REVIEW

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Hydroxysulfonylation of alkenes: an update

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The direct difunctionalization of inexpensive and widely available alkenes has been recognized as a strong and straightforward tool for the rapid fabrication of complex molecules and pharmaceutical targets by introducing two different functional groups on adjacent carbon atoms of common alkene moieties in a single operation. This synthetic strategy avoids the purification and isolation of the intermediates and thus makes synthetic schemes shorter, simpler and cleaner. In this family of reactions, the hydroxysulfonylation of alkenes has emerged as an increasingly promising strategy for the synthesis of β-hydroxysulfones, which are found in many biologically important molecules and widespread applications in organic synthesis. The objective of this review is to illustrate the advancements in the field of hydroxysulfonylation of alkenes with special emphasis on the mechanistic details of the reaction pathways.

1. Introduction

Sulfones are an important class of pharmacophores which are widely found in human and veterinary medicine.[1] About ten FDA-approved drugs contain a sulfone unit in their structure and are used to treat various diseases such as leprosy, lung cancer, trichomoniasis, psoriatic arthritis, migraine headaches, and muscle spasms.[2] In this family of organosulfur compounds, β-hydroxysulfones not only exhibit a range of pharmacological activities (Scheme 1)[3] but are also used as versatile intermediates in organic synthesis.[4] Traditionally, β-hydroxysulfones are obtained through reduction of β-keto-sulfones,[5] hydroxylation of α,β-unsaturated sulfones,[6] and nucleophilic ring opening of epoxides with sulfinate salts.[7] However, these transformations suffer from certain drawbacks, such as production of unwanted byproducts, requirement of pre-functionalized starting materials and harsh reaction conditions.[8] Therefore, development of efficient, straightforward, and environmentally benign synthetic strategies for the preparation of the titled compounds from inexpensive and easily available starting materials is highly desirable.

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Zinatossadat Hossaini was born in Tehran, Iran, in 1976. She received her B.S. degree in pure chemistry from University of Alzahra, Tehran, Iran, and her M.S. degree in organic chemistry from Tarbiat Modares University, Tehran, Iran, in 2003 under the supervision of Prof. I. Yavari. She completed his PhD degree in 2008 under the supervision of P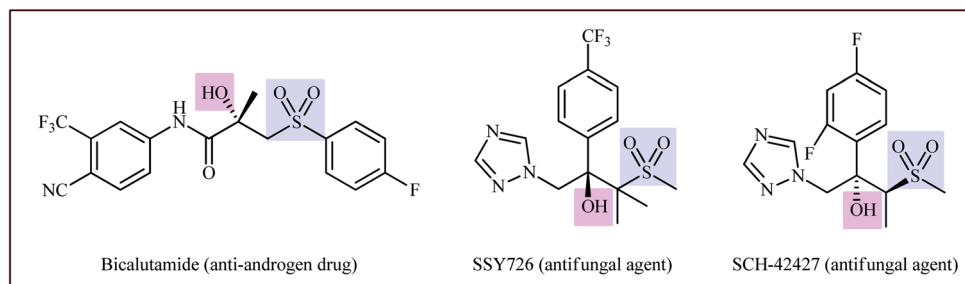rof. I. Yavari. Now he is working at Islamic Azad University as an associate Professor in organic chemistry. Her research interests include synthesis of organic compounds, synthesis of nanocatalyst and new methodologies in organic synthesis and spectral studies of organic compounds.

Evan Abdulkarim Mahmood was born in Erbil, Kurdistan Region, Iraq, in 1990. She is a Biochemistry lecturer. She lives in Iraq/Kurdistan Region. About her educational background, she got a Bachelor degree of Chemistry from University of Sulaimaniyah, College of Science. She completed her Master Degree in Biochemistry at Yüzüncü Yıl University at Van city, Turkey. She is an Assistant Lecturer at University of Human Development, College of Health Science. Also, she worked as a Head of Pharmacy department at National Institute in Sulaimaniyah/Iraq. Her research interests include health, environment, chemistry, clinical biochemistry science.

Scheme 1 Selected examples of bioactive compounds possessing a β-hydroxysulfone unit.

The vicinal difunctionalization of alkenes has evolved to be one of the most effective and straightforward strategies to integrate small molecules toward structurally complex architectures *via* introduction of two different functional groups within a single click.[9,10] In this regard, the direct hydroxysulfonylation of alkenes has emerged as a promising strategy for the construction of β-hydroxysulfone derivatives (Fig. 1). Recently Terent'ev and colleagues briefly highlighted this novel page of β-hydroxysulfone synthesis in their appealing review paper entitled "oxidative sulfonylation of multiple carbon–carbon bonds with sulfonyl hydrazides, sulfinic acids and their salts".[11] However, only eight works were cited in the relevant section and a significant number of recent examples were omitted. Therefore, of course, there is still a need for summarization of available literature on this chemistry in a comprehensive review with insightful mechanistic discussions, which can be helpful to compare efficiency of various protocols and inspire further research efforts on the field. In connection with our review articles on organosulfur chemistry[12] and modern organic synthesis,[13] herein, we will summarize a variety of methods for the synthesis of β-hydroxysulfones *via* the one-pot hydroxysulfonylation of alkenes. For clarity, we structured this topic based on the type of sulfonylating agents. It is worth mentioning that a special emphasis is placed on mechanistic aspects of reactions. Of note, we have not discussed oxosulfonylation reactions, since it has recently been described in another publication.[14]

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Dr Abdol Ghaffar Ebadi finished his doctoral degree in Environmental Biotechnology (Algology) from Tajik Academy of Sciences. Now he is a researcher in TAS in Tajikistan and faculty member at the Islamic Azad University of Jouybar in Mazandaran. Dr Ebadi published more than 400 scientific papers in qualified international journals and attended more than 50 international conferences. He has 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.

