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Alkoxysulfonylation 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 alkoxysulfonylation 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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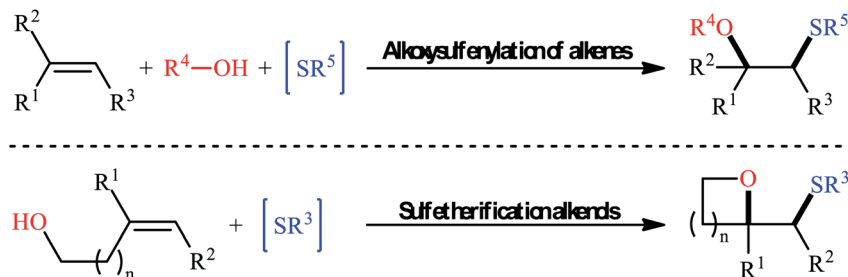


Fig. 1 Inter- and intramolecular alkoxylation of C–C double bonds.

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 alkoxylation of widely available and inexpensive alkenes with alcohols and various sulfenylating agents (*e.g.*, thiols, disulfides, sulfonyl chlorides, sulfonyl hydrazides, sodium sulfonates) 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 alkoxylation of alkene substrates from 1981 till today. For clarity, the topic is divided into two major

parts. The first section covers methods of intermolecular alkoxylation reactions, while the second focuses exclusively on the intramolecular reactions (Fig. 1).

2. Intermolecular alkoxylation of C–C double bonds

After seminal works by the groups of Ogawa¹⁷ and Franck¹⁸ on trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed alkoxylation of a small library of glucal derivatives employing sulfenylating agents, the first general and practical methodology for intermolecular alkoxylation 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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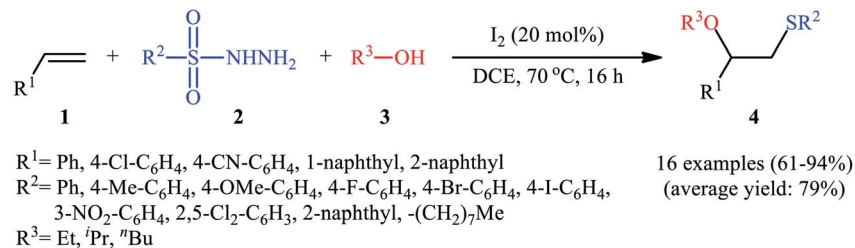
cooperation with many research project teams around world such as China, Malaysia, and Thailand. His interests are Environmental Biotechnology, Biochemistry, Gene pathways in the phytoremediation processes.



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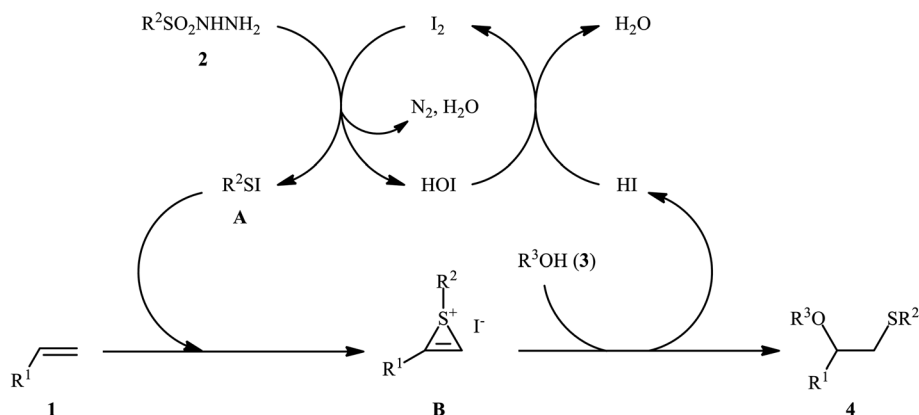


