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Direct 1,2-thiosulfonylation of alkenes: An overview

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ABSTRACT

This review article aims to survey the literature on methodologies for the direct vicinal 1,2-thiosulfonylation of alkenes. This review is divided into two sections based on the type of thiosulfonylating reagents: the first covers the thiosulfonylation of alkenes using bifunctional reagents, while the second focuses on three-component reactions.

1. Introduction

Organosulfur compounds ‘organic molecules containing one or more carbon–sulfur bonds’ represent one of the most important classes of organic compounds, commonly found in bioactive natural products and pharmaceutical drugs [1-7].

Thioethers are a prominent family of organosulfur compounds with extensive applications, particularly in medicinal [8] and agricultural chemistry [9].

Thioethers, with 31 drugs on the market, represent the third most prevalent class of FDA-approved sulfur-containing drugs (Scheme 1) [10].

Among them, twelve contain Csp^3–S–Csp^3 thioethers, fifteen contain Csp^3–S–Csp^2 thioethers, and the remaining six contain Csp^2–S–Csp^2 thioethers, underscoring the importance of aliphatic thioethers in medicinal chemistry. Sulfones are another major class of organosulfur compounds, known for their broad spectrum of biological activities, including antimicrobial, antiviral, antifungal, antioxidant, anticancer, anti-inflammatory, anti-Alzheimer, and antiparasitic effects. [11]. Out of the 249 sulfur-containing drugs approved by the FDA, 8 are derivatives of sulfones [10]. Interestingly, six of the sulfone drugs feature a sulfone group bonded to one sp^3 and one sp^2 carbon, while the remaining two are linked to two sp^3 carbons (Scheme 2), highlighting the significance of aliphatic sulfones in drug design and development.

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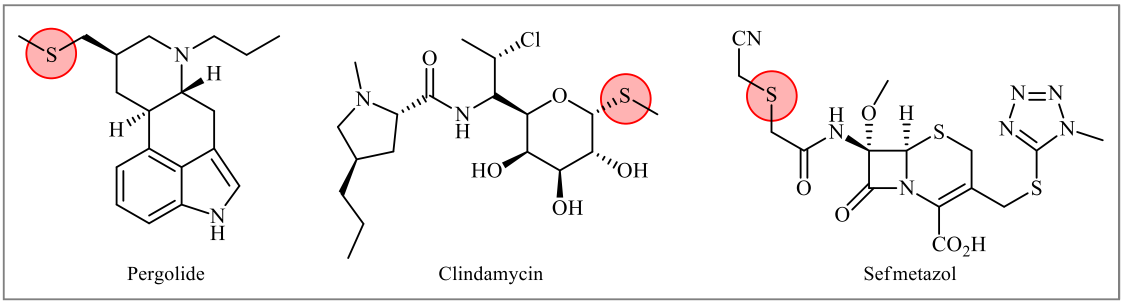
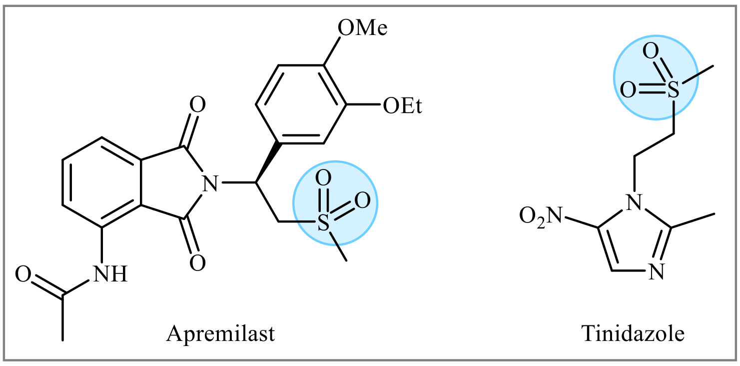


Scheme 1. Selected example of FDA-approved drugs possessing thioether moiety**.**



Scheme 2. Selected examples of the onselling drugs containing sulfone moiety.

Given the significant importance of the titled compounds in various research fields, the development of new and efficient synthetic routes for their preparation from low cost, non-toxic, and readily accessible starting materials remains of great interest [12, 13]. The direct vicinal difunctionalization of alkenes represents a powerful and versatile approach for concomitant introduction of two functional groups into olefinic double bonds, enhancing molecular complexity by forming two chemical bonds in a single step [14, 15].

In this regard, the direct 1,2-thiosulfonylation of alkenes offers an efficient strategy for the selective synthesis of β-thiol-functionalized sulfones by simultaneously installing a thiol group and a sulfonyl functional group on adjacent carbons (Figure 1).

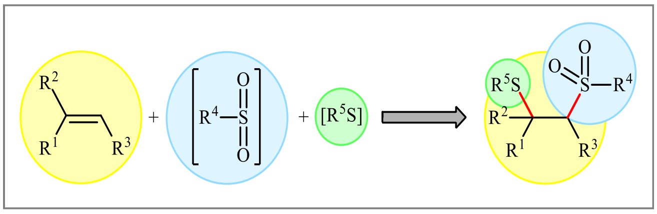


Fig. 1. Direct vicinal 1,2-thiosulfonylation of alkenes.

In 2022, Xu, Chu, and their colleagues published an insightful review paper entitled "1,*n*-thiosulfonylation using thiosulfonates as dual functional reagents" that highlights some of the significant advancements in the thiosulfonylation of unsaturated hydrocarbons [16]. However, only six works were cited in the section relevant to the 1,2-thiosulfonylation of alkenes. Considering the omission of several noteworthy examples and the significant advancements made in this field over the past two years, it is an opportune time to present an updated overview of this chemistry.

Therefore, in this review, we aim to provide a comprehensive overview of the direct vicinal 1,2-thiosulfonylation of alkenes, with the aim of stimulating further progress in this interesting field of research.

2. Two-component reactions

This section provides an overview of the literature on the direct thiosulfonylation of olefinic double bonds, employing thiosulfonates as bifunctional thiosulfonylating agents. The discussion is structured into three sub-sections based on the catalytic system involved: (i) metal-catalyzed reactions; (ii) light-induced photoredox-catalyzed reactions; and (iii) dual metal-photoredox-catalyzed reactions.