Esmail Vessally was born in Sharabiyan, Sarab, Iran, in 1973. He received his B.S. degree in pure chemistry from university of Tabriz, Tabriz, Iran, and his M.S. degree in organic chemistry from Tehran University, Tehran, Iran, in 1999 under the supervision of Prof. H. Pirelahi. He completed his PhD degree in 2005 under the supervision of Prof. M. Z. Kassaee. Now he is working at Payame Noor University as Professor in organic chemistry. His research interests include theoretical organic chemistry, new methodologies in organic synthesis and spectral studies of organic compounds.
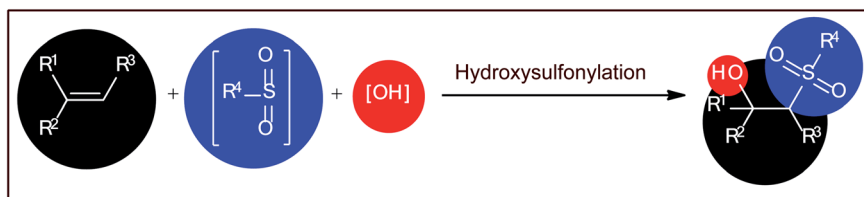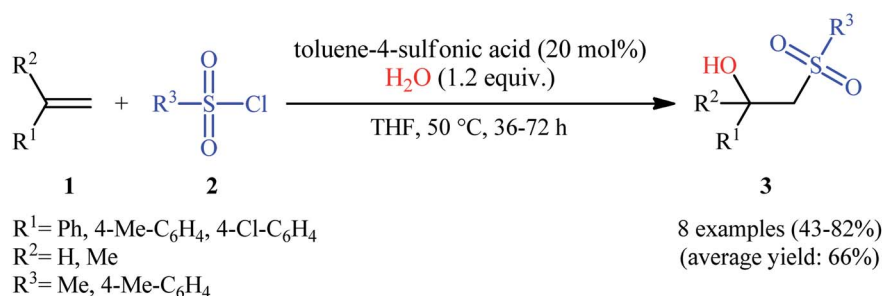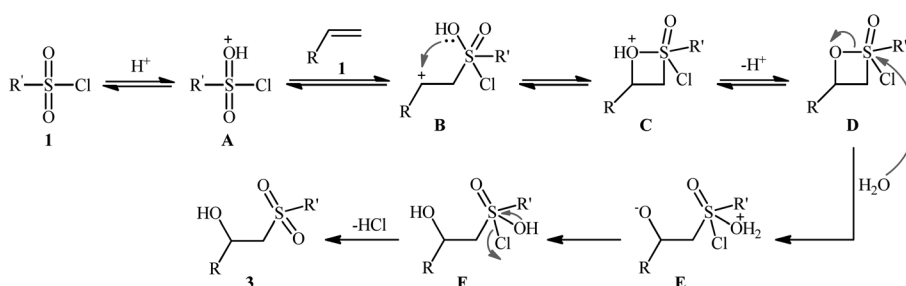
Fig. 1 Direct hydroxysulfonylation of alkenes.
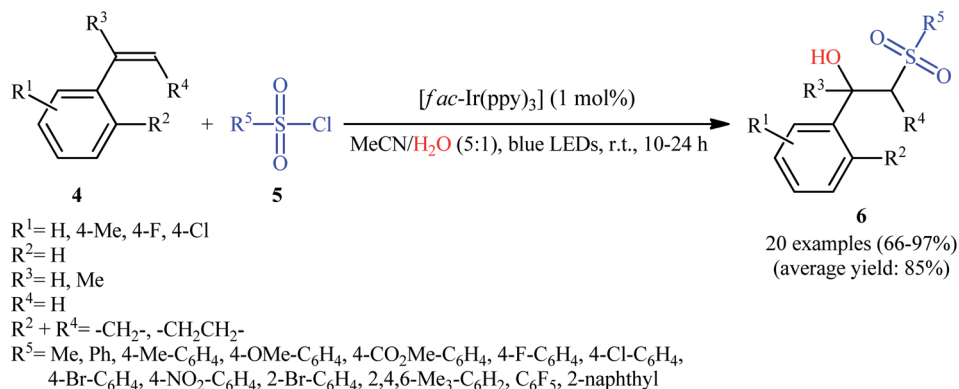
2. Sulfonyl chlorides as sulfonylating agents

The first successful synthesis of β-hydroxysulfones *via* the direct hydroxysulfonylation of corresponding alkenes was disclosed in 2004 by Xi and co-workers,[15] who reported an acid-promoted three-component reaction between terminal alkenes **1**, sulfonyl chlorides **2**, and water in THF (Scheme 2). In this preliminary work, eight β-hydroxysulfone derivatives **3** were synthesized in moderate to high yields, ranging from 43% to 82%. Various mono- and 1,1-di-substituted alkenes and both alkyl and aryl sulfonyl chlorides were compatible substrates in this difunctionalization reaction. However, no internal alkene was exemplified in the protocol. It should be mentioned that the reaction demonstrated an excellent level of regioselectivity, in which the hydroxyl group was predominantly introduced to the more hindered carbon atom of the double bond. The authors described a plausible mechanism for this transformation as illustrated in Scheme 3. It consists of the following key steps: (i) protonation of the oxygen atom in sulfonyl chloride **2** with acid to form the electrophilic intermediate **A**; (ii) nucleophilic attack

of alkene **1** to this intermediate **A** to produce carbocationic intermediate **B**; (iii) intramolecular cyclization of **B** to yield intermediate **C**; (iv) deprotonation of **C** to generate oxathietane **D**; (v) cleavage of the O–S bond of **D** by water to produce the intermediate **E**; (vi) intramolecular H-transfer of **E** to give sulfurochloridous acid **F**; and (vii) elimination of HCl from **F** to give the desired β-hydroxysulfone **3**.
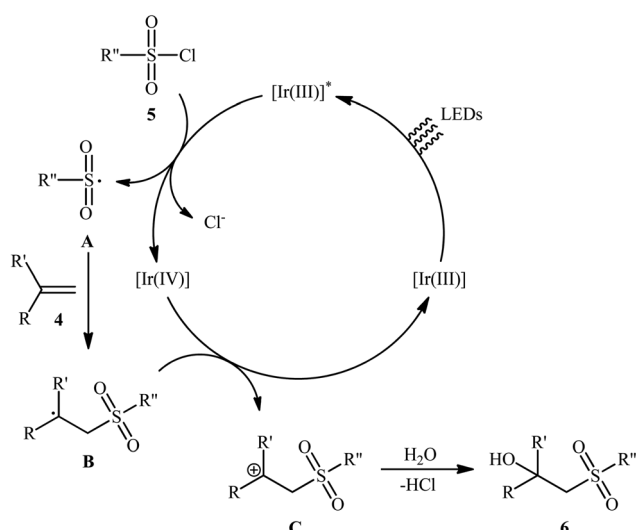
Twelve years later, Reiser's research team developed the photoredox-catalyzed version of this hydroxysulfonylation reaction using [*fac*-Ir(ppy)$_3$] as the photocatalyst.[16] The reaction of various α- and β-substituted styrenes **4** with sulfonyl chlorides **5** in the presence of only 1 mol% of catalyst in binary solvent MeCN/H$_2$O with ratio 5 : 1 under the irradiation of blue LEDs at ambient temperature could give the highly functionalized β-hydroxysulfones **6** in good to almost quantitative yields within 10–24 h (Scheme 4). The catalyst was, however, not effective for aliphatic and benzylic alkenes. In Scheme 5 a plausible mechanism for this transformation is depicted. In the beginning, the ground state Ir(III) photoredox catalyst undergoes excitation by irradiation with blue light to produce the excited state *Ir(III), which after a single-electron transfer (SET) to sulfonyl chloride **5** leads to the formation

R^1= Ph, 4-Me-C$_6$H$_4$, 4-Cl-C$_6$H$_4$
R^2= H, Me
R^3= Me, 4-Me-C$_6$H$_4$

8 examples (43–82%)
(average yield: 66%)

Scheme 2 Acid-promoted of hydroxysulfonylation of alkenes **1** with sulfonyl chlorides **2**, and water.

Scheme 3 Possible mechanism for the reaction in Scheme 2.

