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Review

Advance in the Synthesis of Sulfoxides and Sulfinamides from β-Sulfinyl Esters

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Abstract: Sulfoxides and sulfinamides play important roles in the pharmaceutical industry, organic synthesis and fine chemicals. This review will demonstrate that, under catalysis by transition metals, β-sulfinyl esters, as nucleophilic reagents, react with a variety of electrophilic reagents to produce sulfoxides and sulfinamides. The important prospect of the asymmetric catalytic synthesis of chiral sulfur-containing molecules in this field is described.

Keywords: β-sulfinyl esters; sulfenate anions; sulfoxides; sulfinamides; review

1. Introduction

Sulfoxides and sulfinamides have extensive applications in the pharmaceutical industry, organic synthesis, fine chemical industry and material production. They have shown a wide range of biological activities. More than 30% of chemicals contain sulfur components [1], such as the widely used proton pump inhibitors. The drugs in the proton pump inhibitor class contain a sulfoxide pharmacophore structure, among which Esomeprazole is a chiral sulfoxide molecule (Figure 1) [2]. The well-known drug Modafinil is also a type of sulfoxide (Figure 1) [3]. Both sulfoxides and sulfinamides are also key motifs in the chiral synthesis of chiral molecules, such as chiral auxiliaries, chiral ligands and organocatalysts [4]. For instance, our group has discovered two kinds of cyclic sulfinamide-olefin-type chiral ligands with novel skeletons, that is, chiral N-cinnamyl-2,3-dihydro-1,2-benzoisothiazole 1-oxide and chiral 1,4-di(1-oxo-2,3-dihydro-1,2-benzisothiazolyl)but-2-ene (shorted as DICSO) (Figure 1), which provide extremely high enantioselectivities in rhodium-catalyzed asymmetric addition reactions [5,6]. For example, for chiral sulfoxides, Liao and his co-workers reported that sulfoxide-phosphine ligands (SOP) proved to be excellent ligands in a few catalytically asymmetric reactions (Figure 1) [7]. Chiral *tert*-butanesulfinimide has been extensively adopted for the synthesis of chiral amino-containing drugs and their intermediates, natural products and so on (Figure 1) [4,8], and has become a tool to introduce a chiral amino group into a great number of organic compounds.

It is well known that sulfenate anions (RSO^-) [9] are the conjugate bases of sulfenic acids (RSOH) [10], and they demonstrate their peculiar S-nucleophilicity in various organic reactions. Sulfenate anions can be depicted by two limited valence bond structures, which can effectively elucidate the ambident nature of sulfenate anions, reacting as nucleophiles either at the sulfur atom or at the oxygen atom (Scheme 1).

Sulfenate anions are generally transient intermediates and must be generated in situ from a variety of sulfoxides (Scheme 2). One approach to obtaining sulfenate anions is via transition-metal-catalyzed transformations of benzyl (a) [11] and allyl (b) [12] and sulfoxides. However, it seems that transition-metal-free preparation methods are the better choice, for example, the pyrolyzation of *tert*-butyl aryl sulfoxides and then the base treatment of the resulting sulfenic acids (c) [13,14], the strong nucleophile-caused decomposition of 2-sulfinyl acrylates (d) [15], the fluoride-promoted desilylative fragmentation

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of 2-(trimethylsilyl)ethyl alkyl sulfoxides (e) [16] and the base-promoted retro-Michael reaction of β-sulfinyl esters (f) [17]. Among these generation methods, the preparation of sulfenate anions via the base-promoted retro-Michael reaction of β-sulfinyl esters (f) has developed most rapidly.

