecular alkoxysulfenylation of C–C double bonds

Cyclofunctionalization reactions represent an important strategy for the synthesis of functionalized (hetero)cyclic structures from simple starting materials that would otherwise be difficult to prepare.[29] In this family of reactions, sulfetherification of alkenols offers a promising strategy for the selective synthesis of sulfenyl-substituted oxacycles within a single click. One of the earliest reports on the cyclizative sulfenylation of alkenols was published by Capozzi and co-workers in 1981,[30] who showed that the treatment of *o*-allylphenols **33** with methyl(bismethy1thio)sulfonium hexachloroantimonate **34** in the absence of any catalyst or additive in anhydrous DCM, resulted in the formation of methylthio-substituted dihydrobenzofurans **35** in good yields and selectivities (Scheme 12a). The reaction is noteworthy in that both electron-rich and electron-poor *o*-allylphenols were well tolerated. However, in the case of unsubstituted *o*-allylphenol, besides the desired 2-



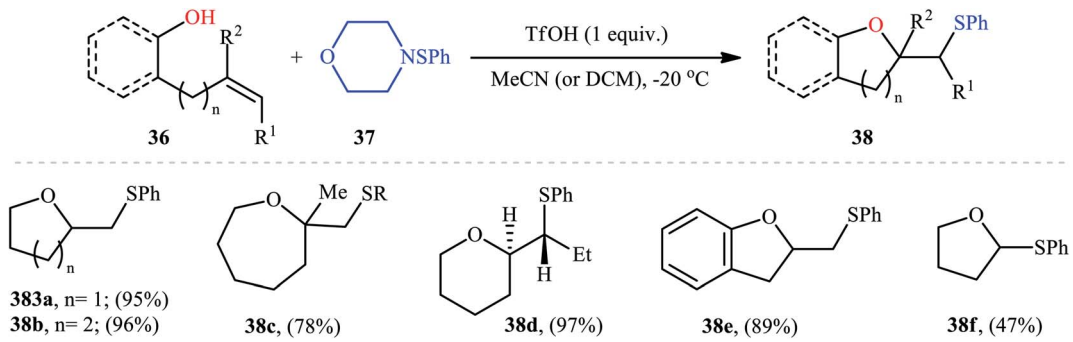
Scheme 11 A plausible mechanism for the reaction in Scheme 10.



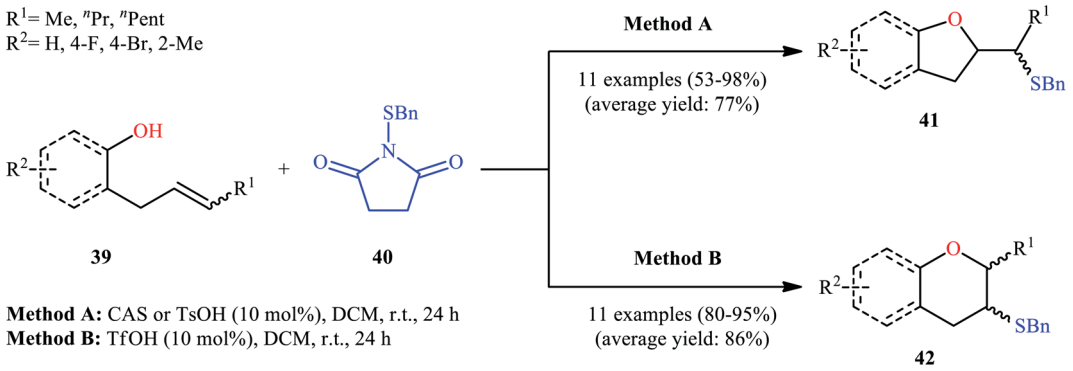
Scheme 12 (a) Synthesis of 2-((methylthio)methyl)-2,3-dihydrobenzofurans **35** through intramolecular sulfetherification of alkenols **33** with methyl(bismethy1thio)sulfonium hexachloroantimonate **34**; (b) the plausible mechanistic pathway for the formation of dihydrobenzofurans **35**.