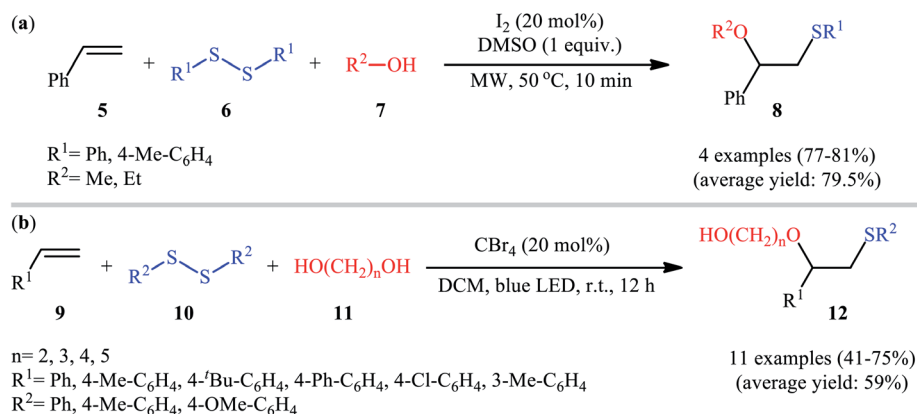
Scheme 1 Tian's synthesis of β-alkoxy sulfides 4.

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 sulfonyl iodide **A** formed from sulfonyl hydrazides **2** and I₂ 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).

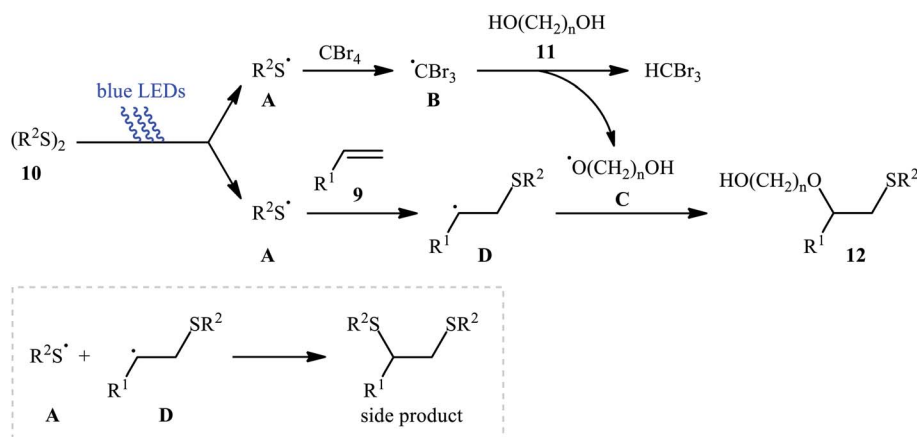
Subsequently, Braga and colleagues demonstrated that the same transformation could be achieved by using disulfides as sulfur sources.²⁰ Thus, in the presence of 20 mol% of I₂ as a catalyst and 1.0 equiv. of DMSO as an oxidant under microwave irradiation, alkoxy-sulfenylation of styrene **5** with a small 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 alkoxy-sulfenylation with sulfonyl hydrazides. Recently, Meng and Wang along with their co-workers demonstrated the similar alkoxy-sulfenylation 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 (CBr₄). 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 H₂O was used in place of diols under the identical conditions, the hydroxysulfonylated 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 CBr₄ 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 homolytic cleavage under the irradiation of blue LED to generate thiyl radical **A**, which after reaction with CBr₄ affords a tribromomethyl radical **B**. Next, abstraction of a hydrogen by the newly formed radical **B** from diol **11** leads to alkoxy radical **C** and HCBR₃. Conversely, the addition of another molecule of thiyl radical **A** to alkene **9** provides carbon-

Scheme 2 I₂-catalyzed alkoxylation of alkenes **1** with sulfonyl hydrazides **2** and alcohols **3**.



