RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2021, **11**, 13138

Received 19th November 2020
Accepted 23rd March 2021

DOI: 10.1039/d0ra09848e

rsc.li/rsc-advances

Intermolecular difunctionalization of alkenes: synthesis of β-hydroxy sulfides

Bayan Azizi,[a] Mohammad Reza Poor Heravi,[b] Zinatossadat Hossaini,[*c] Abdolghaffar Ebadi[d] and Esmail Vessally[b]

Direct difunctionalization of carbon–carbon double bonds is one of the most powerful tools available for concomitant introduction of two functional groups into olefinic substrates. In this context, vicinal hydroxysulfenylation of unactivated alkenes has emerged as a novel and straightforward strategy for the fabrication of β-hydroxy sulfides, which are extremely valuable starting materials in constructing various natural products, pharmaceuticals, and fine chemicals. The aim of this review is to summarize the most representative and important reports on the preparation of β-hydroxy sulfides through intermolecular hydroxysulfenylation of the corresponding alkenes with special emphasis on the mechanistic features of the reactions.

1. Introduction

Organosulfur compounds are ubiquitous in natural products, pharmaceuticals, and agrochemicals.[1–3] In particular, organic sulfides widely exist in many useful commercialized drugs.[4] In this family of organosulfur compounds, β-hydroxy containing sulfides have recently attracted significant attention due to their fascinating biological activities, such as antimicrobial, anti-tumor, anti-HIV, and anti-inflammatory activities (Scheme 1).[4,5] One of the most straightforward synthetic procedure for the preparation of β-hydroxy sulfides is the thiolysis of epoxides with thiols[6] or disulfides.[7] However, this pathway generally suffers from certain disadvantages, such as low yields, poor regioselectivity, harsh reaction conditions, and the formation of undesirable by-products *via* rearrangement of epoxides and oxidation of thiols. Thus, the development of a convenient and

[a]*College of Health Sciences, University of Human Development, Sulaimaniyah, Kurdistan region of Iraq*
[b]*Department of Chemistry, Payame Noor University, P. O. Box 19395-3697, Tehran, Iran*
[c]*Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Qaemshahr, Iran. E-mail: zs.hossaini@qaemiau.ac.ir; zshossaini@yahoo.com*
[d]*Department of Agriculture, Jouybar Branch, Islamic Azad University, Jouybar, Iran*

Bayan Azizi was born in Iraq, in 1986. She received her bachelor degree in Applied Chemistry from Razi University, Iran in 2008. Also, she has received her master degree in Physical Chemistry from Kurdistan University in 2012. After graduation, she has worked at the Quality Control Laboratory in Jahad Daneshgahi (Oslub Sanat Company), Iran and Payam Noor University, Kermanshah in 2013. She was been lecturer at the Technical College of Applied Science, Sulaimani Polytechnic University, Kurdistan Region of Iraq from 2014 to 2018. Currently she is a lecturer at the department of Medical Laboratory Science, University of Human Development, Kurdistan Region of Iraq where she has been since 2018. Her research interests include nano-technology, quantum chemistry, physical chemistry, and clinical chemistry.

Mohammad Reza Poor Heravi was born in Seiyahkal-Lahijan, Guilan, Iran in 1965. He received a B.Sc. degree in pure Chemistry from Tabriz University, Iran, in 1987, and a M.Sc. degree in Organic Chemistry from Tabriz University, Iran in 1990 with Professor A. Shahrisa, and a Ph.D. degree from Isfahan University, Iran, with Professor H. Loghmanim. In 2006 he was a visiting researcher at Sheffield University, UK, with Professor Richard F. W. Jackson. He became a sciences faculty member of Payame Noor University in 1990, and associate Professor in 2012. His research field includes applications of solvent-free conditions, ionic liquids, fluorination reactions, designing fluorinating reagents and ultrasound irradiation in organic synthesis, and the study of methodology in organic chemistry.

truly efficient synthetic strategy for the preparation of the titled compounds remains a challenge.

Direct difunctionalization of C–C unsaturated bonds is one of the most powerful synthetic methodologies toward polyfunctionalized molecules in a very simple manner.[8] In this context, 1,2-hydroxysulfenylation of alkenes with various sulfenyl sources provides an excellent route to the synthesis of β-hydroxy sulfides in one step (Fig. 1). High atom- and step-economy efficiency, high functional group tolerance, good regioselectivity, and the use of inexpensive easily available starting materials are the main advantages motioned for this page of β-hydroxy sulfide synthesis. Recently, Kinfe and co-workers highlighted this synthetic strategy in their interesting review paper entitled "β-hydroxy sulfides and their syntheses".[9] However, several important examples were omitted and generally the explanation of mechanistic pathways of the reactions were ignored. In connection with our recent works on organosulfur chemistry[10] and modern organic synthesis,[11] herein we will attempt to provide a comprehensive overview of the synthesis of β-hydroxy sulfides through intermolecular difunctionalization of the respective alkenes with particular emphasize on the mechanistic aspect of reactions which may allow possible new insights into catalyst improvement.

Zinatossadat Hossaini was born in Tehran, Iran, in 1976. She received her B.S. degree in pure chemistry from the 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 her Ph.D. degree in 2008 under the supervision of Prof. I. Yavari. Now she is working at Islamic Azad University as an associate Professor in organic chemistry. Her research interests include synthesis of organic compounds, synthesis of nanocatalysts and new methodologies in organic synthesis and spectral studies of organic compounds.

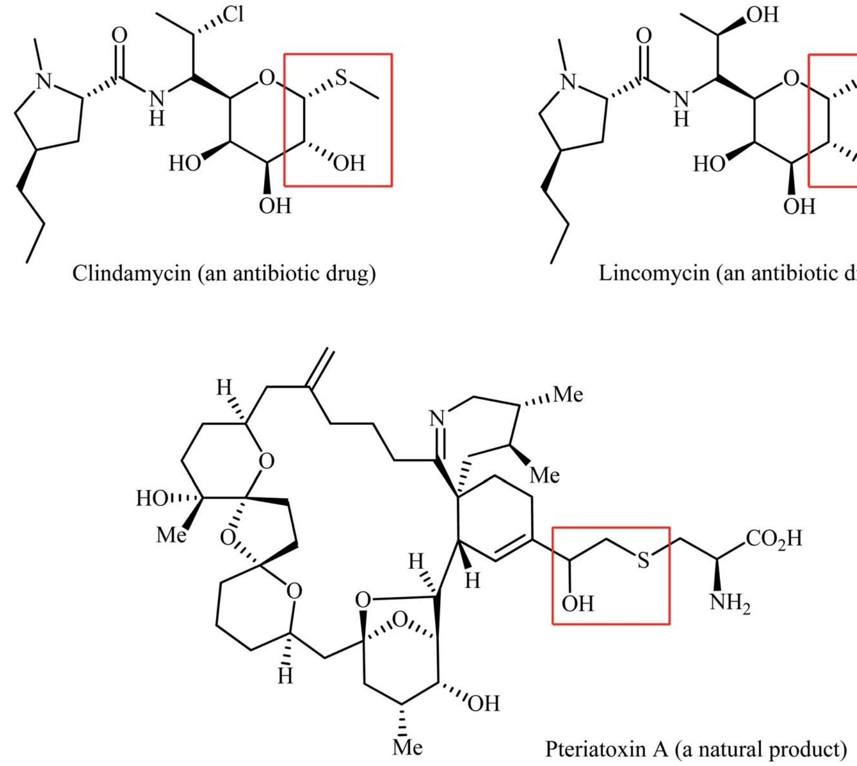
2. Metal-catalyzed/mediated reactions

The fabrication of β-hydroxy sulfides through metal-mediated direct hydroxysulfenylation of alkenes was accomplished first in 1978 by Trost *et al.*[12] They showed that treatment of aliphatic alkenes **1** with aromatic disulfides **2** in the presence of $Pb(OAc)_4$ as an oxidant and CF_3CO_2H as the source of the hydroxyl oxygen in DCM furnished trifluoroacetoxy sulfide intermediate **I** that after hydrolysis in the work-up converted to the corresponding β-hydroxy sulfides **3** in moderate to almost quantitative yields (Scheme 2). The reaction is notable in that both terminal and internal alkenes were tolerated. However, the regioselectivity was poor and in the cases of unsymmetrical alkenes a mixture of two possible isomers were obtained. It is worthwhile to note that under the identical conditions, alkenes bearing a carboxylic acid group underwent sulfenyllactonization to give sulfenylated lactones with good to excellent yields. Eight years later, Mellor's research team improved the efficiency of this process in the terms of regioselectivity and product yields by replacing of $Pb(OAc)_4$ with $Mn(OAc)_3$ and using allylic esters and amides as the substrates.[13] Afterwards, El-Samii successfully applied this procedure in the hydroxysulfenylation of a small series of butadiene derivatives with diphenyldisulfane and di-*p*-tolyldisulfane.[14] Of note, $Pb(OAc)_4$ was also found to be effective oxidant for this transformation, however $Cu(OAc)_2$ and $Fe(OAc)_2$ proved to be completely ineffective.

In 2008, Movassagh and Navidi provided a further example of β-hydroxy sulfide derivatives **6** synthesis from the corresponding styrenes **4** and aromatic disulfides **5** assisted by Zn/$AlCl_3$ system in $MeCN/H_2O$ (4 : 1) under an oxygen atmosphere

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 has 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 in China, Malaysia, and Thailand. His interests are Environmental Biotechnology, Biochemistry, and Gene pathways in phytoremediation processes.

Esmail Vessally was born in Sharabiyan, Sarab, Iran, in 1973. He received his B.S. degree in pure chemistry from the 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 Ph.D. 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.



Scheme 1 Bioactive compounds containing a β-hydroxy sulfide unite.