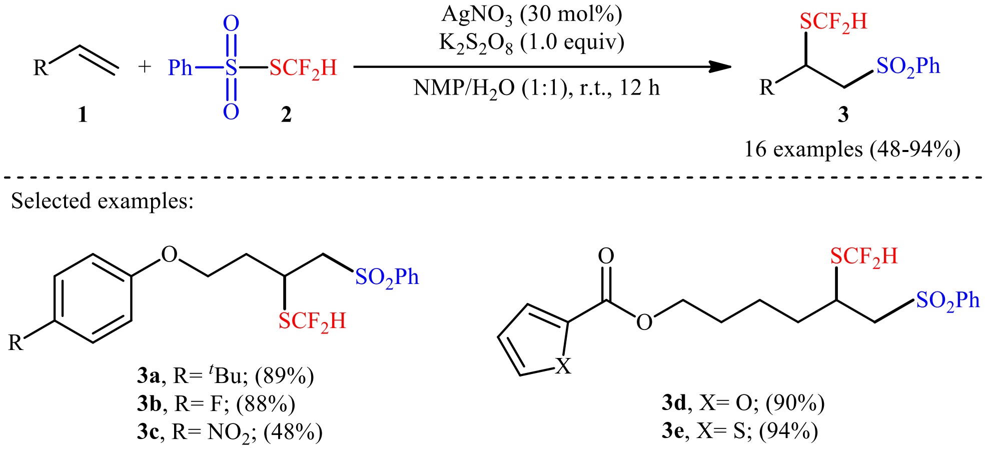
2.1. Metal-catalyzed reactions

The possibility of metal-catalyzed direct thiosulfonylation of alkenes to β-thioalkoxy sulfones was first realized by Shen and co-workers, in 2016 [17], who showed that treatment of unactivated terminal alkenes 1 with *S*-(difluoromethyl) benzenesulfonothioate ($PhSO_2SCF_2H$; 2) in the presence of 30 mol% $AgNO_3$ and 1.0 equivalent of $K_2S_2O_8$ in aqueous *N*-methylpyrrolidone (NMP) solution under ambient conditions resulted in the formation of corresponding phenylsulfonyl-difluoromethylthio difunctionalized products 3 in moderate to excellent yields (Scheme 3). In this transformation, a wide panel of important functional groups, such as fluoro, chloro, bromo, iodo, nitro, aldehyde, ketone, ester, and ether functionalities were well tolerated, indicating its broad applicability. However, under the standard reaction conditions, activated alkenes such as styrenes and α,β-unsaturated esters exhibited significantly reduced reactivity, leading to very low conversions (<10%). Regarding the regioselectivity of the reaction, a high degree of selectivity was observed, in which the sulfonyl group predominantly placed on the less hindered carbon atom of the double bond. The radical trapping experiments with various radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), butylated hydroxytoluene (BHT), and 1,4-dinitrobenzene indicated that the process may proceeds *via* a radical pathway; however, the authors were unable to unravel the exact mechanism of this transformation.

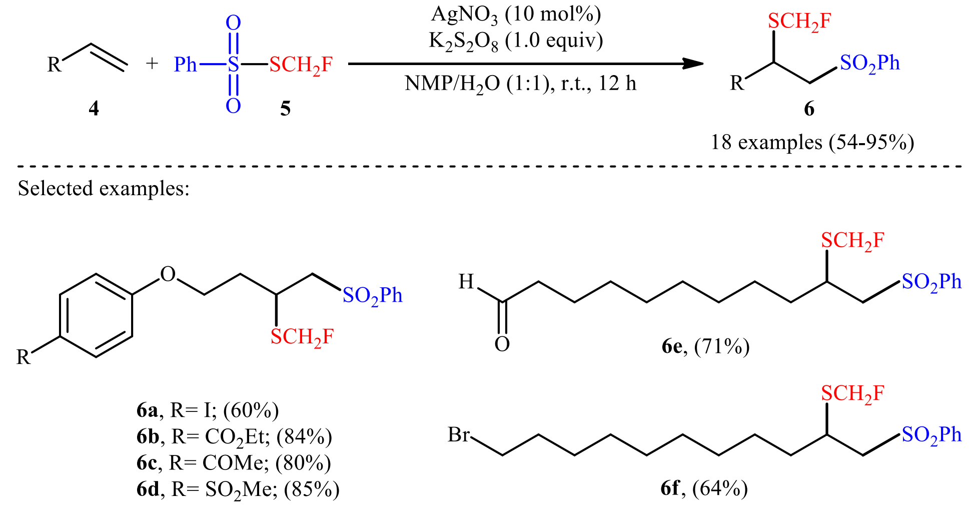
Subsequently, the same authors applied a similar strategy to the monofluoromethylthio-sulfonylation of terminal aliphatic alkenes 4 employing *S*-(monofluoromethyl) benzenesulfonothioate ($PhSO_2SCH_2F$; 5) as a novel bifunctional thiosulfonylating agent under their standard conditions [18]. In this report, eighteen β-monofluoromethylthiolated sulfones 6 were synthesized in fair to almost quantitative yields, ranging from 54% to 95% (Scheme 4). Interestingly, the reaction was successfully performed on a gram scale, affording an isolated yield superior to that obtained from the small-scale reaction. Notably, the reaction was also applicable to the late-stage monofluoromethylthio-sulfonylation of complex natural products and drug molecules (*e.g.*, equipoise, a veterinary steroid).

Very recently, in a related investigation, Shao and Wu along with their co-workers reacted a series of mono-, 1,1-, and 1,2-di-substituted alkenes **7** with *S*-methyl-d_3 arylsulfonothioates **8** in the presence of a combination of $AgNO_3$ (20 mol%), SDS (20 mol%) and $K_2S_2O_8$ (50 mol%) in water to selectively provide β-SCD_3-substituted sulfones **9** in modest to excellent yields (Scheme 5) [19].

The results showed that electron-rich *S*-methyl-d_3 arylsulfonothioates afforded slightly better yields compared to the electron-poor ones. The relative reaction rates of alkenes in this difunctionalization reaction followed the order: terminal alkenes ≈ 1,1-di-substituted alkenes > 1,2-di-substituted alkenes.



Scheme 3. Ag-catalyzed difluoromethylthiosulfonylation of alkenes 1, developed by Shen.