((methylthio)methyl)-substituted dihydrobenzofuran, a small amount of 5-(methylthio)-2-((methylthio)methyl)-2,3-dihydrobenzofuran was obtained as a side-product. Intriguingly, the authors nicely controlled the selectivity of this reaction by using different reaction conditions. The formation of dithiolated product was selectively accomplished simply by using a two-fold excess of the sulfonium salt. A reasonable selectivity for the synthesis of the mono-thiolated dihydrobenzofuran **35a** was obtained running the reaction at −40 °C. The author also provided the possible mechanism for the formation of benzofuran derivatives **35** (Scheme 12b), in which the thiiranium intermediate **A** formed *via* attack of the methylthiolating agent at the double bond of the allylic residue undergoes ring opening through intramolecular nucleophilic attack by the phenolic oxygen at the internal carbon to give regiospecifically the dihydrobenzofuran ring although the possibility of ring closure to a dihydrobenzopyrane ring also exist. Four years later, O'Malley and Cava reported a similar sulfetherification of γ,δ-unsaturated alcohols using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) as the methylsulfenylation reagent and $^{i}Pr_2NEt$ as a base in anhydrous acetonitrile solvent.[31] Notably, γ,δ-unsaturated carboxylic acids could also undergo intramolecular cyclofunctionalization reaction under the identical conditions and give the corresponding lactones in good to high yields. This transformation was later reinvestigated by Okuma and colleagues employing dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) as the sulfenylation agents and good results were observed.[32]

In 1987, Brownbridge introduced the use of N-(phenylthio) morpholine as an efficient phenylthiolating agent for intramolecular sulfenyl etherification of alkenols under metal-free conditions.[33] Thus, a library of thiophenol-functionalized five-, six-, and seven-membered cyclic ethers **38** were successfully synthesized by treatment of the corresponding unsaturated alcohols **36** with *N*-(phenylthio)morpholine **37** in the presence of a stoichiometric amount of triflic acid (TfOH) as a promoter in a dry solvent at −20 °C (Scheme 13). However, cyclization to give four-membered ring systems did not take place by this method. Interestingly, when a *cis*-disubstituted alkenol (5-



Scheme 13 Brownbridge's synthesis of thiol-substituted cyclic ethers **38**.



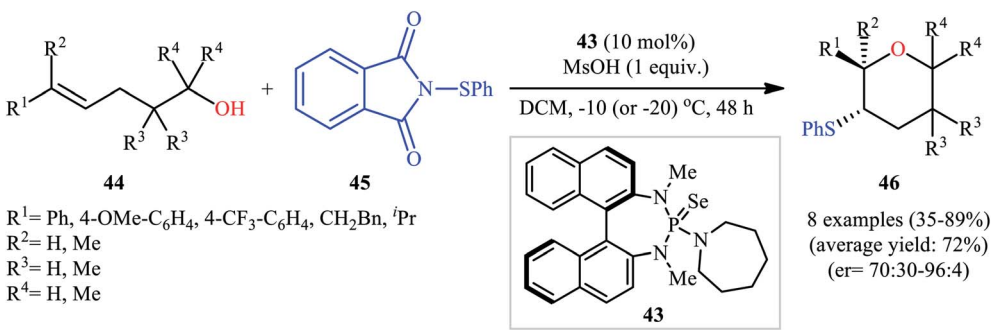
Scheme 14 Acid-dependent regioselective sulfetherification of alkenols **39** in the presence of *N*-(benzylthio)succinimide **40** reported by Shi.

octen-1-ol) subjected to this reaction condition, a single regio- and stereo-isomer **38d** was formed, indicated *trans*-addition without any alkene isomerization. Shortly afterwards, the author found that the regio- and stereo-selectivity of this cyclofunctionalization reaction is highly dependent on the substitution patterns of the employed alkenols.[34] Benzenesulfenyl chloride was also found to be useful for the cyclization, though few examples are available.[35–37]