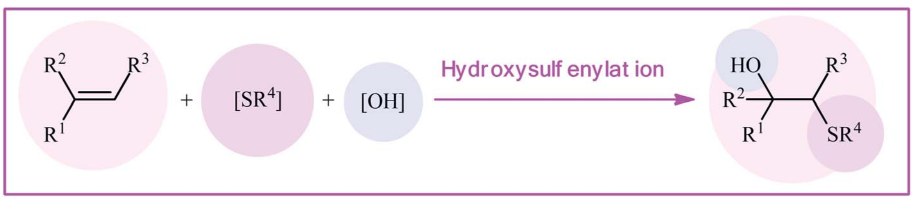


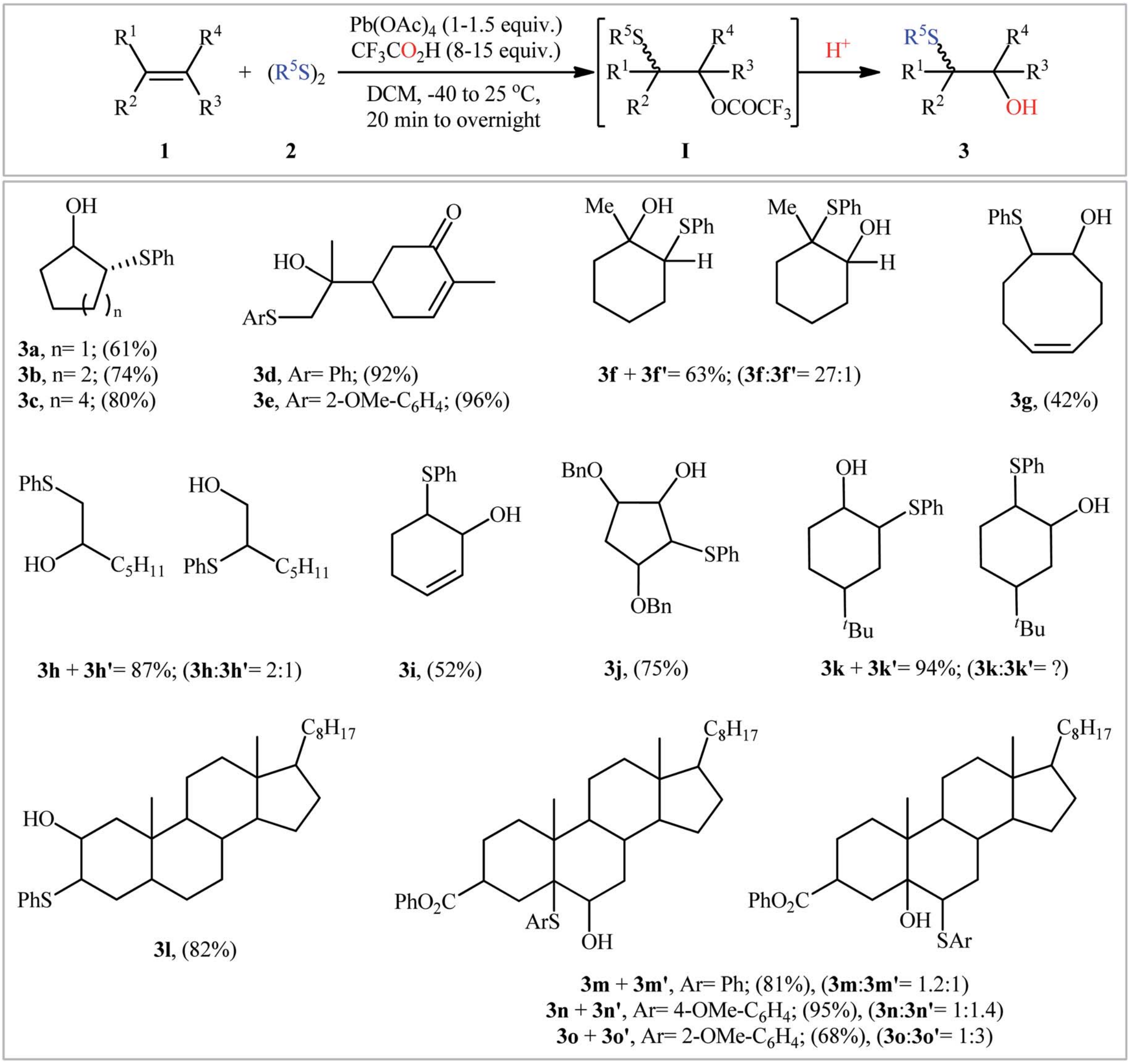
Fig. 1 Direct one-pot hydroxysulfenylation of alkenes.

(Scheme 3).[15] Here, both electron-donating and electron-withdrawing substituents on the styrenes and the disulfides were compatible with the reaction condition and afforded the target products in good yields with high regioselectivities. However, the procedure was unsuccessful for aliphatic alkenes. It should be mentioned that the presence of oxygen is crucial for the success of this reaction since in its absence, the addition of hydrogen and thiolate anion across the double bond ensues, yielding the undesired sulfides.

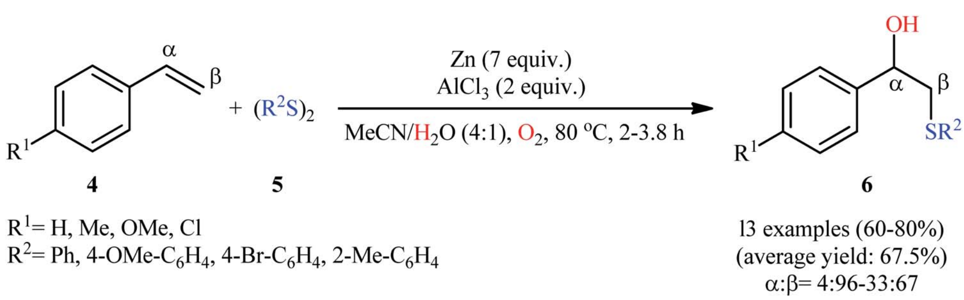
Following these works, Li's research group presented an efficient Cu(II)-catalyzed hydroxysulfenylation of a wide range of alkenes **7** and aromatic thiols **8** into the corresponding β-hydroxy sulfides **9**.[16] The reaction proceeded under an oxygen atmosphere using 5 mol% of $Cu(OAc)_2$ as catalyst and 2 equiv. of $PhCO_2H$ as additive in DCE at 50 °C, tolerated a variety of common functional groups (*e.g.*, fluoro, bromo, nitro, hydroxyl, methoxy, ketone, ester, and amine functionalities) and provided the expected products in moderate to excellent yields and outstanding regioselectivities, in which SR group predominantly added to the less hindered carbon atom of the C=C bond (Scheme 4). Noteworthy, this synthetic procedure was also successfully applied in the high yielding preparation of bicalutamide, an anticancer drug. It is worthwhile to note that other metal catalysts, such as $FeCl_2$, $FeCl_3$, $Fe(OAc)_2$, $Mn(OAc)_2$, $CoCl_2$, CuCl, $CuCl_2$, and CuBr were also found to promote this difunctionalization reaction; albeit at lower efficiencies. Based on a series of control experiments, the authors suggested that the reaction starts with the formation of thiyl radical **II** *via* the oxidation of thiol **8** with O_2, which after addition to alkene **7** leads to the formation of carbon-centered radical **III**. Next, this intermediate undergoes reaction with the *in situ* generated peroxy-copper species **IV** to afford the $Cu^{II/III}OOR'$ species **V** that, after protodemetalation under acidic conditions forms hydroperoxide intermediate **VI**. Finally, reduction of **VI** by the copper catalyst leads to the final product **9** (Scheme 5).

3. Halogen-catalyzed/mediated reactions

In 2017, Peddinti's research team described an interesting metal-free molecular iodine-catalyzed direct

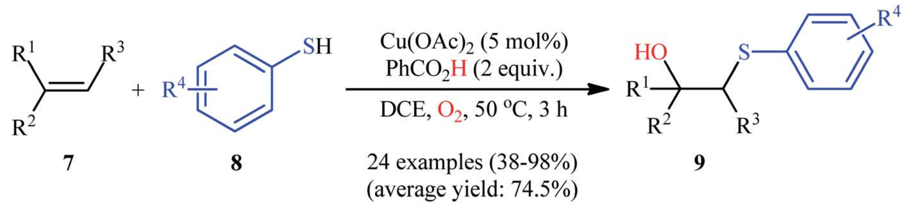


Scheme 2 Pb-catalyzed three component reaction between alkenes **1**, disulfides **2**, and CF_3CO_2H.