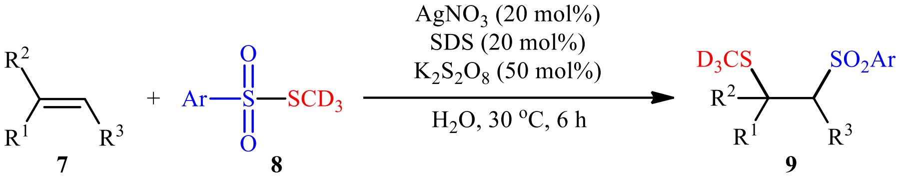
Scheme 4. Ag-catalyzed monofluoromethylthio-sulfonylation of alkenes 4, developed by Shen.

Unfortunately, the scope of the study did not extend to evaluating aromatic alkenes and *S*-methyl-d_3 alkyl sulfonothioates as potential starting materials. The putative mechanism for this dual silver salt and oxidant-catalyzed thiosulfonylation is depicted in Scheme 6. Initially, the oxidation of water-soluble silver(I) salt by $K_2S_2O_8$ in the aqueous phase, followed by its interaction with *S*-methyl-d_3 arylsulfonothioate 8, generates a highly reactive silver(II) species A, which subsequently penetrates into the droplets. Afterwards, the sulfonyl radical adds to the terminal C=C bond of the alkene 7 to afford an alkyl radical intermediate B that is trapped by sulfonothioate 2 to yield the observed product 9. Meanwhile, the sulfonyl radical is regenerated and can participate in the subsequent radical cycle.

Along this line, Xu and co-workers discovered that a combination of a Lewis acid and a bidentate donor ligand can serve as an efficient catalytic system for the regioselective thiosulfonylation of alkenes with sulfonothioates [20]. Thus, in the presence of 20 mol% of $Sc(OTf)_3$ and 1,10-phen (or bpy), the reaction of various styrene derivatives 10 with aryl sulfonothioates 11 took place slowly, leading to the formation of corresponding β-thiosulfones 12 in moderate to high yields (Scheme 7). Interestingly, this protocol afforded thiosulfonylated products with regioselectivity opposite to that observed in previous methods. Both *S*-alkyl and aryl arenesulfonothioates were tolerated by this protocol.

Moreover, in addition to terminal styrenes, β-substituted styrenes and cyclic aliphatic alkenes were also compatible substrates in this transformation. Finally, the protocol was successfully extended to the synthesis of a β-selenosulfone using Se-phenyl benzenesulfonothioate as the selenosulfonylating reagent.

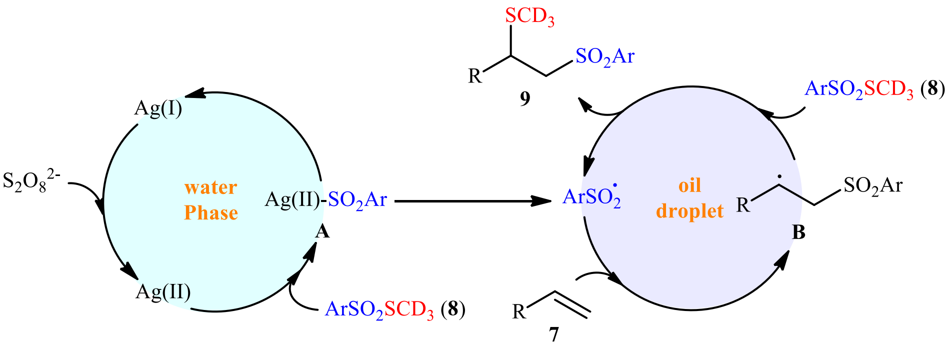
According to the mechanism proposed by the authors (Scheme 8), this transformation begins with the coordination of the sulfonyl oxygen of arenesulfonothioate 11 to the Lewis acid $Sc(OTf)_3$ to form intermediate A, which after reaction with styrene 10 affords thiiranium ion B. Finally, the sulfur of the sulfonyl group attacks the intermediate B to deliver product 12 and regenerate Sc(III) catalyst.



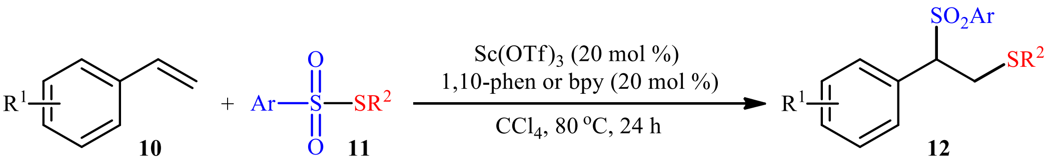
24 examples (44-98%)

R^1= alkyl
R^2= H, Me
R^3= H, alkyl
Ar= 4-Me-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-F-C_6H_4, 3-Br-C_6H_4, 2-F-C_6H_4

Scheme 5. Shao-Wu's synthesis of β-SCD_3-substituted sulfones 9.



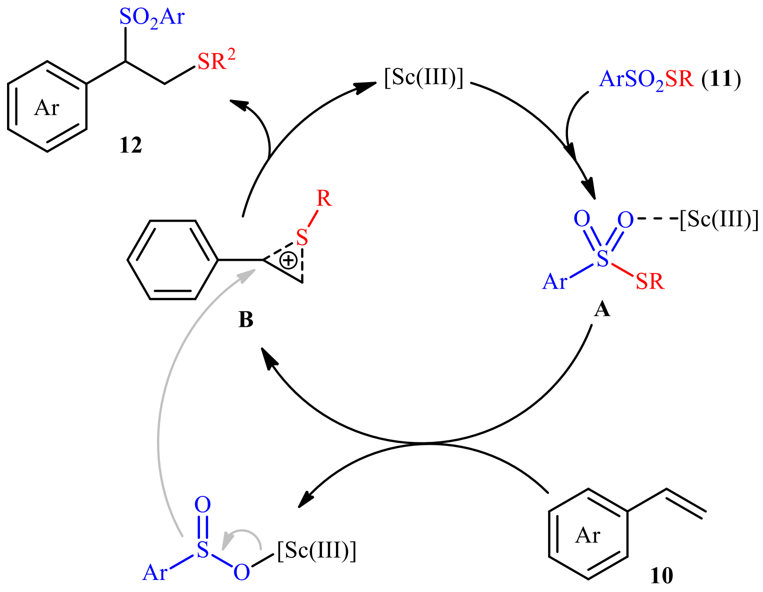
Scheme 6. The plausible reaction mechanism for the formation of β-SCD_3-substituted sulfones 9.