Scheme 4 Visible light mediated synthesis of β-hydroxysulfones **6** through the reaction of styrenes **4** and sulfonyl chlorides **5** in the presence of water.
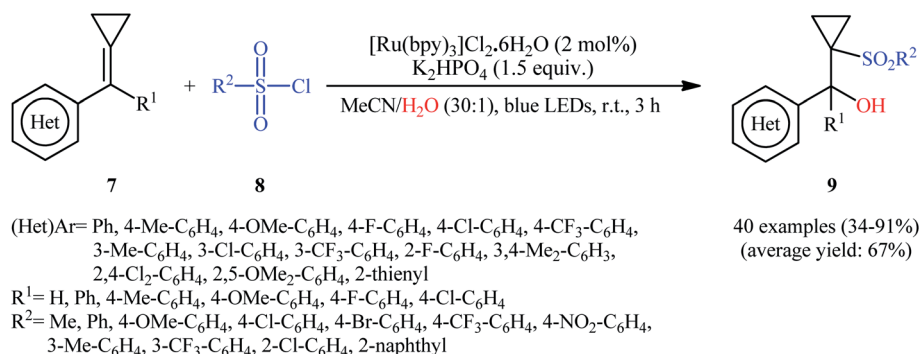

Scheme 5 Mechanistic explanation for the formation of β-hydroxysulfones **6**.

of the sulfonyl chloride **A** and strongly oxidizing Ir(IV). Next, regioselective sulfonyl radical **A** addition to styrene **4** takes place to form the carbon-centered radical intermediate **B** that, after oxidization by Ir(IV) produces the carbocation intermediate **C** and regenerates Ir(III) catalyst. Finally, nucleophilic addition of H_2O on the carbocation **C** provides the desired β-hydroxysulfone **6**.

Very recently, in a related investigation, Li and Wang along with their co-workers reported the use of $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ in combination with K_2HPO_4 for regioselective hydroxysulfonylation of alkylidenecyclopropanes **7** with sulfonyl chloride **8** and water under the irradiation of 12 W blue LEDs.[17] The reactions were implemented under an inert atmosphere (N_2) at room temperature, tolerated a wide range of important functional groups on both the substrates, and afforded the target cyclopropane-containing β-hydroxysulfones **9** in fair to excellent yields (Scheme 6). The authors further demonstrated that cyclobutane-containing β-hydroxysulfones could also be achieved in modest yields when alkylidenecyclobutanes were used as substrates. Noteworthy, the protocol was also applicable for gram-scale synthesis of cyclopropane-containing β-hydroxysulfones as exemplified by the formation of diphenyl(1-tosylcyclopropyl)methanol on a 1.59 g scale (84%).
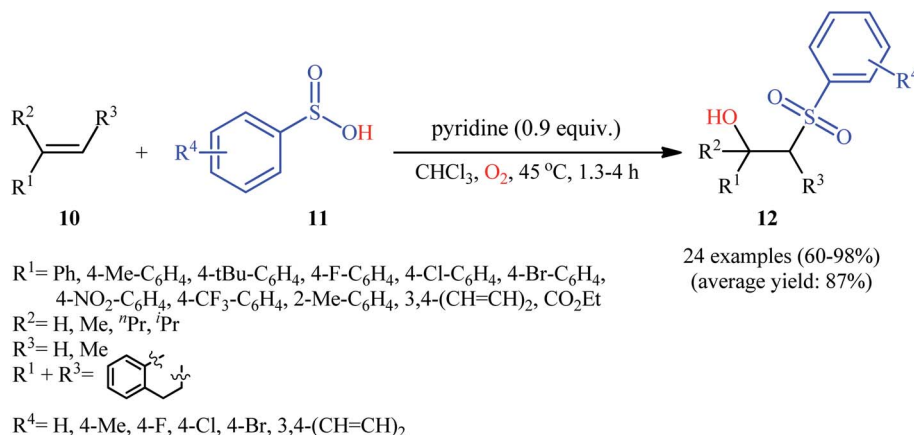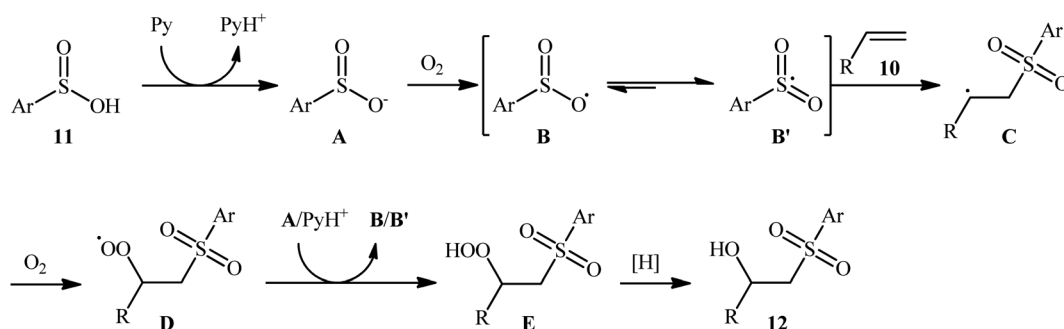
3. Sulfinic acids as sulfonylating agents

In 2013, Lei and co-workers disclosed the first direct oxidative difunctionalization of alkenes **10** with sulfinic acids **11** through dioxygen activation to construct β-hydroxysulfone derivatives **12** (Scheme 7).[18] A near stoichiometric amount of pyridine was used as base and $CHCl_3$ as solvent. Terminal, 1,1- and 1,2-disubstituted alkenes reacted well with various aromatic

Scheme 6 Synthesis of cyclopropane-containing β-hydroxysulfones **9** developed by Li and Wang.
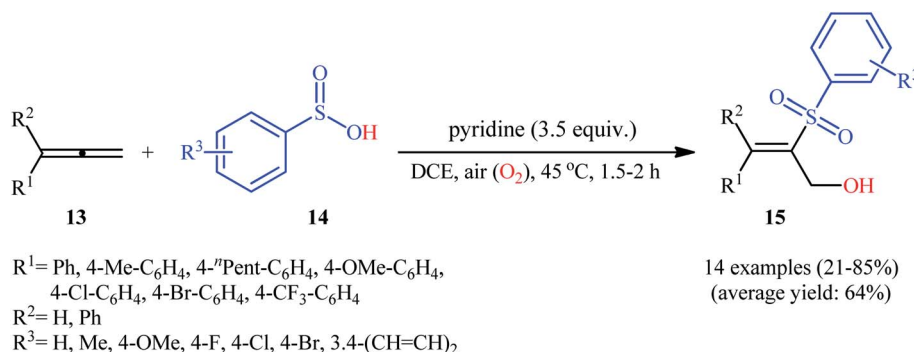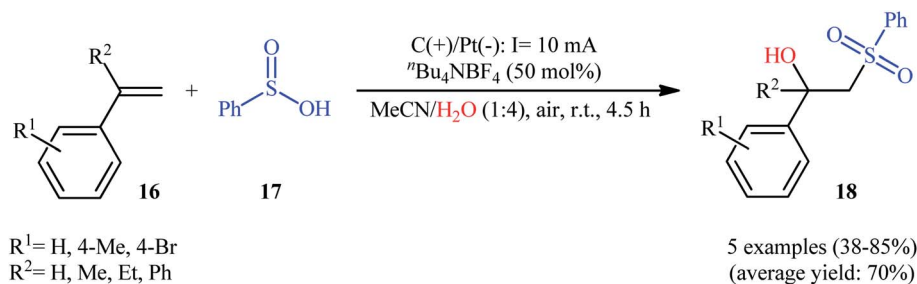
Scheme 7 Base-mediated hydroxysulfonylation of alkenes **10** with sulfinic acids **11** and O_2.