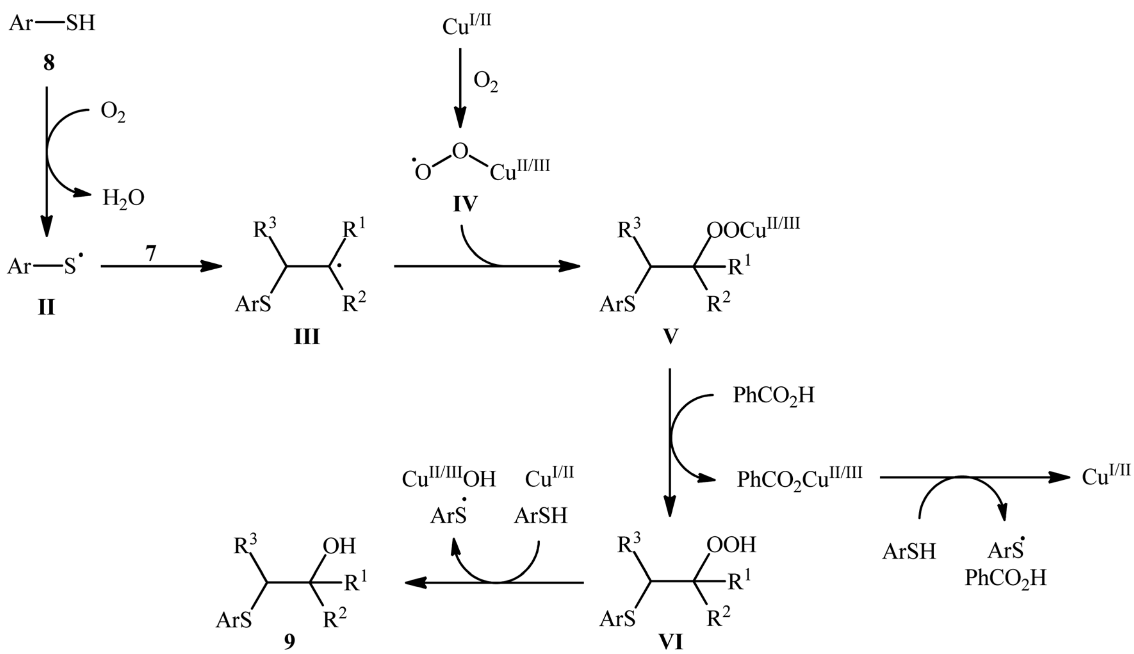
Scheme 3 Movassagh's synthesis of β-hydroxy sulfides **6**.

hydroxysulfenylation of styrene derivatives **10** with thiophenols **11** using DMSO as the oxygen source as well as the solvent.[17] The reaction proceeded slowly at 60 °C under additive-free conditions, tolerated both electron-rich and electron-poor substrates, and provided the desired β-hydroxy sulfides **12** in moderate to excellent yields (Scheme 6a). Importantly, the reaction showed outstanding regioselectivity, in which SAr group predominantly added to the terminal carbon atom of the double bond. The radical trapping experiments with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) pointed toward the radical pathway of the reaction. The plausible mechanistic cycle proposed by the authors for this difunctionalization reaction is illustrated in



R^1 = H, Me, Ph
R^2 = Ph, -CH=CH$_2$, COPh, CO_2Me, CO_2Et, CO_2Ph, $CO_2CH_2CH_2OH$, $CO_2CH_2CH{=}CH_2$, $CONH_2$, CONHPh, CONH-(1-naphthyl), CONH-(4-Me-C_6H_4), CONH-(4-Br-C_6H_4), CONH-(4-NO_2-C_6H_4)
R^3 = H, Me
R^4 = H, 4-OMe, 4-F, 2,4-Me_2, 2,6-Me_2, 3,4-$(CH{=}CH)_2$

Scheme 4 Cu-catalyzed hydroxysulfenylation of alkenes **7** with aromatic thiols **8** in the presence of $PhCO_2H$.

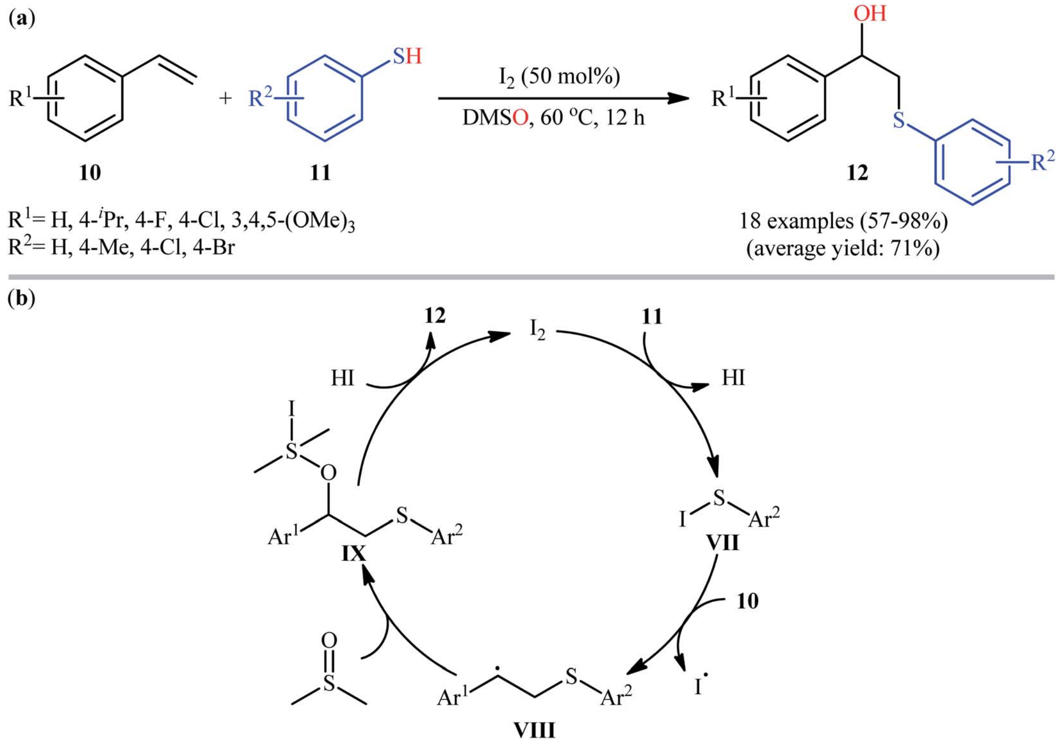


Scheme 5 Plausible reaction mechanism for the formation of β-hydroxy sulfides **9**.

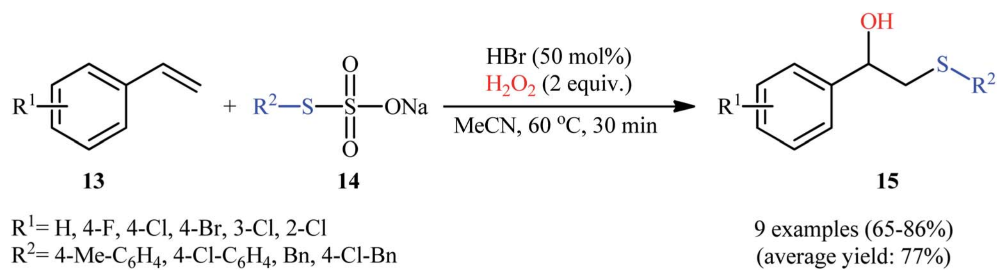
Scheme 6b. Initially, the nucleophilic thiophenol **11** attacks the electrophilic iodine centre leading to the generation of hypoiodothioite intermediate **VII**. Next, this intermediate liberates thiyl radical (ArS$^\bullet$); which reacts with electron-rich styrene **10** to deliver carbon-centered radical **VIII** and iodine free radical (I$^\bullet$). Subsequently, with the aim of iodine free radical, DMSO attacks at benzylic position of intermediate **VIII** to yield intermediate **IX**. Finally, the attack of *in situ* generated HI on **IX** affords the expected β-hydroxy sulfides **12** and regenerates molecular iodine.

In this context, Lin and Yan along with their co-workers developed an interesting HBr-catalyzed regioselective hydroxysulfenylation of styrenes **13** employing thiosulfates **14** as thiol sources.[18] Using 50 mol% of HBr as catalyst and 2 equiv. of H_2O_2 as oxidant, a library of terminal styrenes **13** underwent regioselective hydroxysulfenylation with *S*-aryl thiosulfates **14** to afford the corresponding β-hydroxy sulfides **15** in good to high yields within 30 min (Scheme 7). However, when aliphatic alkenes and *S*-alkyl thiosulfates were employed under the identical conditions, only trace amounts of target products were obtained. Noteworthy, the optimized condition was also effective for the site-selective sulfenylation of 4-hydroxycoumarins at the C3-position.

Recently, Li and Chen described a unique NH_4I-promoted hydroxymethylthiolation of various terminal alkenes **16** using DMSO as an easy-handling methanesulfenyl source and water as an oxygen source.[19] The reaction was carried out in a 1 : 1 mixture of DMSO and H_2O under additive-free conditions and afforded the desired hydroxysulfenylation products **17** in moderate to high yields and outstanding regioselectivities (Scheme 8a). Although the reaction tolerated various functional groups, the need for elevated temperature (130 °C) may limit its range of application. It is worthwhile to note that when the reaction was carried out in dry DMSO, bis-methylsulfanes were



Scheme 6 (a) Three component reaction between styrenes **10**, thiophenols **11** and DMSO using I_2 as the catalyst; (b) mechanistic insights on I_2-catalyzed hydroxysulfenylation of styrenes **10** with thiophenols **11** and DMSO.



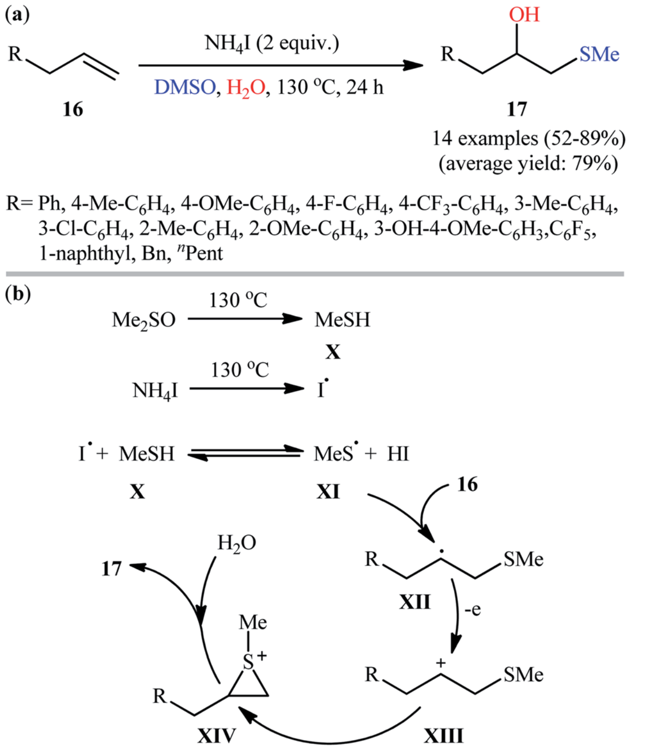
Scheme 7 HBr-catalyzed hydroxysulfenylation of styrenes **13** employing thiosulfates **14** as thiol sources.

obtained as the sole products. The mechanism of this reaction probably involves the initial formation of the iodine radical ($I^•$) and methanthiol **X** through a series of transformations with NH_4I and DMSO at high temperature, which after reaction with each other leads to the radical **XI** and HI. Subsequently, regioselective addition of this intermediate to the terminal C=C double bond of alkene **16** gives carbon-centered radical **XII** which undergoes further single-electron oxidation to form a β-MeS-substituted carbocation **XIII**. Next, intramolecular cyclization of carbocation intermediate **XIII** furnishes thiiranium ion **XVI**. Finally, the nucleophilic attack of H_2O on the thiiranium ion **XVI** produces the observed hydroxysulfenylation product **17** (Scheme 8b).