21 examples (53-88%)

R^1= H, 4-Me, 4-CH_2Cl, 4-^{t}Bu, 4-OAc, 4-F, 4-Cl, 4-Br,
4-CN, 3-Me, 2-Cl, 2,3-$(CH=CH)_2$-, 3,4-$(CH=CH)_2$-
R^2= Me, ^{n}Bu, ^{n}Oct, Bn, Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4
Ar= Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4

Scheme 7. Xu's synthesis of β-thiosulfones 12.



Scheme 8. Plausible reaction mechanism for the formation of β-thiosulfones 12.

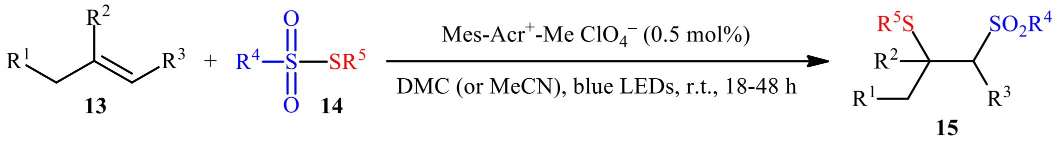
2.2. Light-induced photoredox-catalyzed reactions

One of the earliest reports of the light-induced photoredox-catalyzed direct thiosulfonylation of alkenes was published by Maes and co-workers in 2020 [21], who disclosed that the treatment of various unactivated alkenes 13 with thiosulfonates 14 in the presence of only 0.5 mol% of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$-Me ClO_4^-) under visible light irradiation and ambient conditions resulted in the formation β-thiosulfones 15 in poor to excellent yields (Scheme 9). Various *S*-aryl arenethiosulfonates (symmetrical and unsymmetrical), and *S*-aryl alkanethiosulfonates were applicable to these protocols and in all cases the corresponding β-thiosulfones were selectively obtained. However, *S*-alkyl arenethiosulfonates failed to participate in this reaction. In additions, the scope of alkenes that underwent reaction was broad enough to include terminal, internal (cyclic, acyclic), and tri- substituted aliphatic alkenes. Unfortunately, alkenes with low oxidation potential such as styrene derivatives were insufficiently reactive under the standard conditions. Notably, this difunctionalization methodology was also successfully extended to the thiosulfonylation of terminal aromatic and aliphatic alkynes without any modification to the reaction conditions. On the basis of the control experiments, the authors proposed two plausible photocatalytic and radical chain mechanisms for this reaction, which are believed to occur concomitantly (Scheme 10). Initially, the ground state photoredox catalyst (PC) undergoes excitation by irradiation with visible light to produce the excited state PC*, which after an energy transfer to thiosulfonate 14 leads to the formation of excited thiosulfonate 14* and regeneration of PC. Subsequently, 14* undergoes homolytic cleavage of the SO_2–S bond to afford a sulfenyl radical A and a sulfonyl radical B. Afterwards, addition of sulfonyl radical B to alkene 13 provides C-centered radical C, which subsequently reacts with sulfenyl radical A to afford the target product 15. In a possible radical chain, sulfenyl radical A undergoes reaction with thiosulfonate 14 to deliver disulfide D and sulfonyl radical B. Afterwards, addition of radical B to alkene 13 generates intermediate C, which after reaction with disulfide D affords the observed product 14 along with radical A.

In another possibility, the addition of sulfonyl radical B to the double bond of alkene 13 produces C-centered radical C that, after reaction with thiosulfonate 14 leads to the final product 15 and radical B.

Recently, the Wang group successfully extended this chemistry to dithiosulfonylation of alkene derivatives by using dithiosulfonates ($ArSO_2$-SSR) as dithiosulfonylating reagents (Scheme 11) [22]. Thus, in the presence of 1 mol% of $Ir(ppy)_3$ as a photocatalyst under irradiation of blue LEDs at room temperature, direct vicinal dithiosulfonylation of styrene derivatives 16 with various *S*-alkyl dithiosulfonates 17 furnished the corresponding β-dithiosulfones 18 in poor to excellent yields (45 examples, 32%-91%).

Of note, a scale-up experiment for the difunctionalization of simple styrene with *SS-tert*-butyl 4-methylbenzenesulfono(dithioperoxoate) on a gram scale was carried out to show the practicability of the method, which gave rise to the target product in 72% isolated yield. To showcase the synthetic utility of current protocol, styrene carrying natural products such as estrone, indomethacin, and diacetone-D-glucose were found to be compatible with the reaction system, yielding the corresponding difunctionalized products in 81%, 37%, and 60% yields, respectively. In this study, the authors also developed an alternative catalytic system to mediate the dithiosulfonylation of unactivated alkenes. They demonstrated that the reaction between aliphatic alkenes 16 and *S*-alkyl dithiosulfonates 17 in a mixed solvent (MeCN:H_2O=1: 1) under the action of organophotocatalyst 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) afforded the corresponding β-thiosulfones 18 in high yields and outstanding regioselectivity (15 examples, 35-97%).

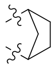


29 examples (15-94%)

R^1= Me, ^{n}Pr, CH_2Br, CH_2OH, CH_2COMe, CH_2CO_2Et, CH_2NPhth, $(CH_2)_2CO_2H$, $(CH_2)CN$, $SiMe_3$, Bn, vinyl, Ph, 3,4-$(OMe)_2$-C_6H_3, OPh, CO_2H