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

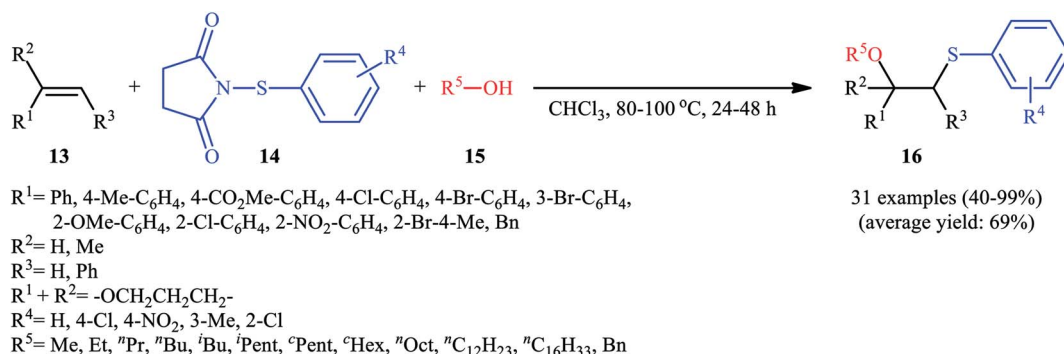


Scheme 4 Possible mechanism for the formation of β -alkoxy sulfides **12**.

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

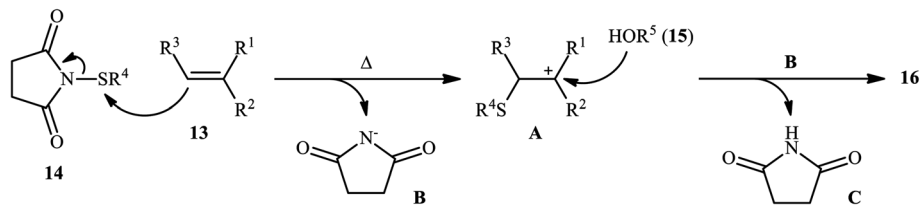
In 2015, Fu's research team disclosed the use of easily available 1-(arythio)pyrrolidine-2,5-diones as an alternative sulfenyating reagent in oxysulfenylation reactions.²² In this investigation, thirty one β -alkoxy sulfides **16** were synthesized in moderate to quantitative yields by direct reaction of various

mono-, 1,1-di-, and 1,2-di-substituted alkenes **13** with functionalized 1-(arythio)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

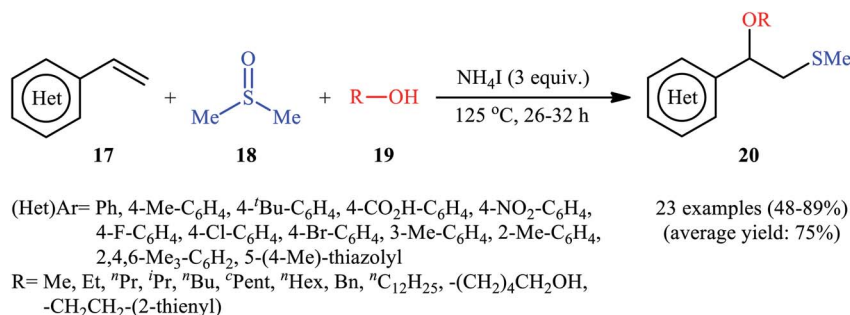


Scheme 5 Catalyst-free oxysulfenylation of alkenes **13** with 1-(arythio)pyrrolidine-2,5-diones **14** and alcohols **15**.





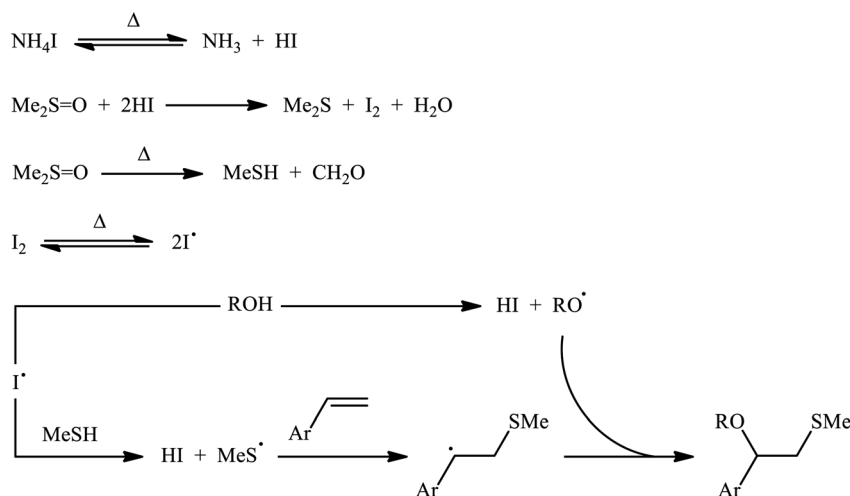
Scheme 6 The plausible mechanistic pathway for the reaction in Scheme 5.