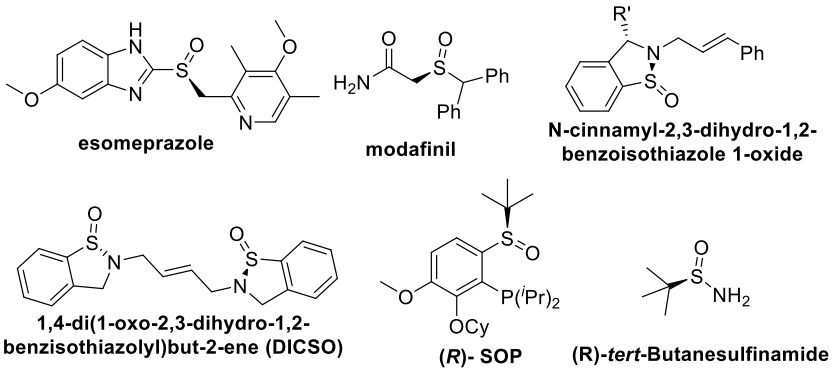
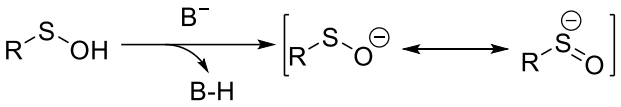
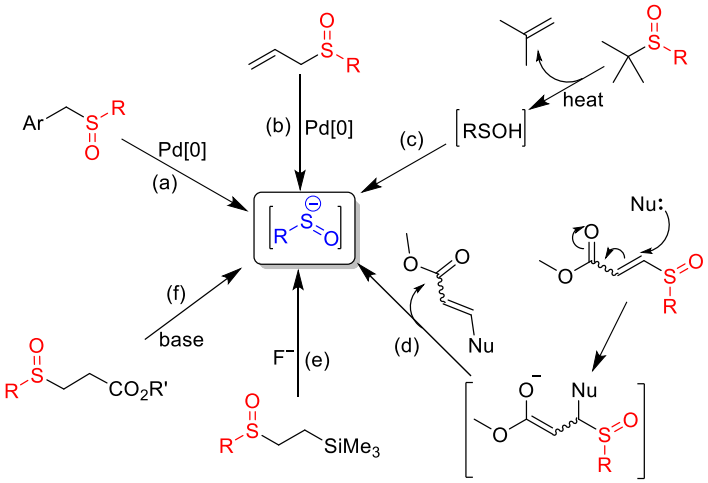


Figure 1. Some typical sulfoxides and sulfinamides.



Scheme 1. Generation of sulfenate anions and their tautomerism.



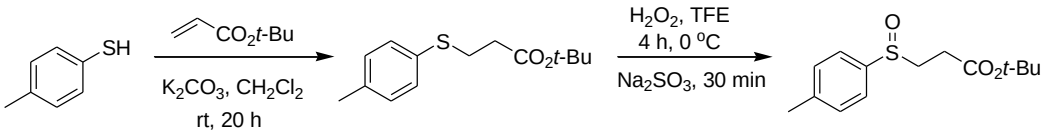
Scheme 2. Some preparation methods of sulfenate anions.

In recent years, chemists have discovered that β-sulfinyl esters can generate sulfenate anions in situ under the action of alkali, and the latter can act as a nucleophile to react with an electrophile to generate sulfoxides and sulfinamides and other sulfur-containing compounds. Moreover, chiral sulfoxides can be synthesized from sulfenate anions.

In view of the rapid development of research in this field and the wide potential application prospects, on the basis of our long-term research on organosulfur chemistry [18,19], here, we provide a brief review of the progress in the synthesis of sulfoxides and sulfinamides from β-sulfinyl esters.

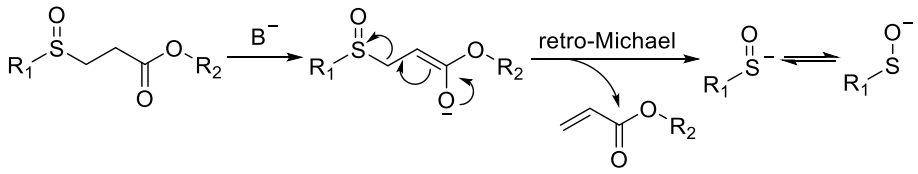
2. Synthesis of β-Sulfinyl Esters and In Situ Generation of Sulfenate Anions

β-Sulfinyl esters are generally obtained by the conjugated addition of thiophenols and acrylates to give thioether intermediates and then the further selective oxidation of the thioether intermediates. The general synthesis of β-sulfinyl esters is illustrated with 4-methylthiophenol as a specific starting reactant example (Scheme 3) [20].



Scheme 3. Typical synthetic method of β-sulfinyl esters.

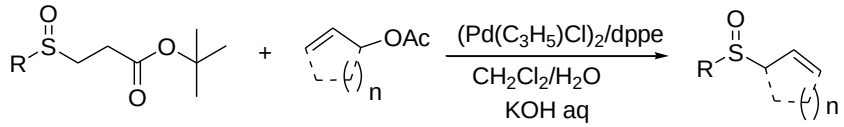
β-Sulfinyl esters are easily deprotonated by inorganic bases, followed by retro-Michael addition to generate sulfenate anions (RSO^-) in situ under mild conditions (Scheme 4) [17].