Very recently, Ni and Niu along with their colleagues extended the substrate scope of this chemistry to disulfides.[20] Thus, a large number of β-hydroxy sulfides **20** were selectively synthesized in moderate to high yields *via* hydroxysulfenylation of the corresponding alkenes **18** with symmetrical aromatic disulfides **19** employing molecular iodine as the catalyst and air as the oxidant (Scheme 9). Although various terminal and internal aromatic and aliphatic alkenes bearing both electron-donating and electron-withdrawing groups were well tolerated under the reaction conditions, the scope of disulfides was limited to the electron-rich and slightly electron-poor aromatic disulfides.

4. Acid-mediated reactions

In 2008, Naito and colleagues demonstrated the usefulness of triethylborane (Et_3B) as a Lewis acid promoter for the direct hydroxysulfenylation of olefinic double bond.[21] They showed that the three-component reaction between α,β-unsaturated imines **21**, thiols **22**, and oxygen in the presence of a catalytic amount of Et_3B in DCM at room temperature afforded the corresponding β-hydroxy sulfides **23** in relatively poor to good yields and excellent regioselectivities (Scheme 10). The relative

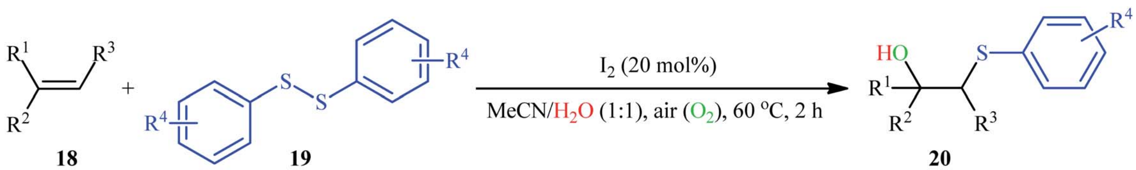


Scheme 8 (a) NH_4I-promoted hydroxymethylthiolation of terminal alkenes **16** with DMSO and water; (b) proposed mechanism for the formation of β-hydroxy sulfides **17**.

anti- and *syn*-geometric configurations of products were determined from NOESY experiments. The results indicated the preferential formation of the *anti*-isomers. The authors explained the observed *anti*/*syn* selectivity by invoking conformer **XX**, in which the C–S bond is eclipsed by the p orbital of the radical center, because electronic and steric effects (Scheme 11).

Eight years later, Shi's research team described an interesting Brønsted acid-promoted regioselective hydroxysulfenylation of alkenes with aromatic thiols employing air as oxygen source.[22] Using a stoichiometric amount of racemic phosphoric acid **24** as the mediator, a number of styrene derivatives **25** underwent hydroxysulfenylation with *ortho*-mercaptobenzyl alcohols **26** to afford the corresponding β-hydroxy sulfides **27** in moderate to high yields within 12 h (Scheme 12). In addition, 1*H*-indene as a cyclic styrene analogue was also successfully employed under the optimized conditions in the reaction with 2-(2-mercaptophenyl)propan-2-ol, offering the desired β-hydroxy sulfide product in a considerable yield of 63%. Interestingly, when thiophenols were subjected to the reactions with styrene under the identical conditions, instead of the expected β-hydroxy sulfide products, the β-hydroxy sulfoxides were obtained as the sole products.

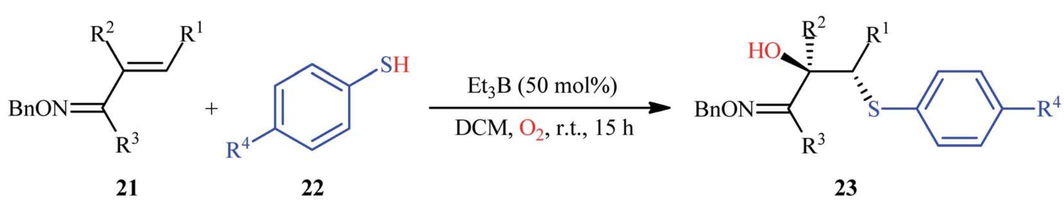
Very recently, Duan and Li along with their co-workers studied the metal-catalyzed hydroxysulfenylation of unactivated C=C double bonds with sulfonyl hydrazides as the sulfenyl sources and water as the oxygen source.[23] Thus, in the



R^1= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 4-CO_2Me-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4, 2-naphthyl, ^{i}Bu, CH_2CH_2Br
R^2= H, Me, Ph
R^3= H, Me
$R^1 + R^3$= -$(CH_2)_4$-
R^4= H, 4-Me, 4-F, 4-Cl, 4-Br, 3,5-Me_2

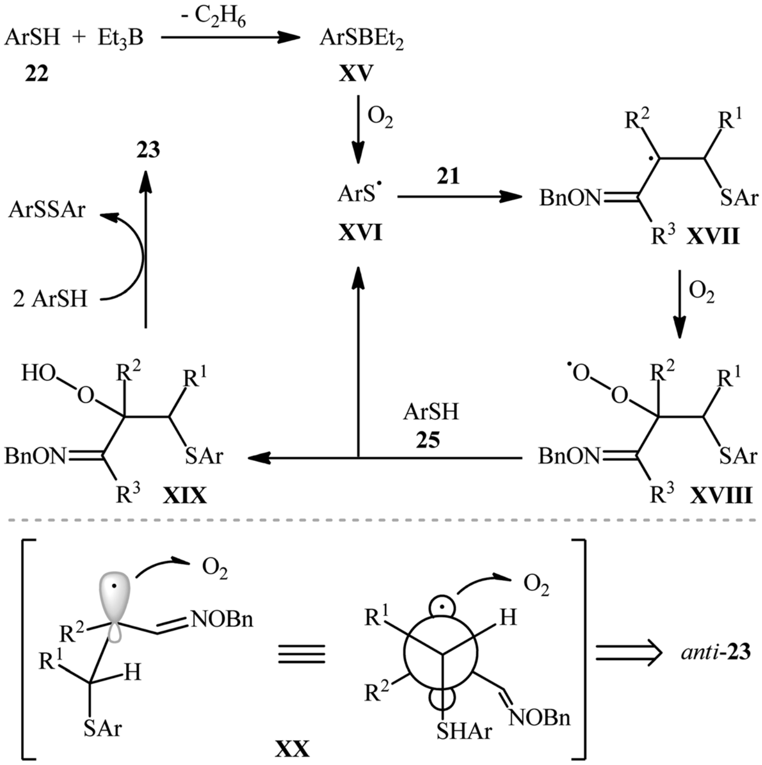
24 examples (51-86%)
(average yield: 70.5%)

Scheme 9 I_2-catalyzed aerobic hydroxysulfenylation of alkenes **18** with disulfides **19** developed by Ni and Niu.

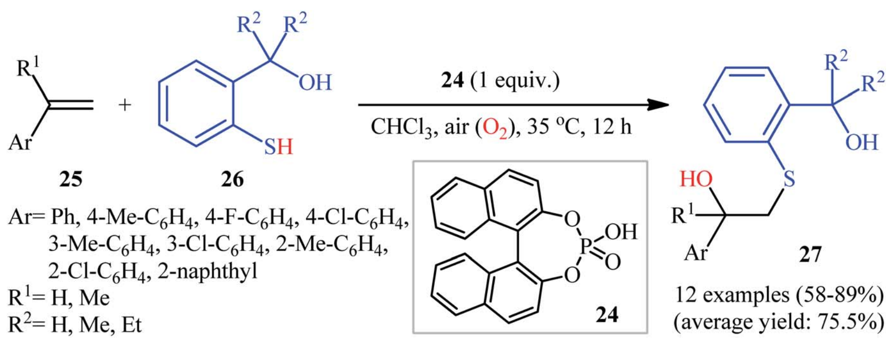


23a, R^1= Me, R^2= R^3= R^4= H; (84%; *anti*/*syn*= 5:6)
23b, R^1= Ph, R^2= R^3= R^4= H; (69%; *anti*/*syn*= 3:1)
23c, R^1= $CO_2{}^tBu$, R^2= R^3= R^4= H; (70%; *anti*/*syn*= 10:1)
23d, R^1= CO_2Et, R^2= Me, R^3= R^4= H; (72%; *anti*/*syn*= 3:2)
23e, R^1= R^3= Me, R^2= R^4= H; (63%; *anti*/*syn*= 20:1)
23f, R^1= SPh, R^2= R^3= R^4= H; (72%)
23g, R^1= CO_2Et, R^2= R^3= R^4= H; (84%)
23h, R^1= CO_2Et, R^2= R^3= H, R^4= 4-Cl; (78%)
23i, R^1= CO_2Et, R^2= R^3= H, R^4= 4-OH; (64%)

Scheme 10 Selected examples of Et_3B-catalyzed hydroxysulfenylation of α,β-unsaturated imines **21**, thiols **22**, and O_2.