Scheme 8 Possible reaction pathway for the formation of β-hydroxysulfone derivatives **12**.

sulfinic acids bearing electron-withdrawing or -donating groups to generate the corresponding products in good to excellent yields. To elucidate the origination of the hydroxyl oxygen atom of the products, the authors performed a $^{18}O_2$ isotope labeling experiment. The results demonstrated that the oxygen atom in β-hydroxysulfones came from O_2. Furthermore, the radical trapping experiments with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,4-di-*tert*-butyl-4-methylphenol) revealed that the radical processes might be involved in this difunctionalization reaction (Scheme 8). In the presence of pyridine and oxygen, the sulfonyl radical **B′** was formed from benzenesulfinic acid **11** by a single-electron transfer process through the intermediate **A**. Addition of this radical **B′** to alkene
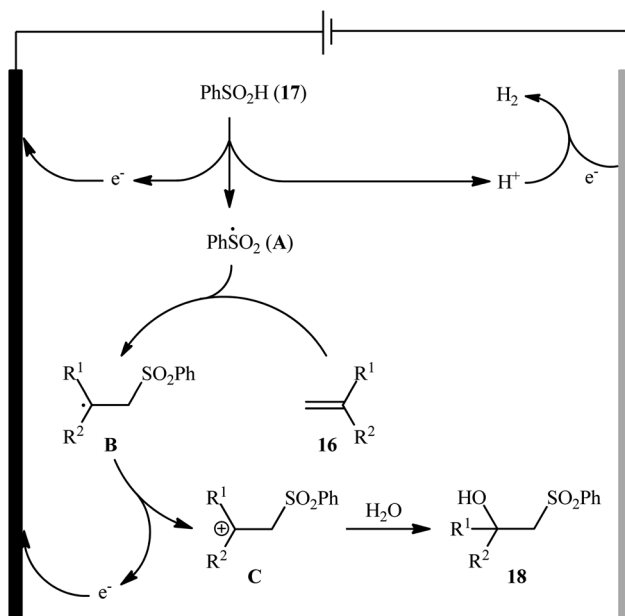
10 provided carbon-centered radical **C**, followed by a redox-transfer process to generate alkylhydroperoxy radical intermediate **D**. Thereafter, the newly formed radical **D** was converted to β-peroxylsulfone intermediate **E** through a SET process and concomitant proton transfer from **A** and pyridium benzenesulfonate. And then, reduction of **E** by benzenesulfinic acid **11** or workup with PPh$_3$ furnished the difunctionalized product **12**.

Three years later, the same group disclosed that synthetically challenging 2-sulfonyl allylic alcohols **15** could be effectively prepared in highly regio- and stereoselective manner from the reaction of allenes **13** with arenesulfinic acids **14** in the presence of 3.5 equiv. of pyridine under air atmosphere (Scheme 9).[19] In the investigation of the scope of this transformation, it was

Scheme 9 Regio- and stereoselective hydroxysulfonylation allenes **13** with arenesulfinic acids **14** reported by Lei.

Scheme 10 Electrochemical synthesis of β-hydroxysulfones **18** developed by Sun.

Scheme 11 Mechanism that accounts for the formation of β-hydroxysulfones **18**.
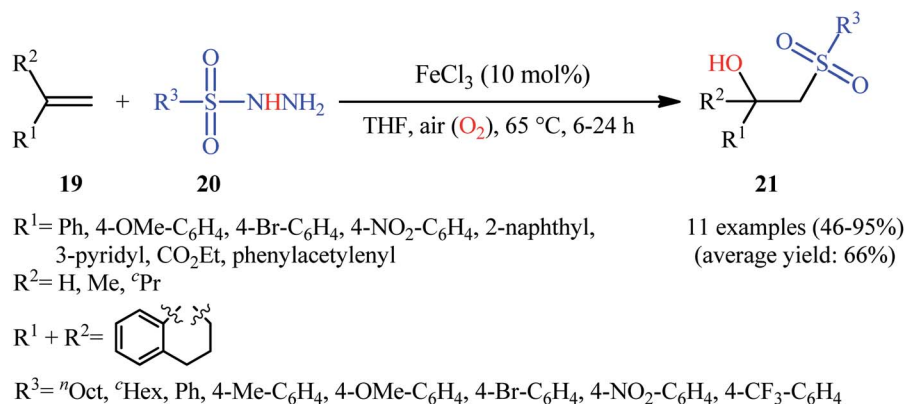
found that the presence of an aryl substituent on the double bond was vital for the success of the reaction. When ester-substituted allenes were used as substrates under the identical conditions, terminal alkene products were generated instead. Moreover, the concentration of dioxygen had a great

influence on the reaction. When the reaction was carried out under O_2 atmosphere instead of air, it turned generated a complex product mixture.

Very recently, Sun and colleagues developed an interesting electrochemical approach for regioselective hydroxysulfonylation of styrene derivatives **16** employing benzenesulfinic acid **17** as the sulfonylating reagent and water as hydroxylating agent.[20] The optimal system was identified using $^nBu_4NBF_4$ (tetrabutylammonium tetrafluoroborate) as an electrolyte with an undivided graphite/Pt-cell in a 4 : 1 mixture of MeCN and H_2O under an inert atmosphere at room temperature. This electrochemical method efficiently provided the target β-hydroxysulfones **18** in fair to high yields under catalyst-free conditions and without consuming any oxidizing agent or additive (Scheme 10). The authors depicted a plausible mechanism for this transformation, which is shown in Scheme 11.
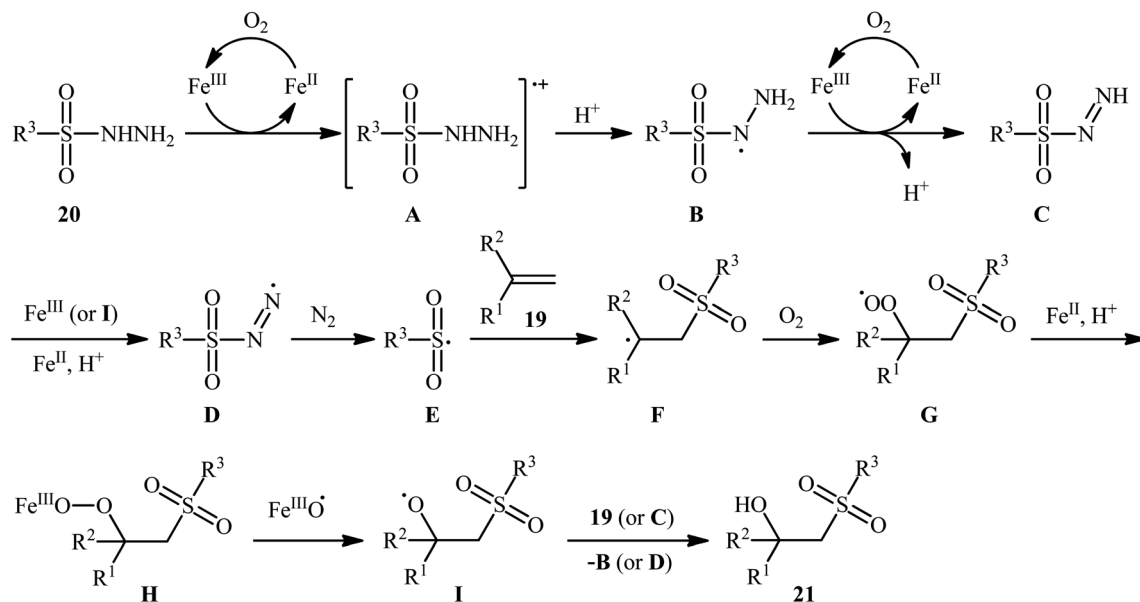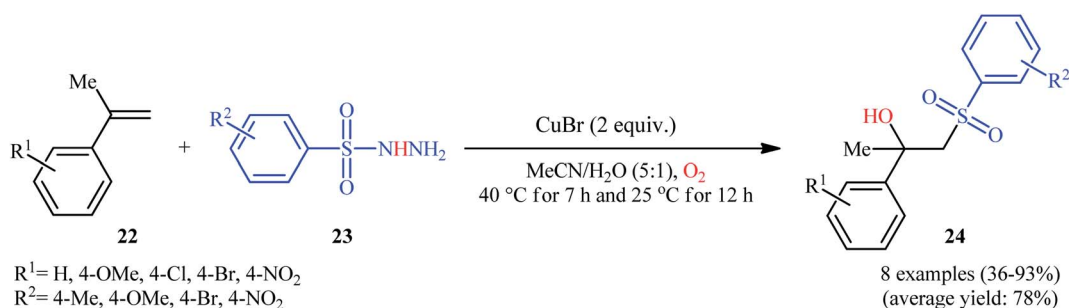
4. Sulfonylhydazides as sulfonylating agents