Scheme 7 Synthesis of β-alkoxy methyl sulfides **20** through the NH₄I-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-(arythio)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 enantioselective 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 NH₄I-mediated alkoxy-sulfenylation 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 (I₂) and methanethiol (MeSH) are formed from NH₄I and DMSO through a series of reactions. Next, I₂ is decomposed under the thermal condition to form iodine radical (I[•]), which is later reacted with precursor

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

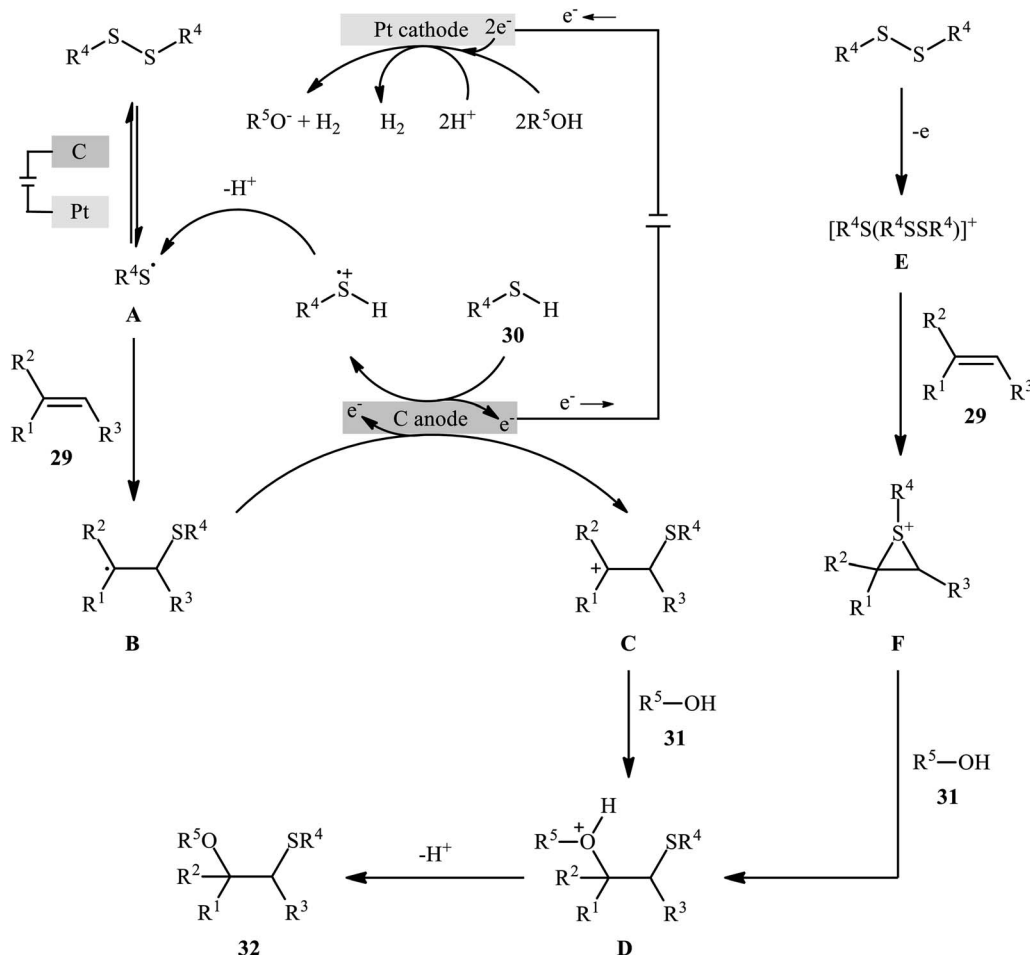
over-stoichiometric amounts of NaI and HBr, styrene derivatives **25** were similarly coupled with various aryl/alkyl-sulfinic acids **26** and alkyl/benzyl-alcohols **27** to obtain β -alkoxy sulfide products **28** with yields of up to 95% (Scheme 9b).²⁷

In 2018, Lei and co-workers developed an elegant electrochemical alkoxy-sulfonylation 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 $n\text{Bu}_4\text{NBF}_4$ 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 sulfonylation 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.