Scheme 11 Proposed mechanism for the reaction in Scheme 10.

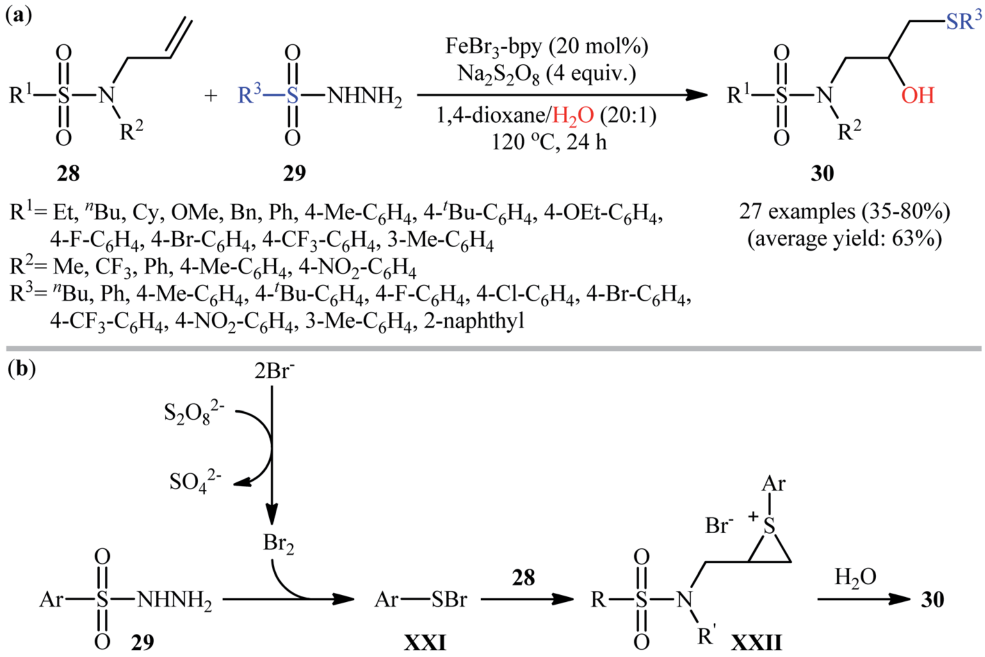


Scheme 12 Brønsted acid-catalyzed aerobic hydroxysulfenylation of styrenes **25** with mercaptobenzyl alcohols **26**.

presence of $FeBr_3$/bpy/$Na_2S_2O_8$ combination as a catalytic system in 1,4-dioxane/H_2O (20 : 1) under air atmosphere, hydroxysulfenylation of *N*-allyl-*N*-sulfonamides **28** with various aromatic sulfonyl hydrazides **29** furnished the corresponding β-hydroxy sulfides **30** in modestly to high yields, ranging from 35% to 80% (Scheme 13a). In this investigation the authors found some limitations in their methodology when they attempted to use sterically hindered *N*-allyl-*N*-sulfonamides and secondary *N*-allyl-*N*-sulfonamides as the substrates. Unfortunately, in these cases, no desired products were observed. The results also revealed that the hydroxysulfenylation reaction could not proceed without sulfonyl groups in the substrates. Butane-1-sulfonohydrazide did not work well in the reaction and therefore no other aliphatic sulfonyl hydrazides were examined in the protocol. The authors proposed mechanistic pathway for this difunctionalization reaction is illustrated in Scheme 13b. It consists of the following key steps: (i) reaction of sulfonyl hydrazide **29** with bromine source in the presence of $Na_2S_2O_8$ to form the sulfenyl bromide intermediate **XXI**; (ii) electrophilic addition of sulfenyl bromide **XXI** to alkene **28** to produce thiiranium ion intermediate **XXII**; and (iii) ring-opening of thiiranium ion **XXII** with H_2O under acidic conditions to produce the desired β-hydroxy sulfides **30**.

5. Catalyst-free reactions

After pioneering works by the groups of Kharasch[24] and Beckwith[25] on catalyst-free intermolecular hydroxysulfenylation of a small library of alkenes with thiols and dioxygen, the first general report of the direct synthesis of β-hydroxylated sulfides



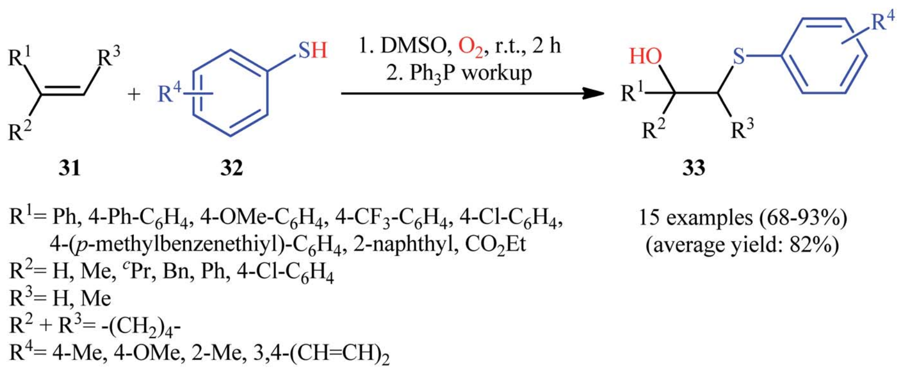
Scheme 13 (a) Fe-catalyzed hydroxysulfenylation of *N*-allylsulfonamides **28** with sulfonyl hydrazides **29** developed by Duan and Li; (b) mechanistic proposal for the formation of β-hydroxy sulfides **30**.

via concomitant introduction of sulfenyl and hydroxyl moieties to the respective alkenes under catalyst- and additive-free conditions was published in 2015 by Lei *et al.*[26] In this investigation, fifteen β-hydroxy sulfides **33** were efficiently prepared through the treatment of corresponding alkenes **31** with electron-rich aromatic thiols **32** under an atmosphere of molecular oxygen as the sole oxidant in DMSO followed by Ph_3P workup (Scheme 14). Although the yields and regioselectivities for this synthetic strategy were good, the diastereoselectivities were modest at the best and a mixture of isomers was usually obtained. Of note, the reaction can be enlarged to gram scale with negligible decrease in yield. Interestingly, when the solvent was changed to DCM and the workup step was ignored, β-hydroxy sulfoxides were exclusively obtained instead of β-hydroxy sulfide products.

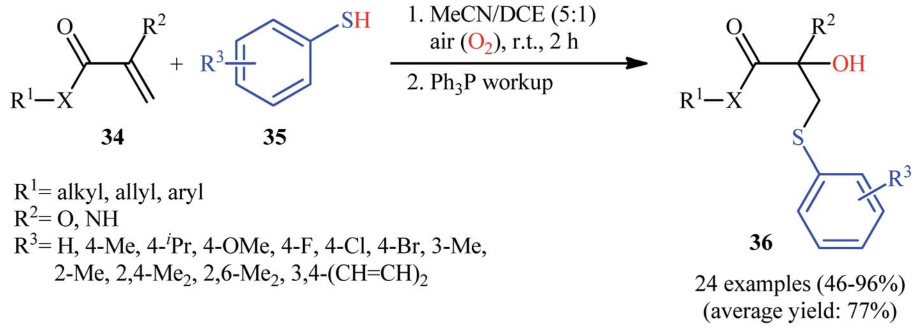
In a related study, Huo and colleagues synthesized a library of β-hydroxy sulfide derivatives **36** in moderate to excellent yields, ranging from 46% to 96%, *via* the reaction of electron-deficient alkenes **34** with various thiophenoles **35** in a binary solvent MeCN/DCE with ratio 5 : 1 under the open air and catalyst-free conditions (Scheme 15).[27] Notably, that the identical condition was also successfully used for hydroxysulfenylation of a series of electron-rich alkenes such as styrenes and 1,3-butadienes. The authors also nicely applied their methodology in the gram scale synthesis of bicalutamide.

6. Miscellaneous reactions

In 2006, the group of Rao disclosed that the treatment of terminal alkenes **37** with aromatic thiols **38** in the presence of 1 equiv. of non-toxic β-cyclodextrin (β-CD) in neat water under oxygen atmosphere afforded the corresponding β-hydroxy sulfide derivatives **39** through an anti-Markovnikov addition procedure (Scheme 16a).[28] The reaction conditions allowed the use of substrates bearing a series of important functional groups including Cl, Br, OMe, and CO_2Me groups. This made



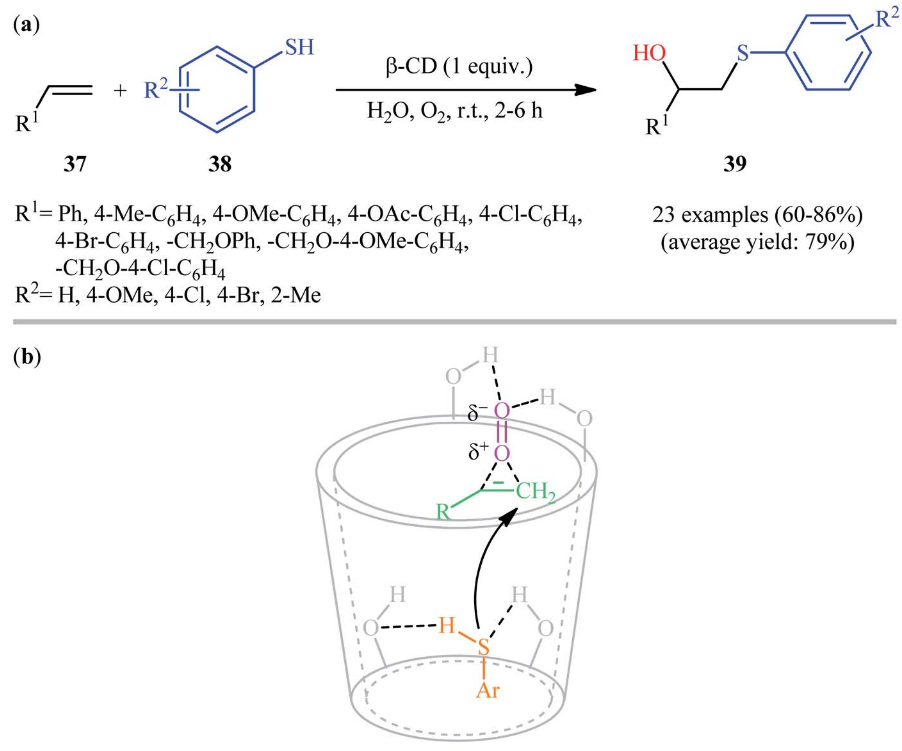
Scheme 14 Catalyst-free intermolecular hydroxysulfenylation of alkenes **31** with electron-rich aromatic thiols **32**.