In 2011, Taniguchi's research team reported the first example of metal-catalyzed direct hydroxysulfonylation of alkenes **19** using sulfonylhydazides **20** as easily available and powerful sulfonyl sources.[21] The reactions were carried out in the presence of a catalytic amount of $FeCl_3$ in THF under air, completed within 6–24 h at 65 °C, and afforded the corresponding β-hydroxysulfones **21** in moderate to excellent yields (Scheme 12). The method showed a broad substrate scope including both
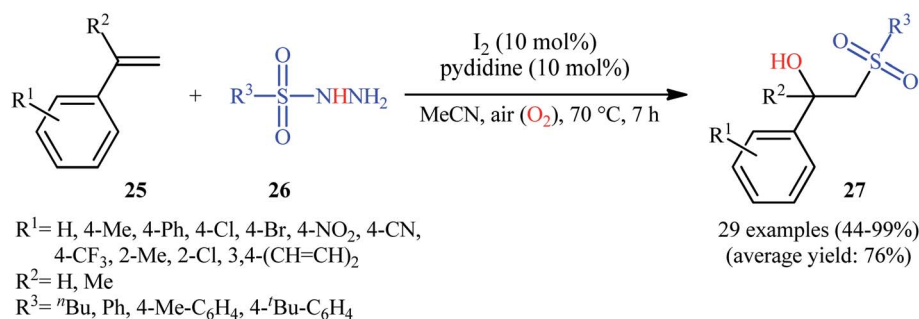

Scheme 12 Fe-catalyzed direct synthesis of β-hydroxysulfones **21** from alkenes **19** and sulfonylhydazides **20**.
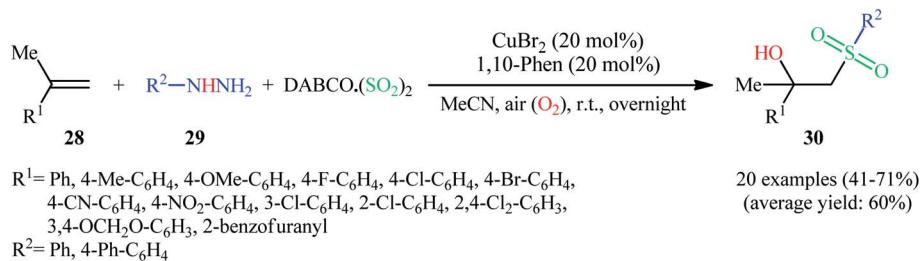
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Scheme 13 A plausible reaction mechanism for the formation of β-hydroxysulfones **21**.

Scheme 14 Cu-mediated synthesis of β-hydroxysulfones **24** from styrenes **22** and sulfonylhydrazides **23** in the presence of O_2.
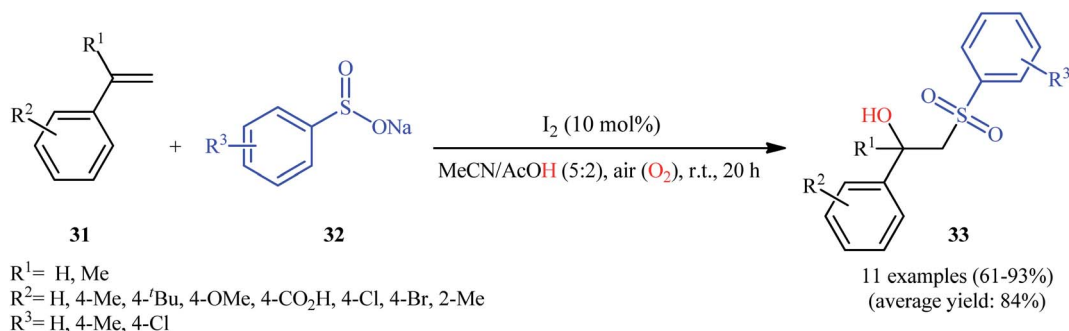
aliphatic and aromatic sulfonylhydazides and various aryl-, ester-, and acetylene-substituted alkenes. However, the reaction failed in the case of an internal alkene. Moreover, 1,1-dialkyl substituted substrates did not work well in this synthetic strategy. A possible mechanism was also proposed (Scheme 13), whereby the reaction is initiated with oxidation of sulfonylhydrazide **20** by Fe(III) to give diazene **C** via the intermediates **A** and **B**, which undergoes further oxidation by iron catalyst

affording nitrogen-centered radical **D**. Subsequently, this radical **D** releases a molecular nitrogen to deliver the sulfonyl radical **E**. The newly formed radical **E** is then reacting with alkene **19** to form alkyl radical **F**, which after interaction with the dioxygen dissolved in THF converts to the peroxy radical **G**. Thereafter, reduction of peroxy radical **G** by Fe(II) yields the alkoxyl radical **I** through the intermediate **H**. Finally, alkoxyl radical **I** abstracts a hydrogen atom from diazene intermediate

Scheme 15 I_2-catalyzed aerobic hydroxysulfonylation of styrenes **25** with sulfonylhydazides **26**.

Scheme 16 Cu-catalyzed synthesis of β-hydroxysulfones **30** through the aerobic oxidative reaction of alkenes **28**, arylhydrazines **29**, and DABCO·(SO$_2$)$_2$.
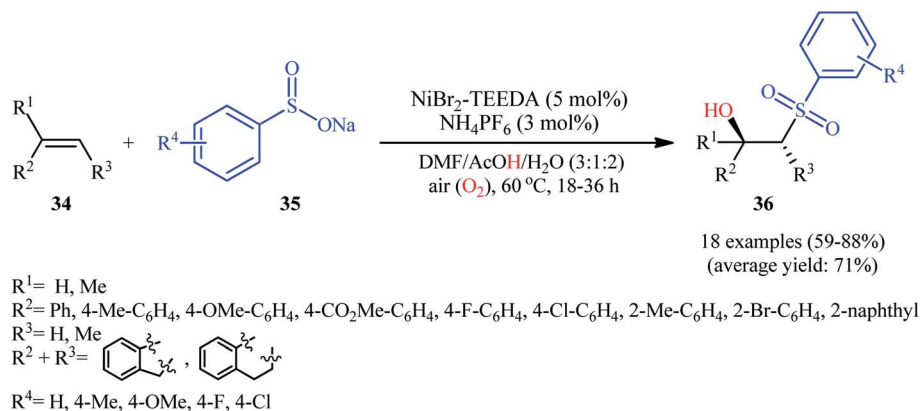
Scheme 17 Itoh's synthesis of β-hydroxysulfones **33**.