R^2= H, Me

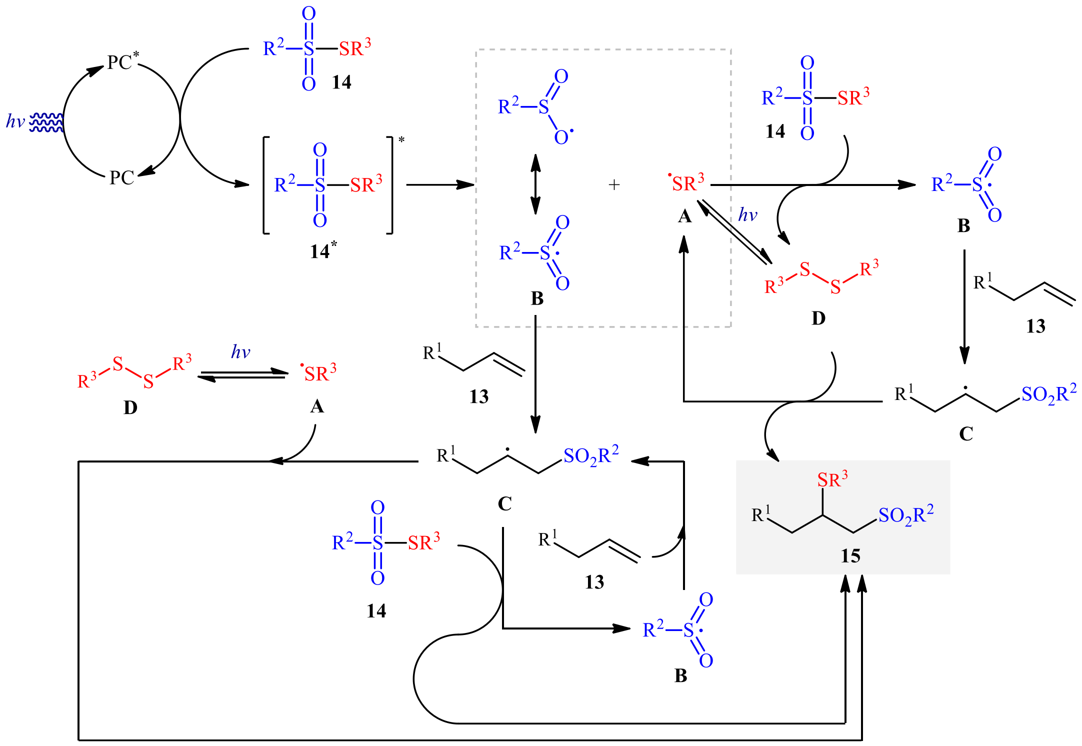
R^3= H

R^1 + R^3= -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2CH_2O$-), 

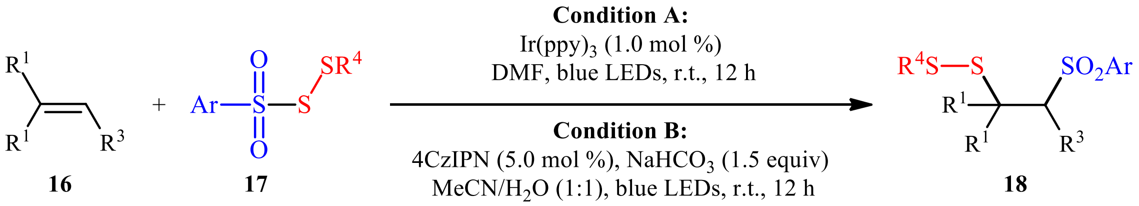
R^4= Me, Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 3,5-$(CF_3)_2$-C_6H_3, 2-thienyl

R^5= CF_3, Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 2-CO_2Me-C_6H_4, 2-NHCOPh-C_6H_4, 3,5-$(CF_3)_2$-C_6H_3, 2-thienyl

Scheme 9. Maes's synthesis of β-thiosulfones 15.



Scheme 10. Possible mechanism for the formation of β-thiosulfones 15.



R^1= alkyl, aryl, heteroaryl
R^2= H, alkyl, aryl, CO_2Et, CF_3
R^3= H, alkyl
R^4= alkyl
Ar= 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4

61 examples (32-97%)

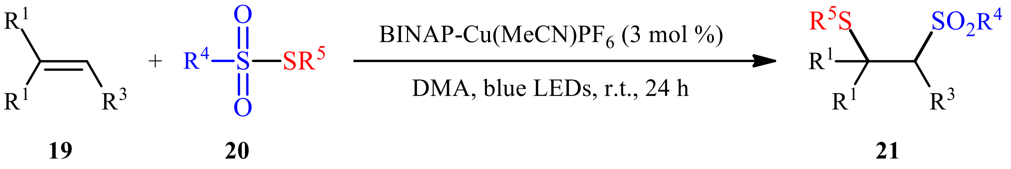
Scheme 11. Wang's synthesis of β-dithiosulfones 18.

Very recently, Ma *et al*. developed a general and practical methodology for the direct and site-selective thiosulfonylation of both activated and unactivated alkenes with thiosulfonates [23]. In this report they showed that the reaction between terminal (aliphatic, aromatic) and internal (cyclic, acyclic) alkenes 19 and various *S*-alkyl and *S*-aryl thiosulfonates 20 catalyzed by BINAP-Cu(MeCN)PF_6 under visible light irradiation afforded the respective β-thiosulfones 21 in modest to excellent yields (Scheme 12). Following a series of mechanistic investigations, it was confirmed that the reaction most likely proceeds *via* a radical pathway as depicted in Scheme 13.

2.3. Dual metal-photoredox-catalyzed reactions

Merging transition metal catalysis and photoredox catalysis has proven to be a successful concept for carrying out direct vicinal difunctionalization of alkenes [24]. In this regard, Xu and co-workers have examined the dual gold and photoredox-catalyzed reaction of styrene derivatives 22 with thiosulfonates 23 using IPrAuCl as a cationic gold catalyst, $Ru(bpy)_3Cl_2$ as a photocatalyst and $AgSbF_6$ as an additive [25]. The reactions were performed in DCM under irradiation with a 100 W blue LED at room temperature, tolerated both terminal and internal alkenes as well as S-aryl and S-alkyl thiosulfonates, and provided the expected β-thiosulfones 24 in fair to excellent yields (Scheme 14). Interestingly, both *trans*-alkenes and *cis*-alkenes afforded the same major products with comparable yields and similar diastereoselectivities, which is not common in a pure radical reaction. According to the authors, the reaction proceeds through two intertwined metal and photoredox catalytic cycles as depicted in Scheme 15.