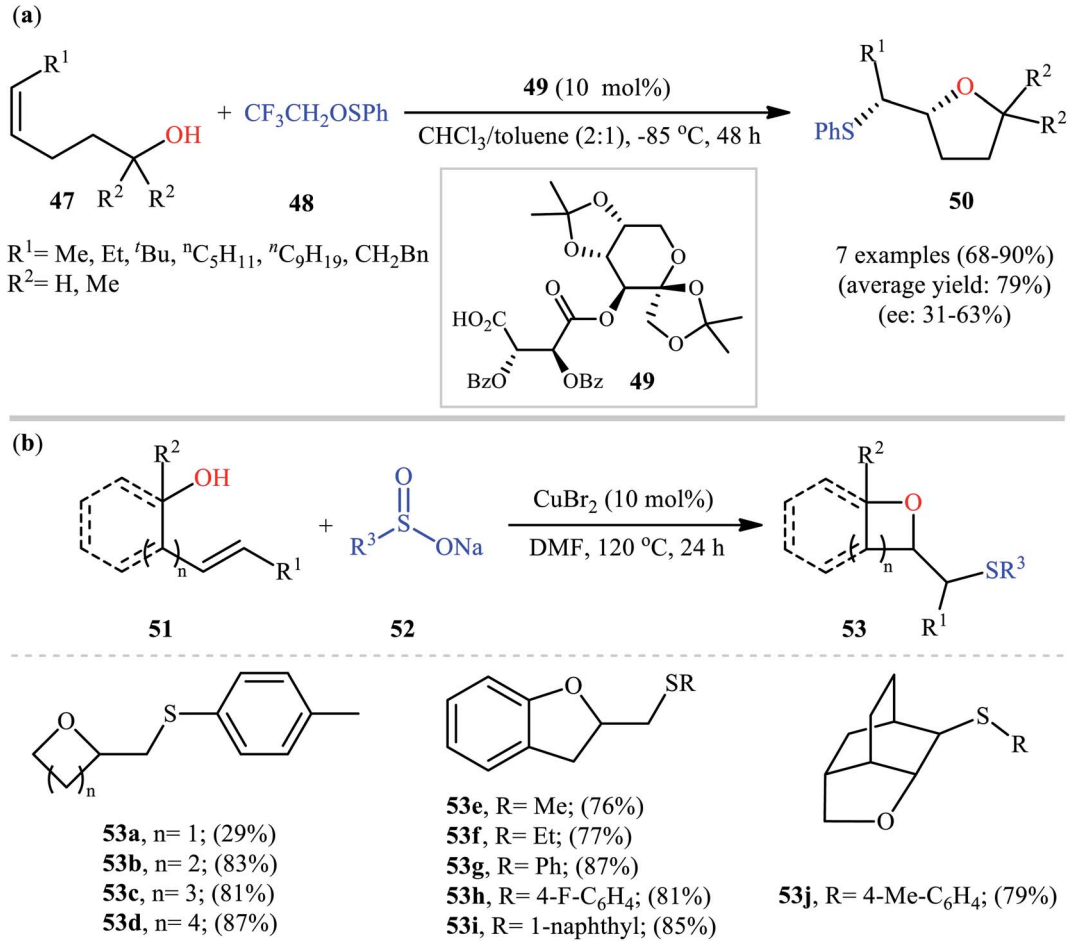
Drawing inspiration from these works, in 2011, Shi's group demonstrated an interesting acid-catalyzed regio- and stereoselective sulfetherification of alkenols **39** with the use of *N*-(benzylthio)succinimide **40**, thus providing either the corresponding tetrahydrofurans **41** and tetrahydropyrans **42** depending upon the acid catalyst used (Scheme 14).[38] Studies indicated the formation of 5-*exo* cyclization products with camphorsulfonic acid (CSA) or tosylic acid (TsOH) and 6-*endo* cyclization products in the presence of triflic acid (TfOH). The results proved that *cis*-alkenes gave higher 5-*exo* selectivity as compared to *trans*-alkenes. The authors ascribed this observation by the steric effect during the cyclization. Studies also showed that when isolated 5-*exo* products were treated with a catalytic amount of TfOH at room temperature, 6-*endo* products were formed in high yields. These results clearly indicated that the cyclization route to tetrahydrofurans **41** was under kinetic control, while the formation of tetrahydropyrans **42** was thermodynamically favored.