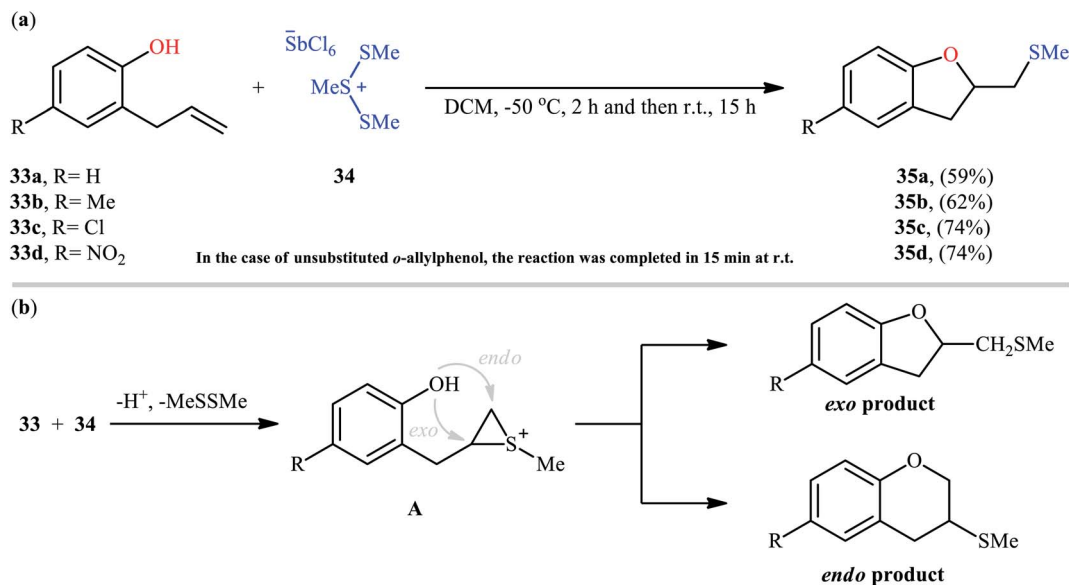
3. Intramolecular alkoxy-sulfonylation of C–C double bonds

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 sulfonyl-substituted oxacycles within a single click. One of the earliest reports on the cyclizative sulfonylation of alkenols was published by Capozzi and co-workers in 1981,³⁰ who showed that the treatment of *o*-allylphenols **33** with methyl(bismethylthio)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.



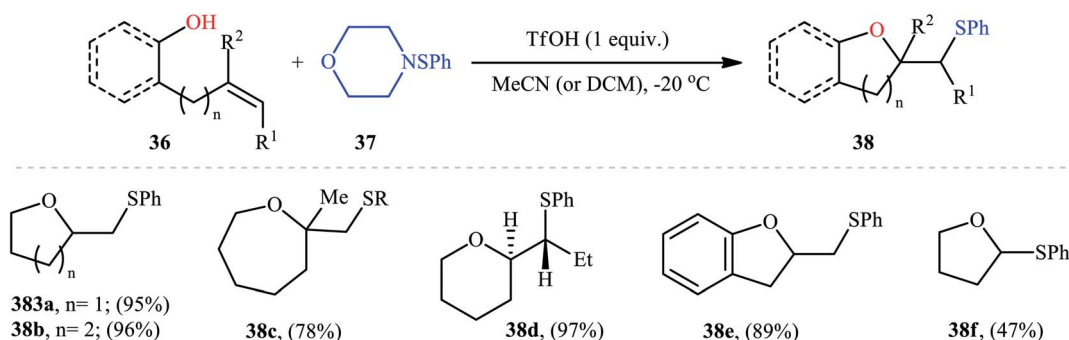


Scheme 12 (a) Synthesis of 2-((methylthio)methyl)-2,3-dihydrobenzofurans **35** through intramolecular sulfetherification of alkenols **33** with methyl(bismethylthio)sulfonium hexachloroantimonate **34**; (b) the plausible mechanistic pathway for the formation of dihydrobenzofurans **35**.