C or another molecule of sulfonylhydrazide **20** to furnish the desired β-hydroxysulfone product **21**.

In 2016, Terent'ev and co-workers reported an analogous methodology for the direct hydroxysulfonylation of α-substituted styrenes **22** with arylsulfonyl hydrazides **23** under O$_2$ atmosphere in the presence of a copper salt (Scheme 14).[22] In their optimization study, the authors found that the use of 2.0 equiv. of CuBr as mediator in MeCN–H$_2$O (5 : 1) gave the best results. Examination of the scope of the reaction revealed that a range of α-substituted styrenes bearing either electron-withdrawing or electron-donating groups and a variety of electron rich- and deficient-substituted arylsulfonyl hydrazide analogues were compatible substrates and afforded the β-hydroxysulfones **24** in moderate to excellent yields. However,

the use of α-unsubstituted styrenes as substrates under the identical conditions led to the mixture of corresponding β-hydroxysulfones and β-sulfonyl ketones.

With the objective of designing a metal-free protocol to β-hydroxylated sulfones through the direct hydroxysulfonylation of the alkenes with sulfonylhydazides, Mal and colleagues were able to reveal that a divers set of functionalized β-hydroxysulfones **27** could be prepared in moderate to quantitative yields from the reaction of styrene derivatives **25** with sulfonylhydazides **26** under ambient atmosphere employing molecular iodine as a catalyst and pyridine as an additive in MeCN (Scheme 15).[23] Noteworthy, when pyridine was solely used as a catalyst no product formation was observed. The results also proved that other halide ion sources such as TBAI and TBAB

Scheme 18 Nickel-catalyzed aerobic hydroxysulfonylation of alkenes **34** with sodium sulfinates **35**.

Scheme 19 Possible pathway of β-hydroxysulfones **36** formation.

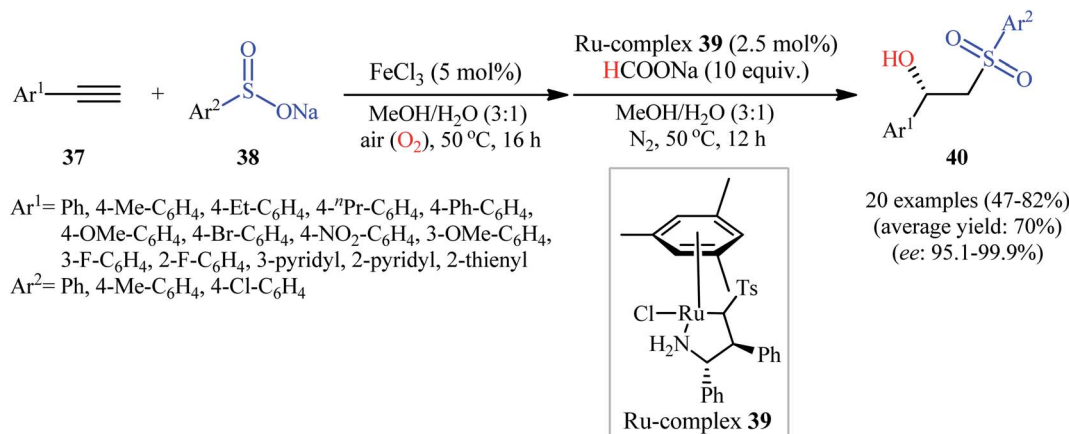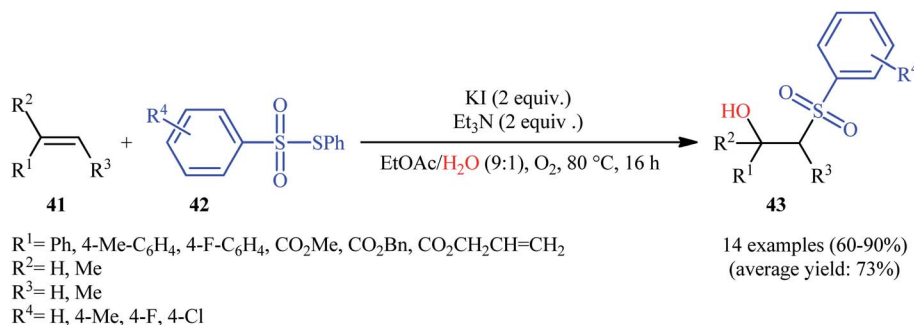were not able to promote this reaction. Some important information of the reactions is listed below: (i) both aromatic and aliphatic sulfonylhydazides were suitable substrates under the optimal condition; (ii) not only α-substituted styrenes but also α-unsubstituted styrenes afforded the desired products with excellent selectivity; (iii) the protocol was not successful in the case of aliphatic alkenes; and (iv) the process could be easily scaled up to the gram quantities without loss of the yields. Along this line, recently, the Zhu group has identified methylene blue (MB) as an efficient photoredox catalyst for hydroxysulfonylation of α-substituted styrenes with 4-methylbenzenesulfonohydrazide under aerobic conditions.[24] In this report, seven β-hydroxysulfones were synthesized in good yields (63–81%) by means of 2 mol% of MB and 1 equiv. of DABCO in EtOH at room temperature under the irradiation of

7 W blue LEDs. However, under the identical conditions, α-unsubstituted styrenes afforded the corresponding β-keto sulfones instead of β-hydroxysulfone products.

Recently, Ye, Wu, and co-workers disclosed an innovative Cu-catalyzed aerobic oxidative three-component reaction of alkenes **28**, arylhydrazines **29**, and DABCO·(SO₂)₂ to prepare the corresponding β-hydroxysulfones **30** through hydroxysulfonylation of C–C double bonds with the insertion of sulfur dioxide (Scheme 16).[25] Here, arylhydrazines served as the precursors of aryl radicals under aerobic atmosphere, which initiated the reaction. During the reaction process, aryl radicals react with sulfur dioxide leading to arylsulfonyl radicals, which subsequently undergo hydroxysulfonylation of alkenes with oxygen to provide β hydroxysulfones.

Scheme 20 Synthesis of chiral β-hydroxysulfones **40** from terminal alkynes **37** and sodium sulfinates **38** *via* Fe-catalyzed aerobic oxysulfonylation and consecutive Ru-catalyzed asymmetric transfer hydrogenation.

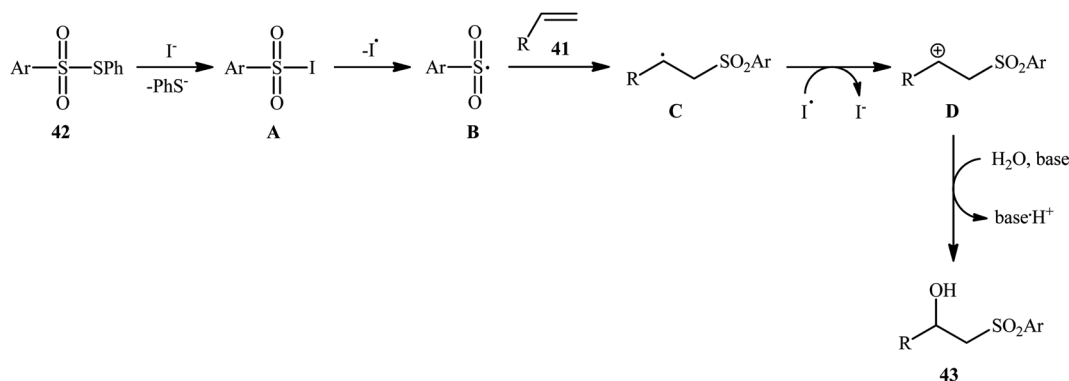**Scheme 21** Jang's synthesis of β-hydroxysulfones **43**.