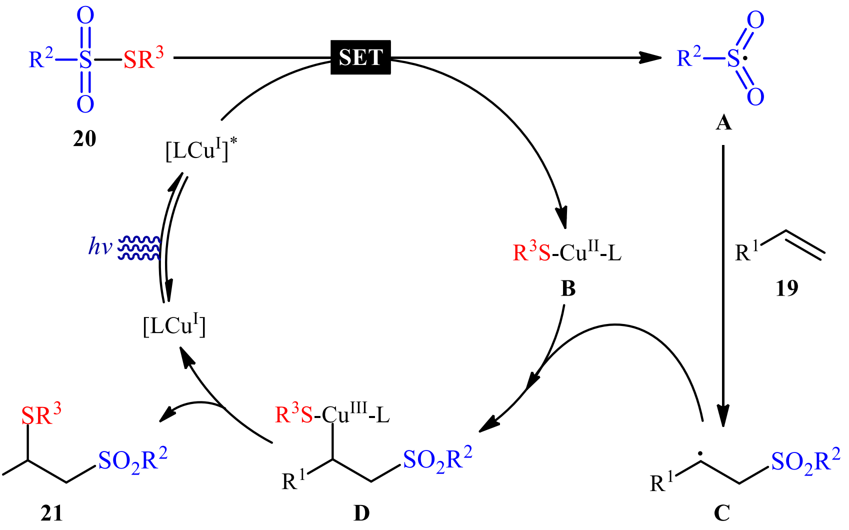
In the beginning, the ground state $Ru(bpy)_3^{2+}$ photoredox catalyst undergoes excitation by irradiation with visible light to produce a long-lived photoexcited state $Ru(bpy)_3^{2+}*$, which after a single-electron transfer (SET) to cationic IPrAu(I) leads to the formation of the highly active IPrAu(0) and $Ru(bpy)_3^{3+}$. Next, IPrAu(0) reduces thiosulfonate 23 to generate IPrAu(I)SR A and a sulfonyl radical B. Subsequently, the reaction of the later with alkene 22 affords an alkyl radical C, which then oxidizes A to the Au(II) intermediate D. Afterwards, intermediate D undergoes further oxidation by $Ru(bpy)_3^{3+}$ to affords the Au(III) intermediate E, accompanied by the regeneration of $Ru(bpy)_3^{2+}$, thus completing the photoredox catalytic cycle. Finally, reductive elimination of the Au(III) intermediate E delivers the observed product 24 and regenerates the Au(I) catalyst.



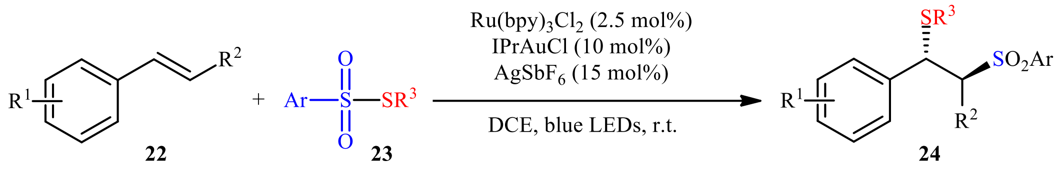
R^1= alkyl, aryl, heteroaryl
R^2= H, alkyl, aryl
R^3= H, alkyl
R^4= alkyl, aryl
R^5= alkyl, aryl, heteroaryl

61 examples (45-90%)

Scheme 12. Ma's synthesis of β-thiosulfones 21.

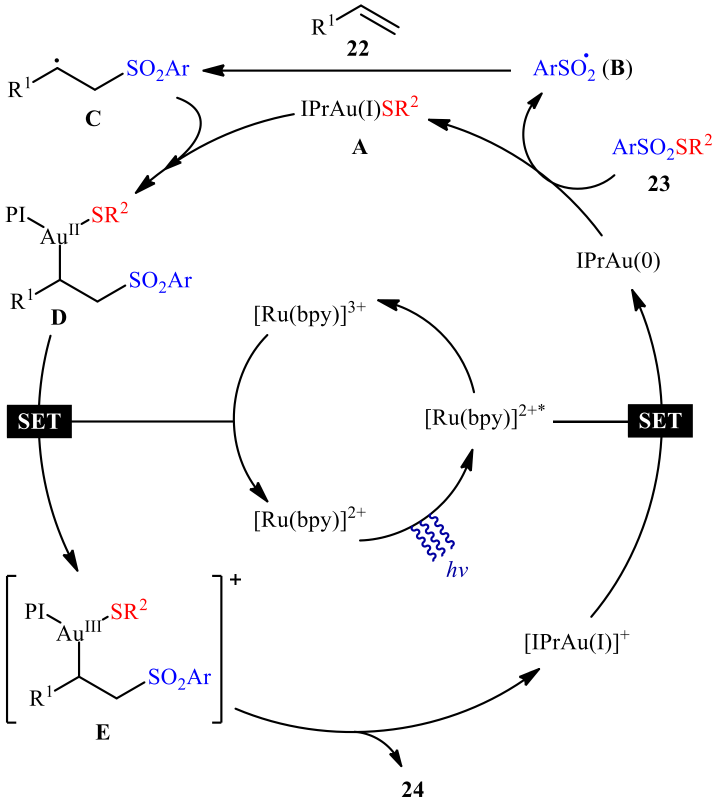


Scheme 13. Proposed Mechanism for the formation of β-thiosulfones 21.



R^1= H, 4-Me, 4-F, 4-Br, 4-CF_3, 4-CO_2Me, 4-OAc, 4-CN, 3-Me, 3-OMe, 3-Br, 2-Cl 41 examples (40-92%)
R^2= H, Me
$R^1 + R^2$= -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-
R^3= Me, ^{n}Bu, CF_3, Bn, Ph, 4-Me-C_6H_4, 4-Br-C_6H_4, $CH_2CH{=}CHCO_2Et$
Ar= Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4

Scheme 14. Xu's synthesis of β-thiosulfones 24.



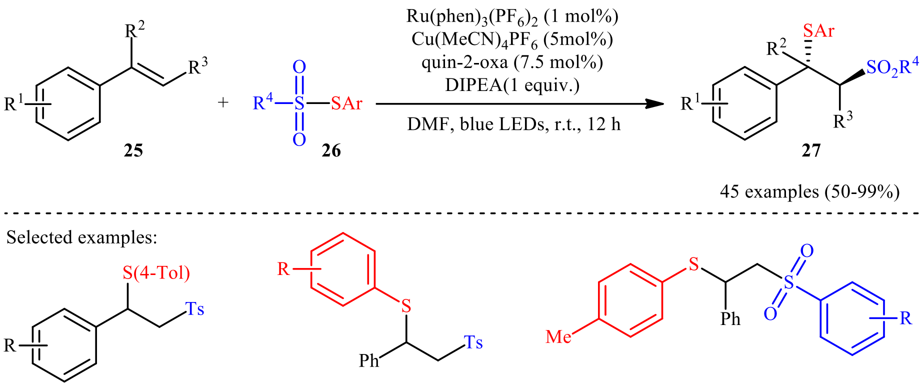
Scheme 15. A plausible reaction mechanism for the formation of β-thiosulfones 24.