Scheme 4. Alkali-induced in situ generation of sulfenate anion by β-sulfinyl esters.

3. Synthesis of Sulfoxides from β-Sulfinyl Esters

In 2006, Maitro et al. reported a method using palladium as a catalyst to catalyze the reaction of sulfenate anions generated in situ from β-sulfinyl carboxylic acid esters as nucleophiles to synthesize allyl sulfoxides (Scheme 5) [21]. During the reaction process, the sulfenate anion interacts with the instantaneously generated η3-allylpalladium complex to generate allyl sulfoxides and regenerate the Pd(0) catalyst.

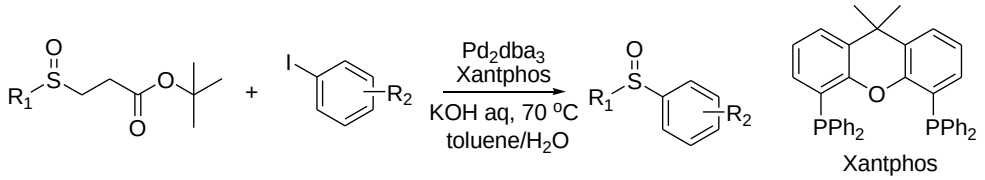


Scheme 5. Palladium-catalyzed synthesis of allyl sulfoxides.

When *tert*-butyl *p*-tolylsulfinylpropionate reacted with allyl acetate in the presence of the palladium complex, the corresponding allyl sulfoxide was obtained in an 82% yield. However, when *tert*-butyl *p*-tolylsulfinylpropionate reacted with cyclic allyl acetate, the yield of the product obtained was extremely low, possibly because steric hindrance had an impact on the reaction.

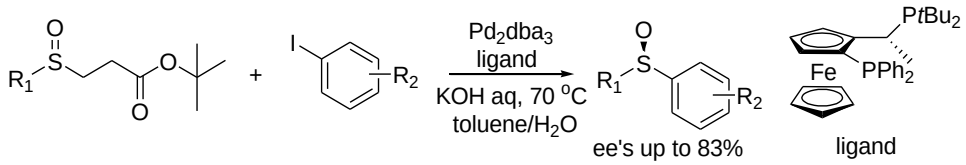
When *tert*-butyl 2-naphthylsulfinyl propionate was used as a raw material to react with allyl acetate compounds, only a 60% yield was obtained. Interestingly, cyclopent-2-enyl-acetate and cyclohex-2-enyl-acetate yielded 43% and 57% of the expected sulfoxides, respectively, when *tert*-butyl 3-isopropylsulfinylpropionate was adopted as the substrate. The reaction was carried out under biphasic conditions, which provides a simple, mild and efficient route for the synthesis of allyl sulfoxides.

Since palladium-catalyzed arylation is the main route to generate carbon–carbon bonds and carbon–hetero bonds, based on their previous experimental work, Maitro et al. proposed a nucleophile hypothesis that sulfenate anions are also suitable for palladium-catalyzed arylation. Subsequently, the palladium-catalyzed arylation of sulfenate anions with iodobenzenes under biphasic conditions was reported [22], thus revealing a new synthetic route to aryl sulfoxides (Scheme 6). In this synthetic method, β-sulfinyl esters and different iodobenzenes could react to give the corresponding products, but bromobenzene compounds did not undergo similar reactions, indicating that, in this reaction, the reactivity of iodobenzene compounds is stronger than that of bromobenzenes. This approach has been further refined and enriched by subsequent developments in which the Pd(0) catalyst could be shared by two independent catalytic cycles.



Scheme 6. Synthesis of aryl sulfoxides catalyzed by palladium.

In their previous work, Maitro et al. used β-sulfinyl esters to react with iodobenzenes to generate diaryl sulfoxides. In 2007, their team continued to use these two compounds as reaction substrates to explore the enantioenriched synthesis of aryl sulfoxides (Scheme 7) [23].



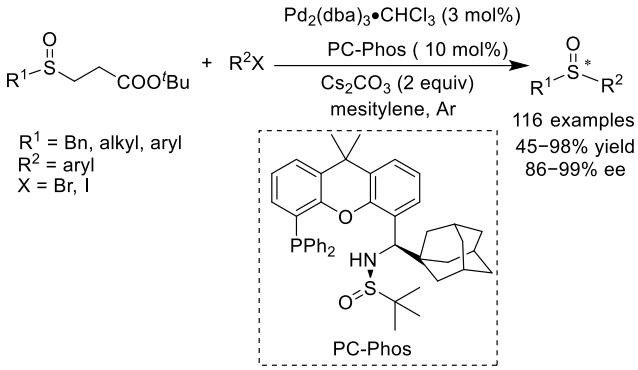
Scheme 7. Synthesis of chiral aryl sulfoxides by reaction of β-sulfinyl esters and iodobenzenes.