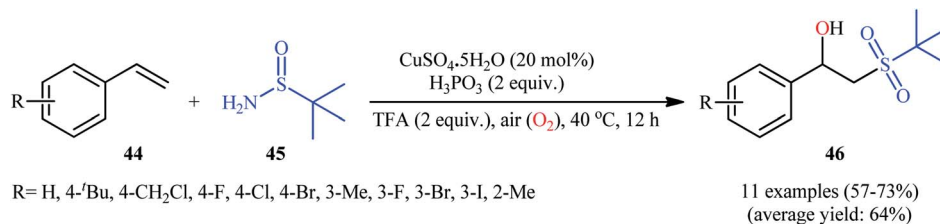# 5. Sodium sulfinates as sulfonylating agents

One of the earliest reports on the utilization of sodium sulfinates as sulfonylationg agents in the direct hydroxysulfonylation of alkenes under oxidative conditions was published by Itoh and colleagues in 2014,[26] who showed that the treatment of styrene derivatives **31** with sodium arylsulfinates **32** in the presence of a catalytic amount of molecular iodine in MeCN/AcOH mixture under air without any additional oxidants, resulted in the formation of the corresponding β-hydroxysulfones **33** in good to excellent yields (Scheme 17). Unfortunately, cyclohexene did not take part in the reaction and therefore no other aliphatic alkenes were examined in the protocol. In their optimization study, the authors found that other iodine sources such as NIS, NaI, MgI_2, CaI_2, and CI_4 could also promote this transformation; albeit, at lower efficiencies. Notably, sulfonylhydazides did not respond to this difunctionalization reaction using I_2 catalyst alone and the presence of a basic additive such as pyridine was crucial for the success of this conversion.[23] Later, Chen and Chang along with their co-workers improved the efficiency of this transformation in the terms of reaction time and yield by switching the iodine source to KI and performing the process in a GCE-Pt electrochemical cell.[27]

In 2015, Taniguchi disclosed the usefulness of nickel catalysts for hydroxysulfonylation of alkenes using sodium sulfinates under air atmosphere.[28] Thus, in the presence of a combination of $NiBr_2$-TEEDA (N,N,N',N'-tetraethylethylenediamine) complex and NH_4PF_6 in DMF–AcOH–H_2O at 60 °C, the reaction of various terminal and internal aklenes **34** with aromatic sodium sulfinates **35** furnished the corresponding β-hydroxysulfones **36** in good to high yields, ranging from 59% to 88% (Scheme 18). However, in the majority of cases, β-ketosulfones were obtained as side products. In this study, the authors found some limitation in their methodology, when they attempted to react heteroaromatic and aliphatic alkenes. Unfortunately, these compounds were ineffective under standard condition. NMR analysis revealed that in the cases of internal alkenes *anti*-adducts were selectively formed. Furthermore, reactions using *cis* and *trans* alkenes gave the same products. A plausible mechanism proposed by the authors was started with Ni(II)-mediated oxidation of sodium sulfinate **35** by air to form sulfonyl radical **A** which was then trapped by alkene **34** to generate **C**-centered radical **B**. Subsequently, the radical **B** attacked air oxygen to achieve peroxy radical **C**. After that, this radical **C** was reduced to peroxy anion **D** by nickel(I) or a sulfonyl anion. Finally, anion intermediate **D** afforded the desired product **36** by reduction with a proton (Scheme 19). In a related investigation, Menezes's research team demonstrated that the merge of 1.0 equiv. of $FeCl_3$ with $(NH_4)_2S_2O_8$ could also promote this difunctionalization reaction.[29] However, selectivity and yield was modest at best.

Recently, Zhou's research team demonstrated an innovative protocol for highly enantioselective synthesis of β-hydroxysulfones from terminal alkynes and sodium sulfinates *via* Fe-catalyzed aerobic oxysulfonylation and consecutive Ru-

Scheme 22 Mechanism that accounts for the formation of β-hydroxysulfones **43**.

Scheme 23 Synthesis of 2-(*tert*-butylsulfonyl)-1-arylylethanols **46** from styrenes **44** and *t*-butylsulfinamide **45** under aerobic Cu-catalyzed conditions.

catalyzed asymmetric transfer hydrogenation in an aqueous medium under mild conditions.[30] Thus, in the presence of 20 mol% of FeCl$_3$ as a catalyst in MeOH/H$_2$O, aerobic oxy-sulfonylation of (hetero)aromatic terminal alkynes **37** with sodium arylsulfinates **38** furnished the corresponding β-keto sulfones which subsequently reduced by HCOONa as

a hydrogen source employing 2.5 mol% of ruthenium complex **39** as a chiral catalyst to give enantiomerically enriched β-hydroxysulfones **40** in moderate to high yields and up to 99.9% ee values (Scheme 20). Various important functional groups in the phenyl ring periphery of either alkynes or sulfinates were well tolerated by this reaction, thus indicating its broad

Scheme 24 A plausible reaction mechanism for the formation of 2-(*tert*-butylsulfonyl)-1-arylylethanols **46**.