((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 (DMTST) as the

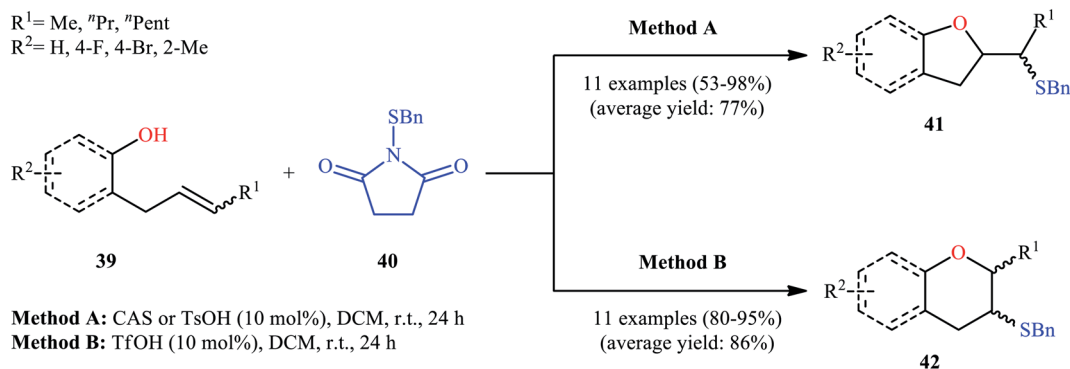
methylsulfenylation reagent and ⁱPr₂NEt as a base in anhydrous acetonitrile solvent.³¹ Notably, γ,δ -unsaturated carboxylic acids could also undergo intramolecular cyclofunctionalization reaction under the identical conditions and give the corresponding lactones in good to high yields. This transformation 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.

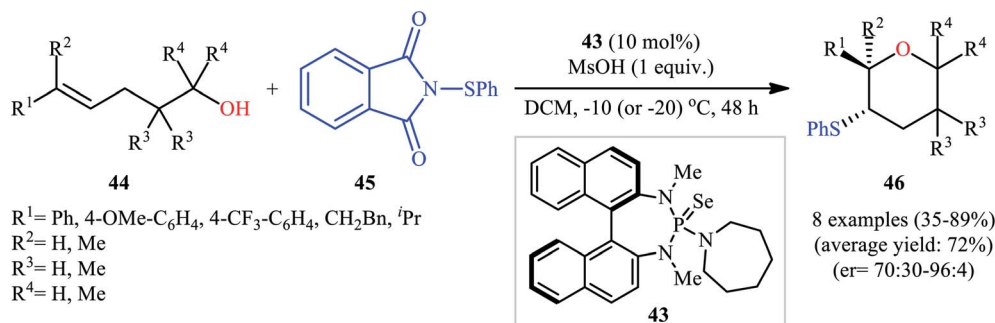
octen-1-ol) subjected to this reaction condition, a single regio- and stereo-isomer **38d** was formed, indicated *trans*-addition without any alkene isomerization. Shortly afterwards, the author found that the regio- and stereo-selectivity of this cyclofunctionalization reaction is highly dependent on the substitution patterns of the employed alkenols.³⁴ Benzene-sulfonyl 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 stereo-selective 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