Concurrently, Denmark and colleagues developed a robust asymmetric sulfetherification of various alkenols using a chiral BINAM-based selenophosphoramide catalyst **43** and a Brønsted acid (methanesulfonic acid, MsOH) additive.[39] A library of conjugated and *trans* nonconjugated alkenes **44** reacted efficiently with *N*-phenylsulfenyl-phthalimide **45** in the presence of 10 mol% of **43** to afford sulfenylated tetrahydropyrans **46** in modest to excellent yields and outstanding enantioselectivities along with a small amount of sulfenylated tetrahydrofuran side-products (Scheme 15). Notably, when unsubstituted, *cis* nonconjugated and geminally disubstituted alkenes were subjected to the same reaction conditions, sulfenylated tetrahydrofurans were formed as the main reaction products, thus suggesting that the regioselectivity of this transformation is strongly dependent on the substitution patterns of the employed alkenols. Besides alkenols, unsaturated carboxylic acids could also be elegantly used in this cyclofunctionalization reaction. Moreover, several successful examples of the intermolecular sulfetherification of simple alkenes with methanol also reported under this reaction condition.

In a related investigation, Shi and co-workers reacted 5-substituted-pent-4-en-1-ols **47** with trifluoroethyl benzenesulfenate **48** in the presence of chiral tartaric acid-based catalyst **49** to selectively provide enantioenriched tetrahydrofurans **50** in good to excellent yields (68–90%) and low to good enantioselectivities (31–63% ee) (Scheme 16a).[40] Although the reaction showed good tolerance to a series of *cis*-alkenols, *trans*-alkenols completely failed to participate in this transformation. Subsequently, Wu and Jiang along with their co-workers demonstrated the synthesis of a diverse range of sulfenylated four-,

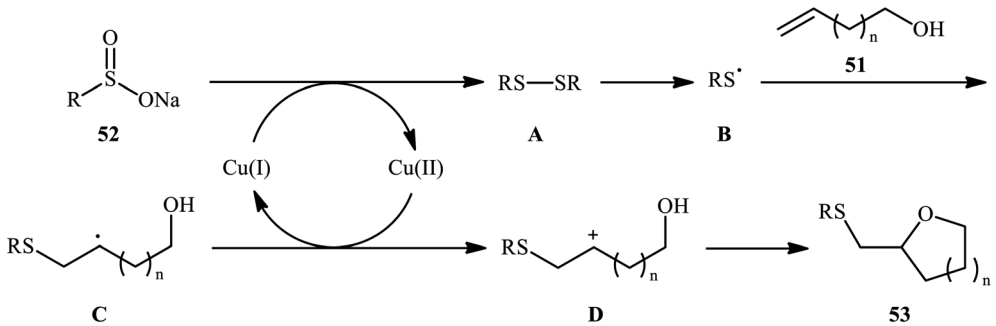


Scheme 15 Denmark's synthesis of chiral sulfenylated tetrahydropyrans **45**.