applicability. The reaction could also be easily conducted on a gram scale (78% yield and 98.7% ee on 10 mmol scale). Drawing inspiration from this work, quite recently, Liu and co-workers designed and synthesized the yolk–shell-structured magnetic nanoparticles with the chiral Ru/diamine species with in the nanochannels of the outer mesoporous silica shell and the FeCl$_3$ species on the inner magnet core, [Fe]@Fe$_3$O$_4$@ [Ru]@[Si] ([Ru] = MesRuArDPEN : Mes = Mesitylene, and ArDPEN = (*S*,*S*)-4-((trimethoxysilyl)ethyl)phenylsulfonyl-1,2-diphenylethylene–diamine; [Fe] = FeCl$_3$), and successfully applied the prepared nanocomposite system as an efficient catalyst for high yielding synthesis of a wide variety of chiral β-hydroxysulfones from the corresponding aryl-substituted terminal alkynes and sodium arylsulfinates *via* the one-pot aerobic oxysulfonylation/asymmetric transfer hydrogenation cascade process.[31]
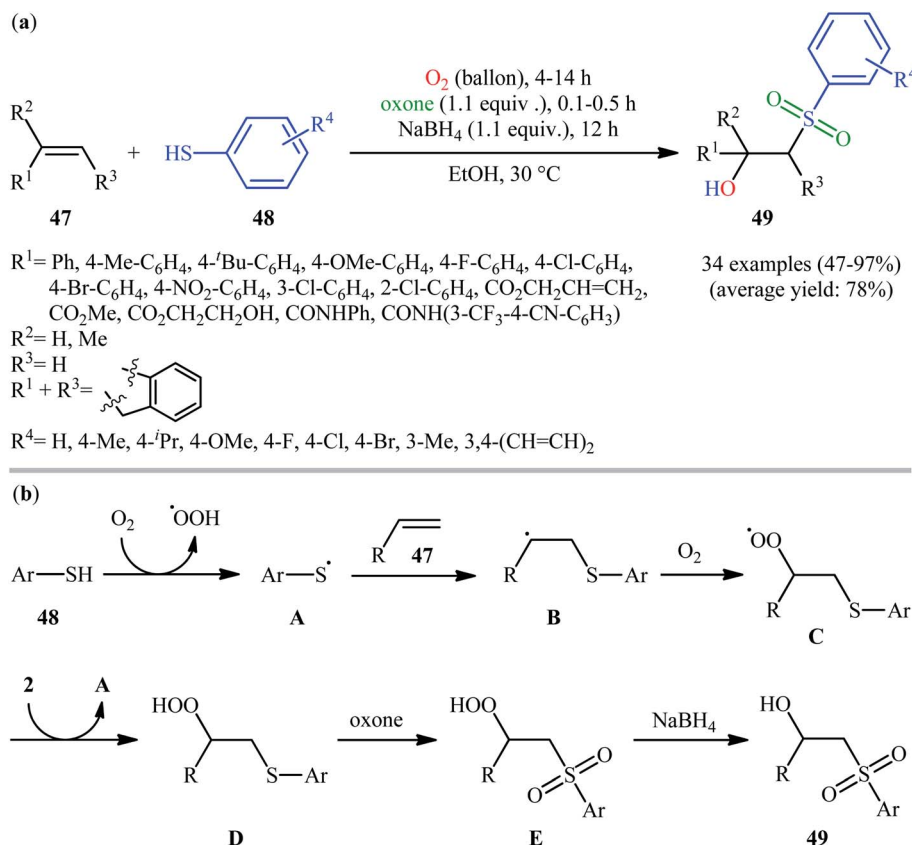
6. Thiosulfonates as sulfonylating agents

Recently, Jang and colleagues reported a new methodology for high yielding preparation of β-hydroxyl sulfone derivatives **43** shown in Scheme 21.[32] These compounds were synthesized by the treatment of the corresponding alkenes **41** with thiosulfonates **42** as aryl sulfonyl sources and water as the source of the hydroxyl group through an KI-catalyzed regioselective vicinal

hydroxysulfonylation reaction. The reaction is noteworthy in that both electron-rich alkenes such as styrene and electron-deficient alkenes such as methyl methacrylate and benzyl methacrylate were well tolerated. In addition, the scope of thiosulfonates that underwent reaction was broad enough to include electron-neutral, electron-rich and electron-poor thiosulfonate derivatives. A plausible mechanism proposed by the authors was started with reaction of thiosulfonate **42** with iodide to form sulfonyl iodide **A** which was then dissociated into sulfonyl radical **B** and iodide radical. Subsequently, the sulfonyl radical **B** attacked the alkene **41** to afford carbon-centered radical **C**. After that, radical **C** was oxidized to carbocationic intermediate **D** by I˙. Finally, the addition of water to the carbocation afforded the desired product **43** (Scheme 22). To the best of our knowledge, this is the only example reported on the hydroxysulfonylation of alkenes with thiosulfonates.

7. Sulfonamides as sulfonylating agents

Recently, in a report by Bi, Feng, and co-workers, a library of 2-(*tert*-butylsulfonyl)-1-arylethanols **46** were synthesized in moderate to good yields by treatment of styrene derivatives **44** with a slight excess of *t*-butylsulfinamide **45** under open-air conditions (Scheme 23).[33] The reaction was performed in the presence of 20 mol% of CuSO$_4$·5H$_2$O as a catalyst and 2 equiv.

Scheme 25 (a) Huo's synthesis of β–hydroxysulfones **49**; (b) mechanistic explanation for the formation of β–hydroxysulfones **49**.

of H_3PO_3 as an additive at 40 °C. Although other copper salts (*e.g.*, CuI, CuBr, Cu(OAc)$_2$, CuSO$_4$) and additives (*e.g.*, DMPH, DEPH, DIPPH, DPPH) also allowed for the reaction to proceed, the efficiency was optimal using the aforementioned conditions. The best results were obtained in the case of aromatic alkenes with electron-withdrawing groups. On the contrary, electron-donating groups were unfavorable for the reaction and led to lower yields. Unfortunately, styrenes with strong electron-donating groups (OMe) as well as disubstituted styrenes completely failed to participate in this reaction. The plausible mechanistic pathway suggested by the authors for this transformation is depicted in Scheme 24. It is worthy of note that when the same reaction was carried out at 120 °C, instead of β-hydroxysulfone compounds, vinyl sulfones were obtained as the sole products. The authors proved that the formation of vinyl sulfones did not proceed through the simple dehydration of β-hydroxysulfones under high temperatures as evidenced by an unsuccessful intermolecular transformation of a β-hydroxysulfone to the corresponding vinyl sulfone by heating at 120 °C for 5 h.

8.   Thiols as sulfonylating agents

In 2017, the Huo group developed an elegant one-pot multi-step method for the synthesis of β-hydroxysulfones **49** from alkenes **47** and thiols **48** under catalyst-free and mild conditions (Scheme 25).[34] This sequential approach involving an auto-oxidative difunctionalization reaction of alkenes and thiols under oxygen atmosphere, oxidation of generated β-hydroperoxysulfide to β-hydroperoxysulfone using oxone as a sustainable oxidant followed by reduction with NaBH$_4$. The optimization of the one-pot process has allowed the preparation of a diverse range of secondary and tertiary β-hydroxysulfones in moderate to excellent yields with outstanding regioselectivities. Notably, the authors nicely applied their methodology in the high yielding multi-gram scale (2.92 g) preparation of bicalutamide, anti-cancer drug.

Finally, it should be noted that transition metal complexes play important role in the hydroxysulfonylation of alkenes and other compounds.[35–42]

9.   Conclusion

β-Hydroxysulfones are valuable skeletons found in many biologically active molecules, and provide useful building blocks in organic synthesis. Traditionally, these compounds are synthesized through reduction of β-keto-sulfones, hydroxylation of α,β-unsaturated sulfones, and nucleophilic ring opening of epoxides with sulfinate salts. However, these transformations suffer from certain drawbacks, such as production of unwanted byproducts, requirement of pre-functionalized starting materials as well as harsh reaction conditions. In order to bypass these limitations, direct hydroxysulfonylation of inexpensive and easily accessible alkenes was recently developed as an efficient and straightforward one-pot approach to the titled compounds. Majority of these difunctionalization reactions have been carried out under metal-free and mild conditions and

can be also scaled up to gram levels without difficulty. Nevertheless, the area still needs much more investigation due to some challenges and limitations in the current reports. For instance: (i) the substrate scope of alkenes is narrow and generally limited to the activated alkenes (*e.g.* styrenes, acrylates). Thus, of course, expanding of substrate scope of this page of β-hydroxysulfone synthesis to unactivated alkenes are necessary; (ii) the hydroxysulfonylation of alkynes still almost remains unexplored and there is a need for further studies the scope and limitations of alkynes in this transformation; and (iii) the exploration of asymmetric hydroxysulfonylations for the synthesis of enantioenriched β-hydroxysulfones still remains an elusive goal. We hope this review will be helpful in the development of improved methods for the synthesis of β-hydroxysulfones as well as other organosulfur compounds.

Conflicts of interest

There are no conflicts to declare.

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