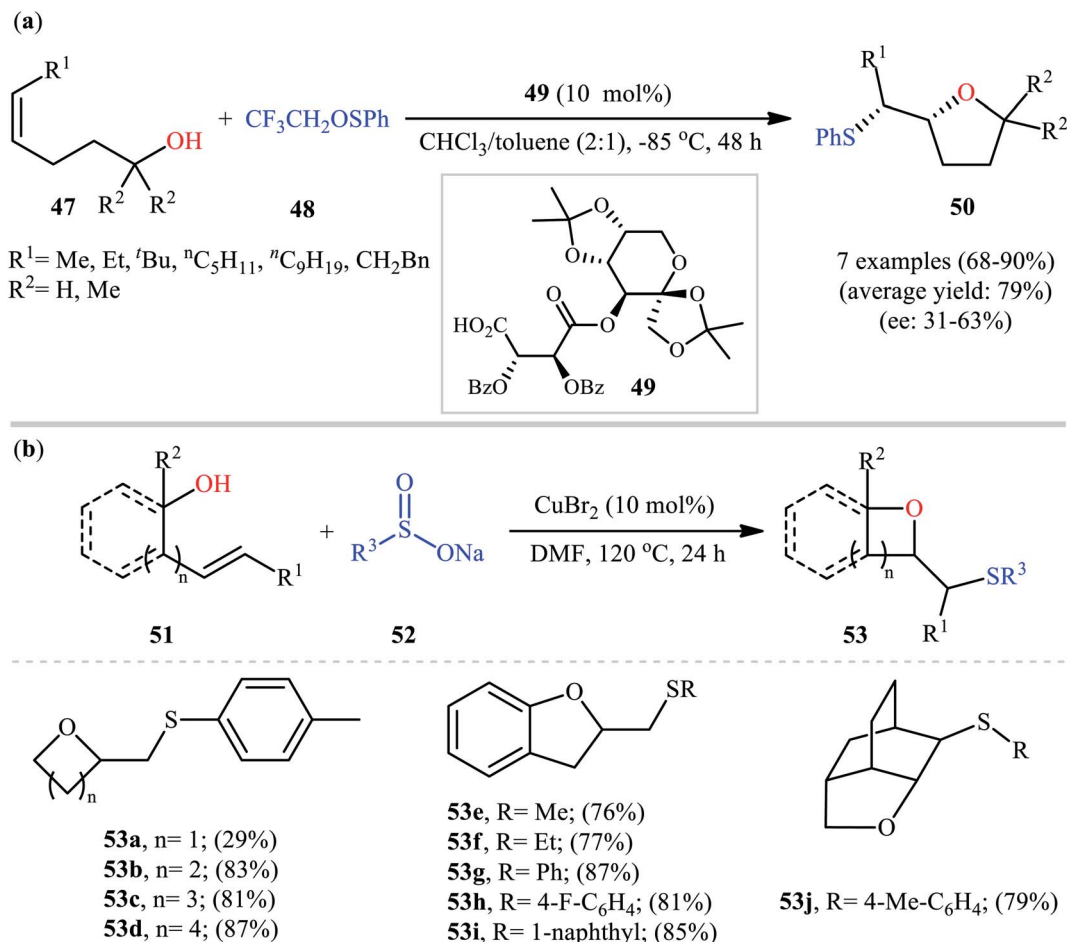
BINAM-based selenophosphoramidate catalyst **43** and a Brønsted acid (methanesulfonic acid, MsOH) additive.³⁹ A library of conjugated and *trans* nonconjugated alkenes **44** reacted efficiently with *N*-phenylsulfonyl-phthalimide **45** in the presence of 10 mol% of **43** to afford sulfenylated tetrahydropyrans **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 benzene-sulfenate **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 **46**.

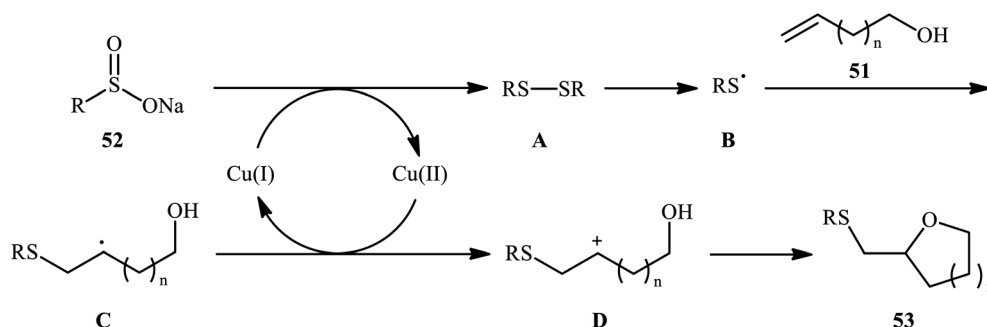




Scheme 16 (a) Shi's synthesis of enantioenriched tetrahydrofurans 50; (b) selected examples of the Cu(II)-catalyzed sulfenyl etherification of alkenols 51 with sodium sulfonates 52 reported by Wu and Jiang.