They chose to synthesize chiral aryl sulfoxide by adding chiral ligands. After screening a series of chiral ligands, they chose the Josiphos-type ligand (R)-(S)-PPF-*t*-Bu_2 as the chiral ligand for this reaction. The ee value of the model reaction product obtained was as high as 83% ee. They subsequently investigated the scope and limitations of this enantioselective transformation by reacting various substituted aryl iodides with β-sulfinyl esters.

The precursor of sulfenate anions, *p*-tolylsulfinyl acrylates, reacted with *p*-iodoanisole and *m*-iodoanisole to give the corresponding isomeric sulfoxides, with yields of 83% and 90%, respectively, and ee values of 73% and 68%. When reacted with o-iodoanisole, the sulfoxide was isolated in its racemic form in only a 78% yield. When using *p*-iodonitrobenzene, the sulfoxide was obtained in a 67% yield with 66% ee, while *p*-iodotrifluoromethylbenzene as a substrate gave an excellent yield of 98% and a higher ee value. The reaction of 2-iodothiophene with an aromatic heterocyclic structure produced the corresponding sulfoxide, but the ee value was only 49%.

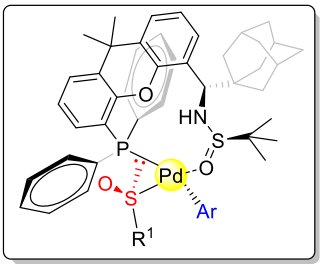
When β-sulfinyl esters with different structures were used, whether they have a benzyl structure or a naphthyl structure, the yields were about 70%, and the chiral benzyl sulfoxide products from the reaction of the β-sulfinyl esters with the benzyl structure had low ee values. It is worth noting that the chiral ligand selected for this reaction could favor the formation of sulfur–carbon bonds through sulfenate anions.

More than ten years later, another new class of chiral ligands was found to perform well in the palladium-catalyzed synthesis of chiral sulfoxides. Until 2018, Zhang and coworkers reported the palladium-catalyzed asymmetric arylation of alkyl and aryl sulfenate anions with a new class of chiral ligands (Scheme 8) [24]. At first, they screened a few chiral ligands, but no satisfactory chiral ligands were suitable for this reaction. Inspired by the excellent performance of Xantphos for the racemic transformations of racemic sulfoxides, the authors used their PC-Phos ligand [25] with the same xanthene skeleton as Xantphos as a chiral ligand. After screening a series of chiral PC-Phos phosphine ligands, the PC-Phos bearing the bulky 1-adamantyl sulfinamide was found to be the best chiral ligand for the palladium-catalyzed synthesis of chiral diorganyl sulfoxides.



Scheme 8. Palladium-catalyzed asymmetric synthesis of chiral sulfoxides from alkyl and aryl sulfenate anions with chiral PC-Phos ligand. Note: * indicates that this atom (here is sulfur) has chirality in this paper.

Importantly, the binding mode of the palladium complex was based on the crystal structure of the complex of the chiral ligand and $PdCl_2$. The Pd/ligand complex showed that the chiral ligand acted as a new type of chiral O,P ligand to coordinate with the center metal palladium with the oxygen atom of the sulfinamide moiety and phosphine. The chirality induction model was proposed (Scheme 9). In the proposed chirality induction model, the aryl group adopted the *cis* position to the sulfenate moiety, which was beneficial to the formation of chiral sulfoxides as the targeted products.