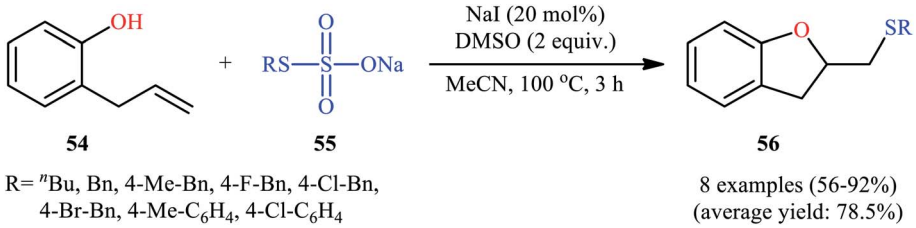


Scheme 16 (a) Shi's synthesis of enantioenriched tetrahydrofurans **50**; (b) selected examples of the Cu(II)-catalyzed sulfenyl etherification of alkenols **51** with sodium sulfinates **52** reported by Wu and Jiang.

five-, six-, and seven-membered cyclic ether derivatives **53** *via* $CuBr_2$-catalyzed sulfetherification of the corresponding alkenols **51** employing sodium sulfinates **52** as sulfenylating agents.[41] The reaction was run in DMF at 120 °C, tolerated various aliphatic, benzylic, and (hetero)aromatic sodium sulfinates, and provided the desired sulfenylated O-heterocycles in good to excellent yield. However, the only example of strained four-membered ring product was obtained in medium yield. Some reported examples are shown in Scheme 16b. It should be mentioned that other simple copper salts such as CuCl, CuBr, CuI, and $CuCl_2$ were also found to catalyze this sulfenylative cyclization reaction, albeit with reduced efficiencies. On the basis of a series of preliminary control experiments, it was suggested that this sulfetherification reaction starts with the formation of disulfide intermediate **A** *via* Cu-catalyzed dimerization of sodium sulfinate **52**, which then undergoes radical cracking to give the sulfur radical **B**. Subsequently, this radical adds to the double bond of alkene **51** to form the α-sulfenyl-



Scheme 17 Mechanism of the Cu(II)-catalyzed sulfetherification of alkenols **51** with sodium sulfinates **52**.



Scheme 18 NaI-catalyzed sulfetherification of 2-allylphenol **54** with thiosulfates **55**.

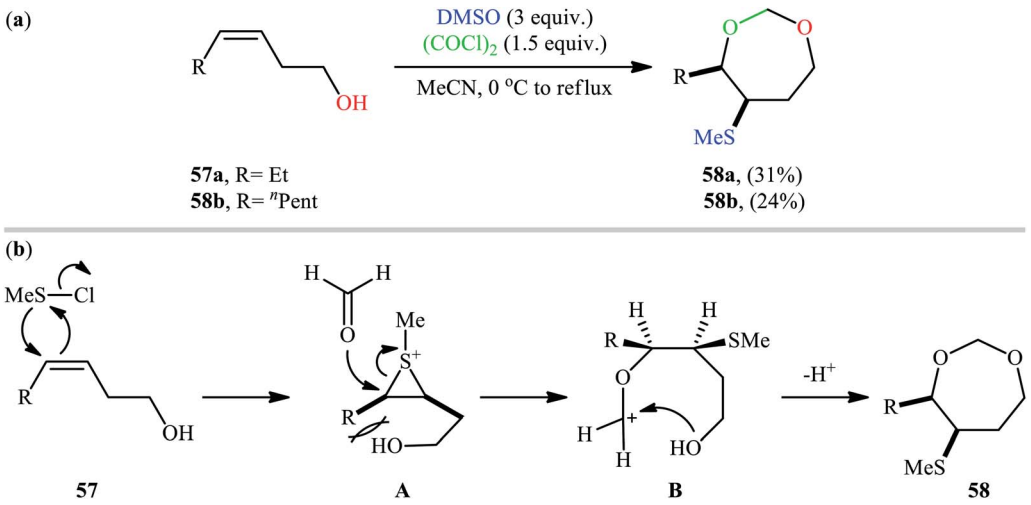
alkyl radical **C** that, after a single-electron oxidation converts to the carbocation **D**. Finally, the internal nucleophilic trapping of the newly formed intermediate **D** affords the desired product **53** (Scheme 17).