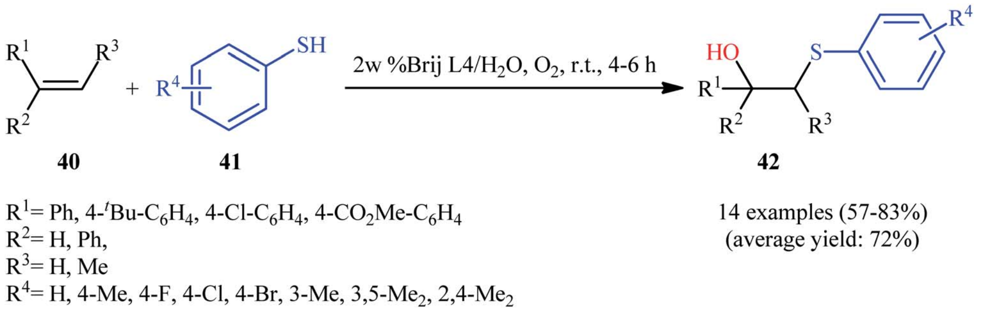
Scheme 15 Huo's synthesis of β-hydroxy sulfide derivatives **36**.

possible the further manipulation of the end products. This green protocol is also applicable for the hydroxysulfenylation of internal alkenes. It should be mentioned that β-cyclodextrin can be easily recovered from the reaction mixture and reused for the next reaction runs. As proposed by the authors, β-cyclodextrin catalyzes this hydroxysulfenylation reaction *via* reversible formation of host–guest complexes by non-covalent bonding as seen in Scheme 16b. Subsequently, Kamal and co-workers reported the synthesis of twenty β-hydroxy sulfides from various terminal and internal alkenes and aromatic thiols using a mixture of ionic liquid [bmim][BF_4] and water in the presence of aerial oxygen under neutral conditions.[29]

Inspired by these results, in 2017, Feng and co-workers investigated the possibility of synthesizing β-hydroxy sulfide through the auto-oxidative radical hydroxysulfenylation of the respective alkenes in surfactant/H_2O system.[30] To determine the optimum conditions, they carefully investigated the activities of different surfactant (*e.g.*, SDS, tergitol, brij L4, brij L23, brij O20, brij C20, TPGS-750-M) in the hydroxysulfenylation of 1,1-diphenylethylene with 4-chlorobenzenethiol under oxygen atmosphere, as a model reaction. The optimal system was recognized using 2 wt% brij L4 at room temperature. A variety of terminal styrenes, as well as α-substituted and β-substituted styrenes **40** were reacted well with functionalized aromatic thiols **41** under the standard reaction conditions to provide the expected hydroxysulfenylated products **42** in fair to high yields (Scheme 17). 1,2-Diphenylethene was also tested and gave product but in rather poor yield. However, neither aliphatic alkenes nor aliphatic thiols were examined in this synthetic strategy. It is important to mentioned that the reaction could be



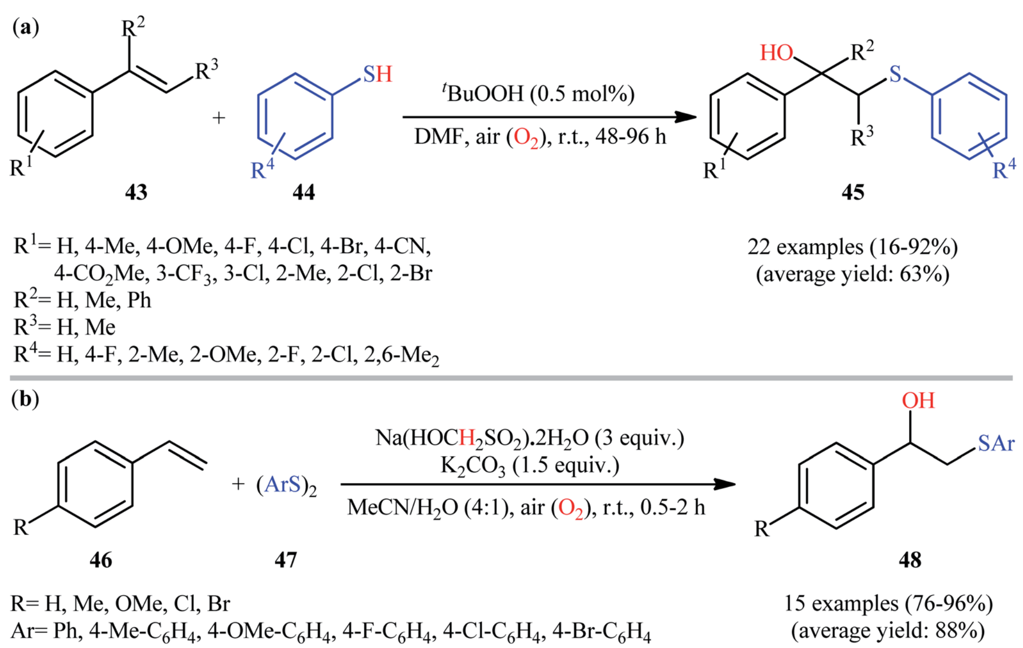
Scheme 16 (a) Synthesis of β-hydroxy sulfides **39** from terminal alkenes **37** and aromatic thiols **38** in the presence of β-CD in neat water; (b) schematic illustration of reaction mechanism for hydroxysulfenylation reactions using β-CD as a mediator.



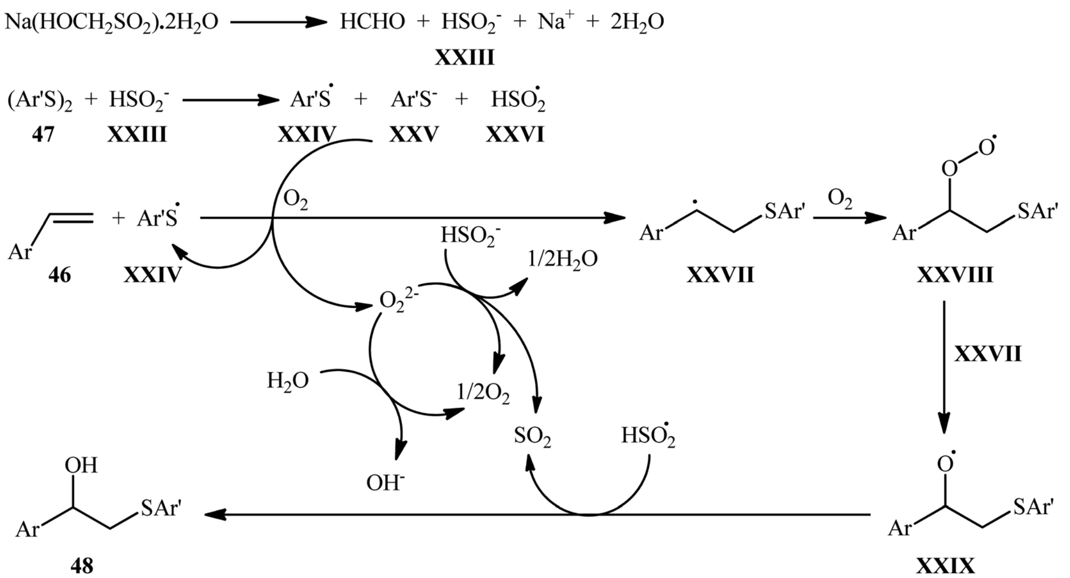
Scheme 17 Feng's synthesis of β-hydroxy sulfides **42**.

easily scaled up to the gram-scale as exemplified by the fubrication of 2-((3,5-dimethylphenyl)thio)-1,1-diphenylethanol on a 0.79 g scale (67%).