Recently, Wang and Bao carried out a computational work to gain further mechanistic insights into this dual gold and photoredox-catalyzed difunctionalization reaction [26]. In a related investigation, Liu and Jia along with their co-workers demonstrated that the merge of $Ru(phen)_3(PF_6)_2$ with $Cu(MeCN)_4PF_6$ and 2-(quinolin-2-yl)-4,5-dihydrooxazole (quin-2-oxa) could also promote this 1,2-thiosulfonylation reaction [27].

In this work, 45 β-thiosulfones 27 were synthesized from the corresponding styrene derivatives 25 and *S*-aryl thiosulfonates 26 (Scheme 16). Various functional groups phenyl ring periphery of either syrenes or thiosulfonates, such as a halide, alcohol, ether, ester, amide, ketone, and aldehyde were well tolerated by this reaction and the corresponding products were obtained in moderate to quantitative yields. Mechanistic studies suggest that this transformation most likely proceeds through a radical pathway, as illustrated in Scheme 17.

3. Three-component reactions

Although the direct 1,2-thiosulfonylation of alkenes using thiosulfonates as bifunctional thiosulfonylating agents is well established, three-component variants of this reaction remain less explored. One of the earliest reports of the three-component vicinal thiosulfonylation of alkenes has been reported by Zhao and colleagues in 2019 [28], when a range of styrene derivatives 28 underwent chemo- and regioselective thiosulfonylation with sulfonyl chlorides 29 (as the sulfonyl sources) and tetraalkylthiuram disulfides 30 (as the thiolating agents) in the presence of 20 mol% of $Cu(OAc)_2$ as a catalyst in 1,4-dioxane to form the corresponding sulfonyl-containing benzyl dithiocarbamates 31 in moderate to high yields and outstanding regioselectivity, in which sulfenyl group selectively attached to the terminal carbon atom of the C–C double bond (Scheme 18).

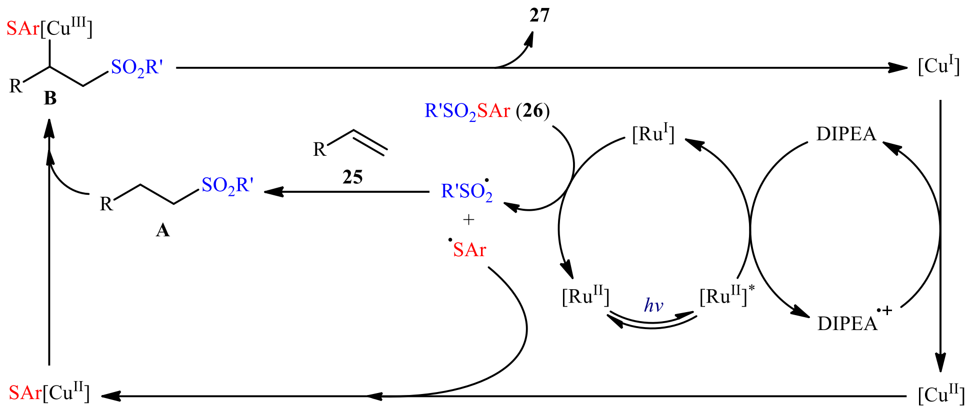


27a, R= H; (93%)
27b, R= 4-Me; (90%)
27c, R= 4-CF$_3$; (83%)
27d, R= 4-NHAc; (80%)

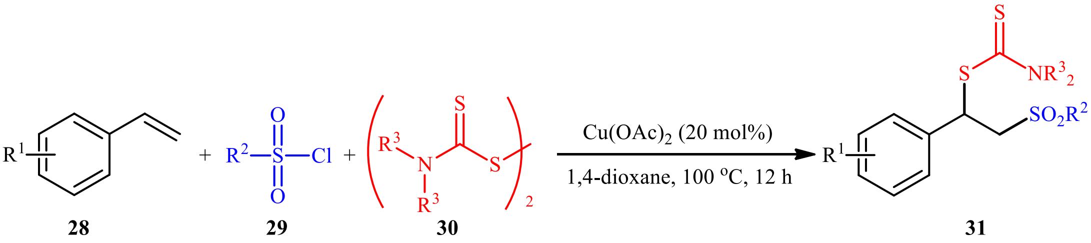
27a, R= H; (86%)
27b, R= 4-OMe; (95%)
27c, R= 4-F; (84%)
27d, R= 4-Cl; (86%)

27a, R= 4-OMe; (85%)
27b, R= 4-F; (80%)
27c, R= 4-Cl; (75%)
27d, R= 4-Br; (76%)

Scheme 16. Liu-Jia's synthesis of β-thiosulfones 27.



Scheme 17. Mechanistic explanation for the formation of β-thiosulfones 27.



R^1= 4-Me, 4-^{t}Bu, 4-F, 4-Cl, 4-Br, 3-Cl, 3-Br, 2-Cl
R^2= Et, ^{c}Pr, Ph, 4-Me-C$_6$H$_4$, 4-^{t}Bu-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 3-Cl-C$_6$H$_4$, 3-Br-C$_6$H$_4$, 2-Me-C$_6$H$_4$, 2-F-C$_6$H$_4$, 2-Cl-C$_6$H$_4$, 2,4,6-(Me)$_3$-C$_6$H$_2$, 1-naphthyl, 3-5-(2-Cl)-pyridyl
R^3= Me, Et, ^{n}Bu

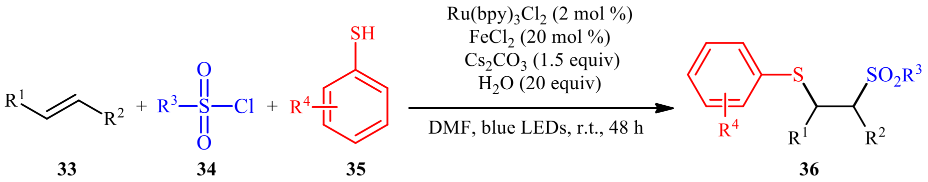
Scheme 18. Zhao's synthesis of sulfonyl-containing benzyl dithiocarbamates **31**.

Drawing inspiration from this work, Xu and co-workers disclosed a robust dual metal-photoredox-catalyzed three-component reaction of alkenes 32, sulfonyl chlorides 33, and thiophenols 34 to prepare the corresponding β-thiosulfones 35 through thiosulfonylation of C–C double bonds (Scheme 19) [29]. Here, sulfonyl chlorides served as the precursors of sulfonyl radicals and broadly available thiophenols as thiolating agents.