In 2017, Zhang, Yan, and Lin studied the possibility of synthesizing sulfenylated 2,3-dihydrobenzofurans through the intramolecular sulfetherification of 2-allylphenol **54** with environmentally friendly thiosulfates **55**.[42] To determine the best conditions, they meticulously probed the activities of different iodine-based catalysts (*e.g.*, I_2, NaI, TBAI, NH_4I) and oxidants (*e.g.*, H_2O_2, DMSO, TBHP, $Cu(OAc)_2$, $K_2S_2O_8$) in the sulfenyl etherification of 2-allylphenol with sodium *S*-benzyl sulfothioate in MeCN, as a model reaction. The optimal system was recognized with the used of 20 mol% NaI and 2 equiv. of DMSO at 100 °C. Under the optimized conditions, 2-allylphenol **54** was reacted with various aromatic, aliphatic, and benzylic thiosulfates **55** to provide the corresponding 2-(thiomethyl)-2,3-dihydrobenzofurans **56** in good to excellent yields within 3 h (Scheme 18). The authors have also examined pent-4-en-1-ol in place of 2-allylphenol to give the respective tetrahydrofuran in good yield. Furthermore, three component reaction between alkenes, acetic acid, and thiosulfates also successfully implemented under the identical conditions to provide the desired β-acetoxy sulfides in good yields.

Along this line, recently, Gao *et al.* found that a combination of dimethyl sulfoxide (DMSO) and oxalyl chloride [$(COCl)_2$] is a suitable reagent for sulfenyletherification of unsaturated alcohols under catalyst- and additive-free conditions.[43] Methanesulfenyl chloride (MeSCl) is assumed to be the compound responsible for the sulfenyletherification, which is generated by the reaction of DMSO and $(COCl)_2$. Various unsaturated alcohols including 3, 4, and 5-alkenols were all compatible by this reaction, thus indicating its broad applicability. However, *cis*-3-alkenols **57** cannot be converted to cyclic ethers due to the effect of steric bulk in the intermediates. In these cases, instead of cyclic ethers, seven-membered cyclic acetals **58** with *cis* configurations were generated as the sole reaction products (Scheme 19a). According to the authors proposed mechanism (Scheme 19b), this transformation began with the addition of methanechloride to the double bond of *cis*-3-alkenol **57** to achieve *cis*-thiiranium ion intermediate **A**. Then, the oxygen of carbonyl group of formaldehyde, generated *in situ* during the formation of methanesulfenyl chloride, was attached at the less substituted carbon atom of thiiranium ion to form carbocation intermediate **B**. Finally, intramolecular cyclization of intermediate **B** led to the observed seven-membered cyclic acetal **58**.

4. Conclusion

Vicinal difunctionalization of alkenes is an attractive and efficient way to incorporation of two new adjacent functional groups onto a carbon–carbon bond, producing complicated



Scheme 19 (a) Gao's synthesis of seven-membered cyclic acetals **58**; (b) plausible reaction mechanism for the formation of seven-membered cyclic acetals **58**.

molecular scaffolds in one step. In this family of reactions, the direct alkoxysulfenylation of alkenes with alcohols and appropriate sulfenylating agents has been attracted considerable attention as an ideal strategy for the preparation of β-alkoxy sulfide derivatives, which serve as versatile building blocks in chemical synthesis. As illustrated, not only intermolecular but also intramolecular version of this transformation using alkenols as both the C–C double bond and hydroxy sources have been extensively investigated. Although several common sulfenylating agents have been successfully applied in this difunctionalization reaction, the scope of alcohols is mainly restricted to the aliphatic alcohols. Additionally, the scope of alkenes is largely limited to styrene derivatives. Therefore, of course, further investigations and improvements are still needed that this research field matures.

Conflicts of interest

There are no conflicts to declare.

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