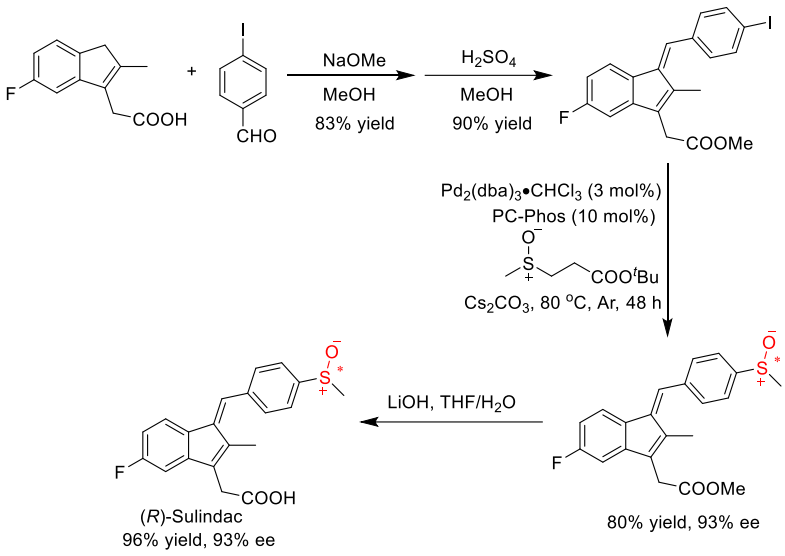
Scheme 9. The proposed transition state of palladium-catalyzed enantioselective arylation of sulfenate anions.

The versatility of this method was demonstrated by the application of over one hundred kinds of sulfoxides and, mostly, an enantiomeric excess higher than 90%. Furthermore, in this work, the authors also presented a novel and efficient synthetic route to (*R*)-Sulindac (Scheme 10), which is a nonsteroidal anti-inflammatory drug (NSAID).

This method led to more than a hundred examples, and most of the product chiral sulfoxides demonstrated excellent enantiomeric excess, which means that this protocol is an excellent tool to prepare chiral sulfoxides. Additionally, this paper also reported an efficient synthetic route for the synthesis of (R)-Sulindac, a nonsteroidal anti-inflammatory drug (Scheme 10).

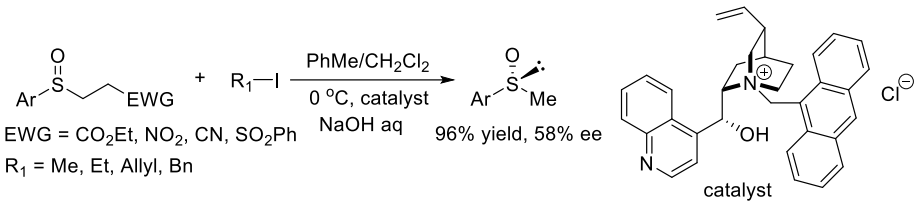
With commercially available carboxylic acid and 4-iodobenzaldehyde as the starting materials, esterification and then condensation gave the intermediate. The intermediate carried out palladium-catalyzed asymmetric arylation with the in situ formed sulfenate anion to provide the chiral sulfoxide in a good yield with an excellent ee value (93% ee), which afforded the target compound (R)-Sulindac after hydrolyzation in an extremely high yield (96%).

This study exhibited extensive sulfenate precursors, but no alkyl electrophile was reported as the coupling partner.



Scheme 10. Synthesis of (R)-Sulindac via palladium-catalyzed enantioselective synthesis with sulfenate anions.

In 2011, Gelat et al. described the chiral phase-transfer-catalyst-mediated asymmetric alkylation of β-sulfinyl esters with alkyl halides, which provided a new path for the synthesis of chiral sulfoxides (Scheme 11) [25]. When various alkyl halides were used to react with the corresponding sulfenate anions generated in situ from the corresponding β-sulfinyl esters, the desired sulfoxides were effectively obtained with certain enantioselectivities.



Scheme 11. Synthesis of chiral sulfoxides via reaction of β-sulfinyl esters with alkyl iodides.

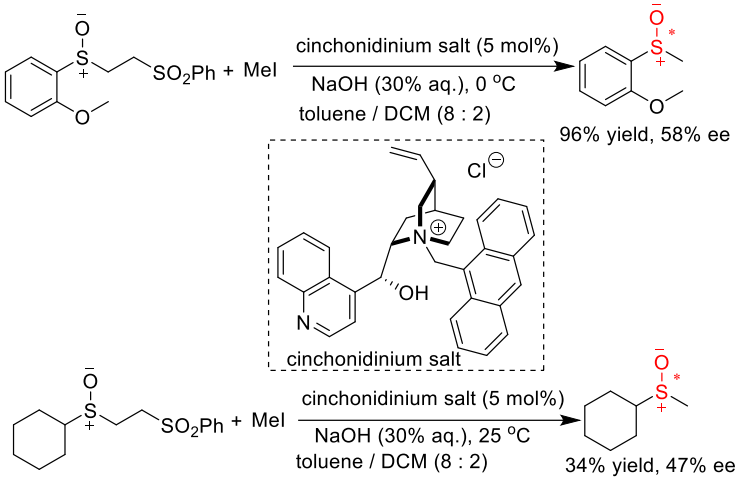
When methyl iodide reacted with β-sulfinyl esters with p-tolyl groups, the corresponding structure of sulfoxide was obtained in a 77% yield with 57% ee. When investigating the scope of the substrates, it was found that the use of ethyl iodide as the alkyl halide required an excess of the electrophile to achieve a yield of 63%, while the yield of the product obtained according to the template reaction conditions was only 34%. When ethyl iodide and allyl iodide were used to react with β-sulfinyl esters with p-tolyl, the ee values of both of the products decreased.