In 2015, Pan and Zou along with their colleagues developed a convenient and mild approach for regioselective synthesis of β-hydroxy sulfides **45** through the *tert*-butyl hydroperoxide (^{t}BuOOH)-initiated air oxidative radical hydroxysulfenylation of styrenes **43** with arylthiols **44**.[31] This radical difunctionalization reaction was run in DMF at room temperature under ambient air and provided substituted β-hydroxy sulfides **45** in poor to excellent yields (Scheme 18a); nonetheless the reaction failed completely for heteroaryl thiols, nitro and amino-substituted aryl arylthiols, aliphatic alkenes, and nitro-substituted styrenes. Interestingly, when styrenes bearing an easily removable leaving group at the α-position were used as substrates, β-oxosulfides were obtained as the sole products. In a similar manner, the reaction of styrenes bearing a leaving group at the β-position with arylthiols gave the corresponding β-oxythioacetals. At the same year, Yadav's research team presented the high yielding synthesis of a library of β-hydroxy sulfides **48** *via* rongalite-mediated hydroxysulfenylation of styrenes **46** with aromatic disulfides **47** employing 1.5 equiv. of K_2CO_3 as the base in a 4 : 1 mixture of MeCN and H_2O at room temperature (Scheme 18b).[32] According to the authors proposed mechanism, this conversion is likely to follow the pathway illustrated in Scheme 19. Initially, thermal decomposition of rongalite generates formaldehyde and HSO_2^- anion **XXIII**, which reacts with the disulfide **47** to give radicals **XXIV** and **XXVI** along with the thiolate anion **XXV**. Subsequently, the thiolate anion **XXV** reacts with oxygen to form a thiyl radical **XXIV** and peroxide anion. Next, this radical regioselectively adds to the terminal C–C double bond of styrene **46** to produce benzylic radical **XXVII** that after reaction with O_2 provides a peroxy radical **XXVIII**. The newly formed reacts with **XXVII** to form radical **XXIX.** Finally, the alkoxy radical **XXIX** abstracts a hydrogen atom from **XXVI** to afford hydroxysulfenylated product **48.** It should be mentioned that aliphatic alkenes and dialkyl disulfides were completely inert in the present protocol. The authors speculated that the unreactivity of aliphatic alkenes in this strategy is related to the far less stability of the alkyl free radicals formed



Scheme 18 (a) TBHP-initiated air oxidative radical hydroxysulfenylation of styrenes **43** with arylthiols **44**; (b) rongalite-mediated hydroxysulfenylation of styrenes **46** with aromatic disulfides **47** under ambient air.



Scheme 19 Proposed mechanism for the generation of β-hydroxy sulfides **48**.

after the attack of the thiyl radical on the aliphatic alkenes. They also explained the reason of unreactivity of dialkyl disulfides to their strong S–S bond.

Finally, it should be noted that transition metal complexes play important role in synthesis of β-hydroxy sulfides and other compounds.[33–54]

7. Conclusion

1,2-Difunctionalization of alkenes has received continuous interests as it provides a valuable and versatile synthetic route to introduce two functional groups at the C═C bonds in a single click. Among them, intermolecular hydroxysulfenylation of alkenes is one of the most efficient and convenient pathways to the construction of biologically and synthetically important β-hydroxysulfides through the simultaneous C–O and C–S bond formation. As illustrated, various thiols, disulfides, sulfonyl hydrazides, and thiosulfates were successfully employed as the sulfenyl sources in this chemistry. Moreover, most of the developed systems were compatible with both terminal and internal alkenes. Despite the remarkable accomplishments during the past few years on this interesting page of β-hydroxysulfides synthesis, the construction of chiral β-hydroxysulfides through this chemistry, has, to date, been rarely described. Therefore, the development of chiral catalysts and ligands that allow asymmetric synthesis of titled compounds would be highly desirable. It is our hope that this Mini-Review will stimulate continued interest in the fabrication of β-hydroxysulfide derivatives directly from alkenes and make it a prolonged and prominent research arena for developing straightforward and extremely effective methodology used for pharmaceutical products syntheses.

Conflicts of interest

There are no conflicts to declare.

References

1 (*a*) C. Christophersen and U. Anthoni, *Sulfur Rep.*, 1986, **4**, 365–442; (*b*) S. Shafiei and S. Davaran, *Chem. Rev. Lett.*, 2020, **3**, 19–22; (*c*) S. Majedi and S. Majedi, *J. Chem. Lett.*, 2020, **1**, 2–8; (*d*) F. Nareetsile, J. T. P. Matshwele, S. Ndlovu and M. Ngaski, *Chem. Rev. Lett.*, 2020, **3**, 140–160; (*e*) F. Behmagham, Z. Asadi and Y. J. Sadeghi, *Chem. Rev. Lett.*, 2018, **1**, 68–76.
2 M. Feng, B. Tang, S. H Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200–1216.
3 P. Devendar and G.-F. Yang, *Top. Curr. Chem.*, 2019, **375**, 82.
4 K. A. Scott and J. T. Njardarson, *Top. Curr. Chem.*, 2018, **376**, 5.
5 (*a*) S. S. Cho, L. N. Jungheim and A. J. Baxter, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 715–720; (*b*) G. Valoti, M. I. Nicoletti, A. Pellegrino, J. Jimeno, H. Hendriks, M. D'Incalci, G. Faircloth and R. Giavazzi, *Clin. Cancer Res.*, 1998, **4**, 1977–1983; (*c*) F. Viola, G. Balliano, P. Milla, L. Cattel, F. Rocco and M. Ceruti, *Bioorg. Med. Chem.*, 2000, **8**, 223–232; (*d*) R. S. Pavelyev, S. G. Gnevashev, R. M. Vafina, O. I. Gnezdilov, A. B. Dobrynin, S. A. Lisovskaya, L. E. Nikitina and E. N. Klimovitskii, *Mendeleev Commun.*, 2012, **22**, 127–128; (*e*) B. Guruswamy and R. Arul, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2013, **188**, 1205–1213; (*f*) R. S. Pavelyev, R. M. Vafina, K. V. Balakin, O. I. Gnezdilov, A. B. Dobrynin, O. A. Lodochnikova, R. Z. Musin, G. A. Chmutova, S. A. Lisovskaya and L. E. Nikitina, *J. Chem.*, 2018, 3589342.
6 (*a*) F. Fringuelli, F. Pizzo, S. Tortoioli and L. Vaccaro, *J. Org. Chem.*, 2003, **68**, 8248–8251; (*b*) F. Fringuelli, F. Pizzo and L. Vaccaro, *J. Org. Chem.*, 2004, **69**, 2315–2321; (*c*) M. M. Mojtahedi, M. S. Abaee, A. Rajabi, P. Mahmoodi and S. Bagherpoor, *J. Mol. Catal. A: Chem.*, 2012, **361**, 68–71; (*d*) N. Azizi and M. Edrisi, *Tetrahedron Lett.*, 2016, **57**, 525–528.

7 (*a*) M. M. Khodaei, A. R. Khosropour and K. Ghozati, *J. Braz. Chem. Soc.*, 2005, **16**, 673–676; (*b*) B. C. Ranu and T. Mandal, *Can. J. Chem.*, 2006, **84**, 762–770; (*c*) V. Ganesh and S. Chandrasekaran, *Synthesis*, 2009, 3267–3278; (*d*) M. Soleiman-Beigi and H. Kohzadi, *Arabian J. Chem.*, 2019, **12**, 1532–1536.

8 (*a*) E. M. Beccalli, G. Broggini, S. Gazzola and A. Mazza, *Org. Biomol. Chem.*, 2014, **12**, 6767–6789; (*b*) J. B. Peng, *Adv. Synth. Catal.*, 2020, **362**, 3059–3080; (*c*) J. Lin, R. J. Song, M. Hu and J. H. Li, *Chem. Rec.*, 2019, **19**, 440–451; (*d*) N. Yue and F. R. Sheykhahmad, *J. Fluorine Chem.*, 2020, 109629; (*e*) L. Feng, X. Li, B. Liu and E. Vessally, *J. CO_2 Util.*, 2020, **40**, 101220.

9 M. B. Marakalala, E. M. Mmutlane and H. H. Kinfe, *Beilstein J. Org. Chem.*, 2018, **14**, 1668–1692.

10 (*a*) S. Arshadi, E. Vessally, L. Edjlali, R. Hosseinzadeh-Khanmiri and E. Ghorbani-Kalhor, *Beilstein J. Org. Chem.*, 2017, **13**, 625–638; (*b*) E. Vessally, K. Didehban, M. Babazadeh, A. Hosseinian and L. Edjlali, *J. CO_2 Util.*, 2017, **21**, 480–490; (*c*) E. Vessally, K. Didehban, R. Mohammadi, A. Hosseinian and M. Babazadeh, *J. Sulfur Chem.*, 2018, **39**, 332–349; (*d*) E. Vessally, R. Mohammadi, A. Hosseinian, K. Didehban and L. Edjlali, *J. Sulfur Chem.*, 2018, **39**, 443–463; (*e*) A. Hosseinian, L. Zare Fekri, A. Monfared, E. Vessally and M. Nikpassand, *J. Sulfur Chem.*, 2018, **39**, 674–698; (*f*) A. Hosseinian, P. D. K. Nezhad, S. Ahmadi, Z. Rahmani and A. Monfared, *J. Sulfur Chem.*, 2019, **40**, 88–112; (*g*) A. Monfared, S. Ahmadi, Z. Rahmani, P. D. K. Nezhad and A. Hosseinian, *J. Sulfur Chem.*, 2019, **40**, 209–231; (*h*) A. Hosseinian, S. Arshadi, S. Sarhandi, A. Monfared and E. Vessally, *J. Sulfur Chem.*, 2019, **40**, 289–311; (*i*) F. A. H. Nasab, L. Z. Fekri, A. Monfared, A. Hosseinian and E. Vessally, *RSC Adv.*, 2018, **8**, 18456–18469; (*j*) A. Hosseinian, S. Ahmadi, F. A. H. Nasab, R. Mohammadi and E. Vessally, *Top. Curr. Chem.*, 2018, **376**, 39; (*k*) E. Vessally, A. Monfared, Z. Eskandari, M. Abdoli and A. Hosseinian, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2020, **196**, 1–5.