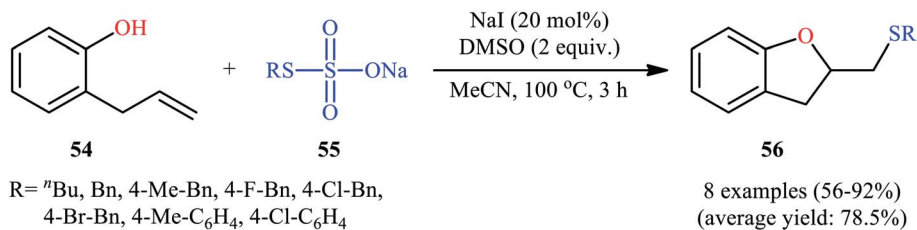
five-, six-, and seven-membered cyclic ether derivatives 53 *via* CuBr₂-catalyzed sulfetherification of the corresponding alkenols 51 employing sodium sulfonates 52 as sulfenylating agents.⁴¹ The reaction was run in DMF at 120 °C, tolerated various aliphatic, benzylic, and (hetero)aromatic sodium sulfonates, 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 CuCl₂ 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 sulfonate 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 sulfonates 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).

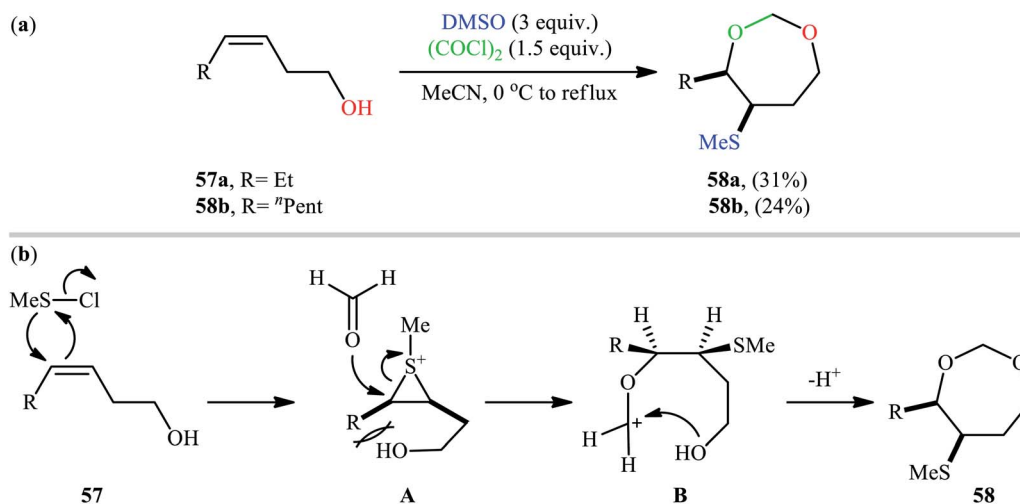
In 2017, Zhang, Yan, and Lin studied the possibility of synthesizing sulfenylated 2,3-dihydrobenzofurans through the intramolecular sulfetherification of 2-allylphenol **54** with environmentally friendly thiosulfates **55**.⁴² To determine the best conditions, they meticulously probed the activities of different iodine-based catalysts (*e.g.*, I_2 , NaI, TBAI, NH_4I) and oxidants (*e.g.*, H_2O_2 , DMSO, TBHP, $\text{Cu}(\text{OAc})_2$, $\text{K}_2\text{S}_2\text{O}_8$) in the sulfenyl etherification of 2-allylphenol with sodium *S*-benzyl sulfthioate 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 [$(\text{COCl})_2$] is

a suitable reagent for sulfenyletherification of unsaturated alcohols under catalyst- and additive-free conditions.⁴³ Methanesulfonyl chloride (MeSOCl) is assumed to be the compound responsible for the sulfenyletherification, which is generated by the reaction of DMSO and $(\text{COCl})_2$. 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 methanesulfonyl chloride 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 methanesulfonyl 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 alkoxylation 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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