The use of the more reactive benzyl iodide to react with β-sulfinyl esters with p-tolyl groups still provided lower enantioselectivities than alkylation with methyl iodide, suggesting that enantioselectivity depends greatly on the nature of the halide. Extremely electron-deficient β-sulfinyl esters with a trifluoromethyl-substituted aryl group reacted with methyl iodide resulted in a drop in ee to 18%, although the product yield was as high as 81%.

The position of the methoxy substituent on the aryl moieties of the β-sulfinyl esters has no effect on the enantioselectivity, as exemplified by experimental results obtained for the *ortho*, *meta* and *para* isomers. Similar conclusions were obtained for chlorinated compounds. In particular, the reaction of β-sulfinyl esters with *tert*-butyl substitution on the aryl moieties with methyl iodide still retained good enantioselectivity.

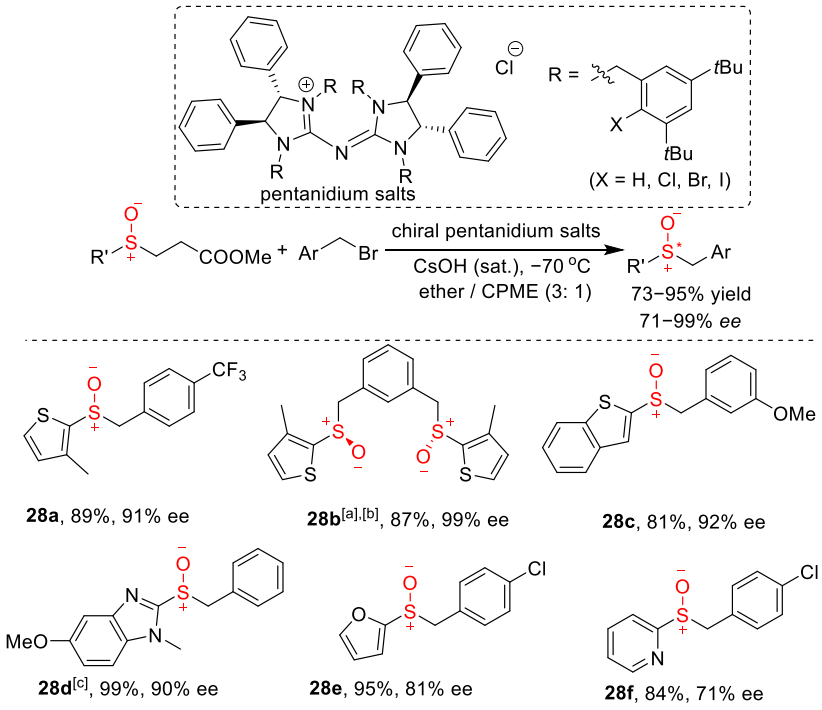
In their subsequent study, the asymmetric alkylation of alkyl sulfenates in low yields with moderate ee values was reported under similar conditions (Scheme 12) [26]. This

catalytic system only gave low to modest ee values, and a wide scope of substrates was expected to be explored.



Scheme 12. The phase-transfer catalyst of cinchonidinium salt used in asymmetric alkylation of both aryl and alkyl sulfenates.

In 2014, the Tan group developed structurally novel chiral pentanidium salts with halogenated benzyl groups as phase-transfer catalysts (PTCs) for the enantioselective alkylation of sulfenate anions [27], which gave excellent results compared to commercially available PTCs (Scheme 13).



Scheme 13. Chiral pentanidium salts with halogenated benzyl groups as phase-transfer catalysts in asymmetric benzylation of (hetero)aryl sulfenate salts.