11 (*a*) S. Arshadi, E. Vessally, L. Edjlali, E. Ghorbani-Kalhor and R. Hosseinzadeh-Khanmiri, *RSC Adv.*, 2017, **7**, 13198–13211; (*b*) K. Nejati, S. Ahmadi, M. Nikpassand, P. D. K. Nezhad and E. Vessally, *RSC Adv.*, 2018, **8**, 19125–19143; (*c*) A. Monfared, R. Mohammadi, S. Ahmadi, M. Nikpassand and A. Hosseinian, *RSC Adv.*, 2019, **9**, 3185–3202; (*d*) A. Hosseinian, R. Mohammadi, S. Ahmadi, A. Monfared and Z. Rahmani, *RSC Adv.*, 2018, **8**, 33828–33844; (*e*) A. Hosseinian, S. Ahmadi, R. Mohammadi, A. Monfared and Z. Rahmani, *J. CO_2 Util.*, 2018, **27**, 381–389; (*f*) A. Monfared, R. Mohammadi, A. Hosseinian, S. Sarhandi and P. D. Nezhad, *RSC Adv.*, 2019, **9**, 3884–3899; (*g*) S. Ebrahimiasl, F. Behmagham, S. Abdolmohammadi, R. Kojabad and E. Vessally, *Curr. Org. Chem.*, 2019, **23**, 2489–2503; (*h*) J. Wang, P. Sub, S. Abdolmohammadi and E. Vessally, *RSC Adv.*, 2019, **9**, 41684–41702; (*i*) Y. Yang, D. Zhang and E. Vessally, *Top. Curr. Chem.*, 2020, **378**, 37; (*j*) Z. He, D. Wu and E. Vessally, *Top. Curr. Chem.*, 2020, **378**, 46; (*k*) S. Sarhandi, M. Daghagheleh, M. Vali, R. Moghadami and E. Vessally, *Chem. Rev. Lett.*, 2018, **1**, 9–15; (*l*) L. Sreerama, E. Vessally and F. Behmagham, *J. Chem. Lett.*, 2020, **1**, 9–18; (*m*) S. Mohammadi, M. Musavi, F. Abdollahzadeh, S. Babadoust and A. Hosseinian, *Chem. Rev. Lett.*, 2018, **1**, 49–55; (*n*) M. Daghagheleh, M. Vali, Z. Rahmani, S. Sarhandi and E. Vessally, *Chem. Rev. Lett.*, 2018, **1**, 23–30; (*o*) S. Farshbaf, L. Sreerama, T. Khodayari and E. Vessally, *Chem. Rev. Lett.*, 2018, **1**, 56–67; (*p*) S. Majedi, L. Sreerama, E. Vessally and F. Behmagham, *J. Chem. Lett.*, 2020, **1**, 25–31; (*q*) S. Majedi, S. Majedi and F. Behmagham, *Chem. Rev. Lett.*, 2019, **2**, 187–192; (*r*) E. A. Mahmood, B. Azizi and S. Majedi, *Chem. Rev. Lett.*, 2020, **3**, 2–8; (*s*) S. Shahidi, P. Farajzadeh, P. Ojaghloo, A. Karbakhshzadeh and A. Hosseinian, *Chem. Rev. Lett.*, 2018, **1**, 37–44; (*t*) M. R. J. Sarvestani, N. Mert, P. Charehjou and E. Vessally, *J. Chem. Lett.*, 2020, **1**, 93–102.

12 B. M. Trost, M. Ochiai and P. G. McDougal, *J. Am. Chem. Soc.*, 1978, **100**, 7103–7106.

13 Z. K. Abd El Samii, M. I. Al Ashmawy and J. M. Mellor, *Tetrahedron Lett.*, 1986, **27**, 5289–5292.

14 Z. K. Abd El-Samii, *Arch. Pharm.*, 1991, **324**, 461–463.

15 B. Movassagh and M. Navidi, *Tetrahedron Lett.*, 2008, **49**, 6712–6714.

16 H. Xi, B. Deng, Z. Zong, S. Lu and Z. Li, *Org. Lett.*, 2015, **17**, 1180–1183.

17 P. Tehri, B. Aegurula and R. K. Peddinti, *Tetrahedron Lett.*, 2017, **58**, 2062–2065.

18 R. Zhang, S. Jin, Y. Wan, S. Lin and Z. Yan, *Tetrahedron Lett.*, 2018, **59**, 841–847.

19 R. He, X. Chen, Y. Li, Q. Liu, C. Liao, L. Chen and Y. Huang, *J. Org. Chem.*, 2019, **84**, 8750–8758.

20 B.-q. Ni, Y. He, X. Rong and T.-f. Niu, *Synlett*, 2019, **30**, 1830–1834.

21 M. Ueda, H. Miyabe, H. Shimizu, H. Sugino, O. Miyata and T. Naito, *Angew. Chem., Int. Ed.*, 2008, **120**, 5682–5686.

22 J.-J. Zhao, M. Tang, H.-H. Zhang, M.-M. Xu and F. Shi, *Chem. Commun.*, 2016, **52**, 5953–5956.

23 Z.-Q. Xu, L.-C. Zheng, L. Li, L. Duan and Y.-M. Li, *Tetrahedron*, 2019, **75**, 643–651.

24 M. Kharasch, W. Nudenberg and G. Mantell, *J. Org. Chem.*, 1951, **16**, 524–532.

25 A. L. Beckwith and R. D. Wagner, *J. Org. Chem.*, 1981, **46**, 3638–3645.

26 H. Wang, Q. Lu, C. Qian, C. Liu, W. Liu, K. Chen and A. Lei, *Angew. Chem., Int. Ed.*, 2016, **55**, 1094–1097.

27 C. Huo, Y. Wang, Y. Yuan, F. Chen and J. Tang, *Chem. Commun.*, 2016, **52**, 7233–7236.

28 K. Surendra, N. S. Krishnaveni, R. Sridhar and K. R. Rao, *J. Org. Chem.*, 2006, **71**, 5819–5821.

29 A. Kamal and D. R. Reddy, *J. Mol. Catal. A: Chem.*, 2007, **272**, 26–30.

30 B. Zhang, T. Liu, Y. Bian, T. Lu and J. Feng, *ACS Sustainable Chem. Eng.*, 2018, **6**, 2651–2655.

31 S.-F. Zhou, X. Pan, Z.-H. Zhou, A. Shoberu and J.-P. Zou, *J. Org. Chem.*, 2015, **80**, 3682–3687.

32 V. K. Yadav, V. P. Srivastava and L. D. S. Yadav, *Tetrahedron Lett.*, 2015, **56**, 2892–2895.
33 P. Xu, W. Lu, J. Zhang and L. Zhang, *ACS Sustainable Chem. Eng.*, 2020, **8**, 12366–12377.
34 P. Wang, T. Yao, Z. Li, W. Wei, Q. Xie, W. Duan and H. Han, *Compos. Sci. Technol.*, 2020, **198**, 108307.
35 R. Zhaoa, *et al.*, *Cem. Concr. Res.*, 2021, **144**, 106420.
36 J. Zhu, K. Yang, Y. Chen, G. Fan, L. Zhang, B. Guo and R. Zhao, *J. Hazard. Mater.*, 2021, **409**, 124504.
37 H. Zhang, W. Guan, L. Zhang, X. Guan and S. Wang, *ACS Omega*, 2020, **5**, 18007–18012.
38 H. Zhang, M. Sun, L. Song, J. Guo and L. Zhang, *Biochem. Eng. J.*, 2019, **147**, 146–152.
39 J. Zhu, Y. Chen, L. Zhang, B. Guo, G. Fan, X. Guan and R. Zhao, *J. Cleaner Prod.*, 2021, **295**, 126405.
40 Y. Liu, B. Hu, S. Wu, M. Wang, Z. Zhang, B. Cui and M. Du, *Appl. Catal., B*, 2019, **258**, 117970.
41 Y. Song, M. Xu, Z. Li, L. He, M. Hu, L. He and M. Du, *Sens. Actuators, B*, 2020, **321**, 128527.
42 M. Wang, M. Hu, Z. Li, L. He, Y. Song, Q. Jia and M. Du, *Biosens. Bioelectron.*, 2019, **142**, 111536.
43 M. Wang, L. Yang, B. Hu, J. Liu, L. He, Q. Jia and Z. Zhang, *Biosens. Bioelectron.*, 2018, **113**, 16.
44 Z. Lei, S. Hao, J. Yang, L. Zhang, B. Fang, K. Wei and C. Weif, *Chemosphere*, 2020, 128646.
45 Y. Wang, K. Huang, X. Lai, Z. Shi, J. Liu and G. Qiu, *Org. Biomol. Chem.*, 2021, 1940–1944.
46 Y. Qi, J. Wei, R. Qu, G. Al-Basher, X. Pan, A. A. Dar and Z. Wang, *Chem. Eng. J.*, 2021, **403**, 126396.
47 Y. Liu, T. Xu, Y. Liu, Y. Gao and C. Di, *J. Mater. Res. Technol.*, 2020, **9**, 8283–8288.
48 C. L. Shen, Q. Lou, J. H. Zang, K. K. Liu, S. N. Qu, L. Dong and C. X. Shan, *Adv. Sci.*, 2020, **7**, 1903525.
49 S. Ahmadi, A. Hosseinian, P. D. Kheirollahi Nezhad, A. Monfared and E. Vessally, *Iran. J. Chem. Chem. Eng.*, 2019, **38**, 1–19.
50 W. Xiang, J. Chang, R. Qu, G. Albasher, Z. Wang, D. Zhou and C. Sun, *Chemosphere*, 2021, **265**, 129112.
51 Y. Wang, K. Huang, X. Lai, Z. Shi, J. Liu and G. Qiu, *Org. Biomol. Chem.*, 2021, 1940–1944.
52 F. Gharibzadeh, E. Vessally, L. Edjlali, M. Es haghi and R. Mohammadi, *Iran. J. Chem. Chem. Eng.*, 2020, **39**, 51–62.
53 H. Zhang, W. Guan, L. Zhang, X. Guan and S. Wang, *ACS Omega*, 2020, **5**, 18007–18012.
54 E. Vessally, S. Mohammadi, M. Abdoli, A. Hosseinian and P. Ojaghloo, *Iran. J. Chem. Chem. Eng.*, 2020, **39**, 11–19.