In this study, various photocatalysts, iron catalysts, base, and additives were examined and it was found that using Ru(bpy)$_3$Cl$_2$/FeCl$_2$/Cs$_2$CO$_3$/H$_2$O combination as a catalytic system resulted in the best yields. This reaction tolerated a wide range of functional groups (*e.g.*, F, Cl, Br, CN, NO$_2$, OH, OMe, OAc, CF$_3$) and could be applied to both aromatic and aliphatic alkenes and sulfonyl chlorides. Moreover, the protocol is amenable to gram-scale synthesis and late-stage modification of complex molecules.

A plausible mechanism for this thiosulfonylation reaction involves the following steps (Scheme 20): (i) irradiation of photocatalyst PC with blue LEDs to form the excited state PC*; (ii) single-electron transfer from PC* to sulfonyl chlorid 34 to yield sulfonyl radical A and an oxidized photocatalyst $PC^{\bullet+}$; (iii) addition of sulfonyl radical A to alkene 33 to generate the more stable benzyl radical intermediate B; (iv) interaction of thiophenol 35 with Fe(II) catalyst in the presence of base to produce an iron–sulfur intermediate C; (v) coupling of radical B with intermediate C to give intermediate D; and (vi) reductive elimination of intermediate D to afford the final product 36 along with the regeneration of Fe(II) catalyst and photocatalyst. In this realm, Wang and Wu along with their co-workers developed an interesting visible-light-promoted CO_2 oxidative three-component 1,2-thiosulfonylation of styrenes 37 with sodium sulfinates 38 and thiophenols 39 under room temperature [30]. Herein, the combination of $Ru(phen)_3(PF_6)_2$, $FeCl_3$, and Cs_2CO_3 was identified as the optimal catalytic system for the transformation.

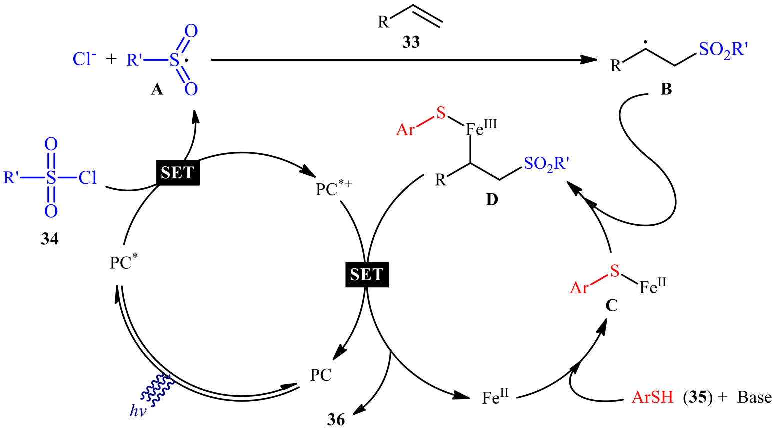
The substrate scope was evaluated on 19 functionalized aromatic alkenes and proved that substrates bearing both electron-donating and electron-withdrawing groups were well tolerated (Scheme 21). This protocol was compatible with both aliphatic and aromatic sodium sulfinates as well as thiophenols, but proved unsuitable for aliphatic alkenes. It should be mentioned that the presence of CO_2 as an oxidant was crucial to the success of this transformation. No target product was detected in the absence of CO_2.



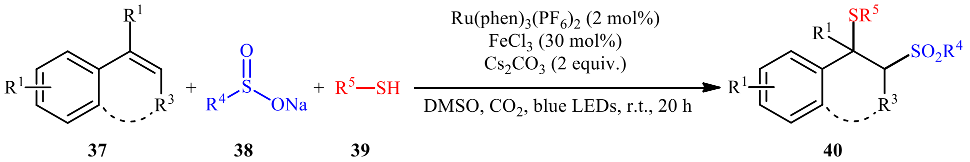
35 examples (40-83%)

R^1= 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CO_2Me-C_6H_4, 4-OAc-C_6H_4, C_6F_5, 2-naphthyl, 2-thienyl, 5-(4-Me)-isothiazolyl, Bn, CH_2Bn, $(CH_2)_2$Br, CH_2OH, CH_2OPh, CH_2OCOMe, $(CH_2)_2$Nphth
R^2= H
R^1 + R^2= -$(CH_2)_3$-
R^3= Et, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 3-Me-C_6H_4, 2-naphthyl, 2-thienyl
R^4= 4-Me, 4-^{i}Pr, 4-OMe, 4-F, 4-Br, 4-CF_3, 4-NO_2, 2,3,4,5,6-$(Cl)_5$

Scheme 19. Xu's synthesis of β-thiosulfones 36.



Scheme 20. Mechanistic explanation for the formation of β-thiosulfones 36.



38 examples (19-95%)

R^1= H, 4-Me, 4-Ph, 4-OMe, 4-F, 4-Cl, 4-CF_3, 4-CO_2Me, 4-OAc, 3-Cl, 2-Me, 2-OMe, 3,4-$(CH=CH)_2$, 3,4-(CH=CH-NTs)-
R^2= H, Me, Ph
R^3= H, Me
R^1 + R^3= -CH_2-, -$(CH_2)_2$-
R^4= Me, ^{i}Pr, ^{c}Hex, Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-CF_3-C_6H_4, 4-CN-C_6H_4, 4-CO_2Me-C_6H_4, 2-Cl-C_6H_4, 2-thienyl
R^5= Bn, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 2-Me-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 2-Me-4-F-C_6H_3, 2-thienyl

Scheme 21. Wang-Wu's synthesis of β-thiosulfones 40.

4. Conclusion

The direct vicinal 1,2-difunctionalization of alkenes represents one of the most straightforward and atom-economical strategies for rapidly increasing molecular complexity, as it enables the simultaneous installation of two functional groups across a carbon–carbon double bond in a single step, making it highly valuable in synthetic organic chemistry. In this context, the direct 1,2-thiosulfonylation of alkenes has emerged as a promising and efficient strategy for the construction of β-thiosulfone derivatives, which are of significant interest due to their biological activity and synthetic utility. Despite the remarkable progress made in recent years in this exciting area of research, the scope of thiosulfonylating agents remains largely limited to thiosulfonate derivatives. Therefore, further investigations and the expansion of thiosulfonylating agents to more easily accessible thiolation and sulfonylation sources are highly desirable to broaden the applicability and synthetic potential of this transformation.

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