First, *β*-sulfinyl methyl esters were converted into the corresponding enolates with the strong base CsOH. The *β*-sulfinyl methyl esters were decomposed into methyl acrylate and sulfenate anions, which interacted with the cationic part of the PTC to form transient chiral complexes, that is, the catalytic transition state. Theoretical calculations of the molecular

mechanism with the ONIOM method, as implemented in Gaussian 09, revealed that non-classical halogen bonds were formed between the phase-transfer catalysts and the leaving halide groups of the benzylating substrates in the transition state, which is the origin of the enantioselectivity of the product chiral sulfoxides. The presence of the non-classical Br-I halogen bond was used to explain the observed experimental results.

The preliminary optimization of the reaction showed that the presence of halogen atoms in the catalyst had a stronger effect on stereoselectivity than on reactivity if the leaving group was a bromide anion (yield of 76% with 61% ee, compared with 72% and 81% ee if non-halogenated or brominated analogs were used).

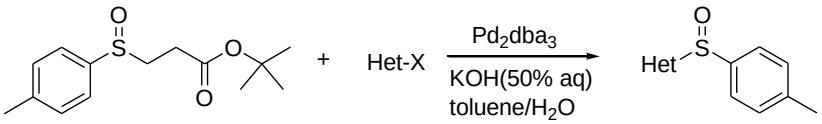
However, when benzyl substrates were used with chloride as the leaving group, the presence of halogen atoms in the phase-transfer catalysts has a more complicated effect on reactivity than on selectivity. If non-halogenated or iodide analogs were used, only 27% of the by-product was obtained after 48 h, while the yield of the product after 24 h was 29%, and the ee was 90%.

When an anionic intermediate attacked the initially released methyl acrylate, the formation of by-products occurred when alkyl halides were omitted from the reaction mixture or when less active electrophiles were used with non-halogenated or chlorinated versions of the phase-transfer catalyst.

It was also shown that while iodination catalysts had the best results, brominated analogs should be used instead in specific cases. By optimizing the conditions, a group of products was obtained with moderate to high yields (65–88%) and high to excellent stereoselectivity (77–94% ee).

This protocol afforded a wide range of optically active sulfoxides with aryl groups, especially those bearing heteroaryl moieties (Scheme 13), for instance, furan, thiophen, benzimidazole, benzothiophene and pyridine. On the other hand, aryl halides with both electron-donating groups and electron-withdrawing groups were all suitable substrates. Unfortunately, no alkyl sulfenate anions were reported as nucleophiles in this paper.

In 2007, Colobert et al. introduced the palladium-catalyzed heteroarylation of sulfenate anions [28], which could effectively synthesize heteroaryl sulfoxides. Afterward, Abarca and his collaborators also reported a related synthetic method [29]. Triazolopyridinyl sulfoxide, pyridinyl sulfoxide and thiophene sulfoxide could all be obtained at high yields under mild conditions from the reaction of the corresponding heteroaryl bromides with sulfenate anions (Scheme 14).

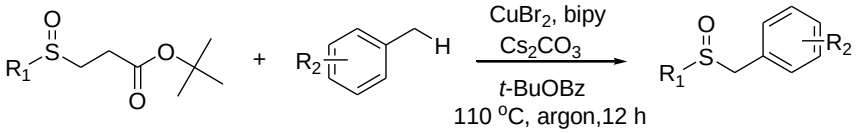


Scheme 14. Heteroarylation of β-sulfinyl esters to synthesize heteroaryl sulfoxides.

They used this method to prepare the corresponding heteroaryl sulfoxides from bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine, 4-bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine and 5-bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine with sulfenate anions with good to excellent yields. However, 6-bromo-3-methyl-[1,2,3]triazolo[1,5-a]pyridine had low reactivity, so only a trace amount of the target product was obtained.

6-Bromo-[1,2,3]triazolo[1,5-a]pyridine failed to undergo such a reaction to give the corresponding sulfoxide. This indicates that different halogenated sites on heterocyclic arylates resulted in significantly different reactivities of the reaction.

In 2018, Yu's group developed a method for the non-directed oxidation of the sp^3 C-H bond, that is, the copper-catalyzed sulfoxidation of benzyl C-H bonds (Scheme 15) [30]. The process was carried out using sulfenate anions, which are produced by the alkali-mediated elimination of β-sulfinyl esters. The reaction used low-cost and easily available methyl aromatic hydrocarbons as raw materials to synthesize a variety of functionalized benzyl sulfoxides, which had the advantages of high functional group tolerance and good product yields.



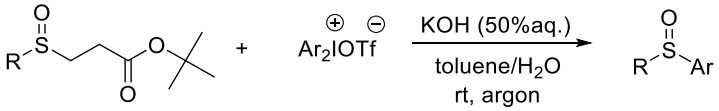
Scheme 15. Copper-catalyzed reaction of *β*-sulfinyl esters with methyl aromatic hydrocarbons to synthesize benzyl sulfoxides.

When the substrate scope of *β*-sulfinyl esters was investigated, it was found that the corresponding benzyl sulfoxides were synthesized at yields between 35% and 82%. The best results were obtained in the synthesis of aryl benzyl sulfoxides, which had an average yield of 72%. Neither the electron nor spatial effects induced by substituents on aromatic hydrocarbons had a significant effect on this reaction. It is worth noting that the yields of *β*-sulfinyl esters with different halogen substitutions on the benzene ring were different; that is, the yield of bromine substitution was significantly better than that of chlorine substitution.

β-Sulfinyl esters with a heteroaromatic ring structure gave the target product with lower yields of only 60%, suggesting that the efficiency of catalytic metal coordination was impaired by multiple heteroatoms in the starting material and product. Extremely low yields of 50% and 35% were found for benzyl isopropyl sulfoxide and dibenzyl sulfoxide, respectively, which may be due to competitive oxidation processes on branched-chain aliphatic and benzyl sulfur substituents.

When the substrates of methyl aromatic hydrocarbons with different structures were investigated, all three isomers of xylene produced the expected sulfoxides with similar yields. When halogen-containing methyl aromatic hydrocarbons reacted with *β*-sulfinyl esters, ortho-substituted halogenated aromatic hydrocarbons performed the best. Methyl naphthalene provided the corresponding sulfoxides at a yield of 54%.

In the same year, Yu's group still used *β*-sulfinyl esters as raw materials, and the sulfinate ions generated in situ reacted with diaryl iododonium salts to form diaryl sulfoxides without transition-metal catalysis (Scheme 16) [31]. The reaction conditions were mild, even at room temperature, and the substrate scope was broad.



Scheme 16. Reaction of *β*-sulfinyl esters with diaryl iododonium salts to synthesize diaryl sulfoxides.

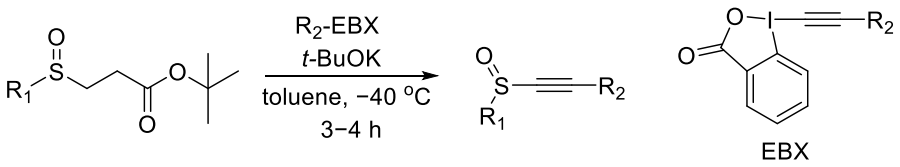
When the effects of various *β*-sulfinyl esters on the reaction were examined, on the whole, the yields were high. However, when the aryl moiety on some *β*-sulfinyl esters had substituents such as *o*-ethyl, *p*-*tert*-butyl and *o*-aryl, the yields were slightly lower because of the large steric hindrance, which affects the reaction results. In addition, *β*-sulfinyl esters with a heteroaryl structure can be used to prepare sulfoxides with heterocyclic aryl groups with an extremely high yield of up to 98%.

Unfortunately, *β*-sulfinyl with aliphatic substituents only produced sulfoxides at lower yields. When different diaryl iododonium salts were used, the yields of the resulting sulfoxides varied greatly. Among them, *para*-substituted diaryl iododonium salts reacted well, and the results of *tert*-butyl-containing derivatives were the best, with an isolated yield of 97%.

The yields of halo substituents on aryl groups were slightly lower, so the yields of sulfoxides with *p*-fluoro, *p*-chloro and *p*-bromoaryl were only 65–85%. Products with two methyl substituents in the *ortho* and *para* positions were separated at about 80% yields. The heterocyclic bis(2-thienyl)iodine salt had a great influence on the reaction yield, and only 19% yield of the corresponding sulfoxide was obtained.

In 2019, the Amos group reported an extremely rare synthesis method for alkyne sulfoxide compounds [32]. They used an ethynylbenzozoline (EBX) reagent as an electrophilic

acetylene transfer agent to react with sulfinyl negative ions generated in situ from β-sulfinyl esters via an inverse Michael reaction under metal-free catalyzed conditions (Scheme 17).



Scheme 17. Synthesis of alkynyl sulfoxides.

When exploring the substrate scope of β-sulfinyl esters, it was found that the *para*-position of the aryl moiety on β-sulfinyl esters with both an electron-absorbing group and an electron-donating group afforded the corresponding alkyne sulfoxides with a moderate to excellent yield (55–90%), and the substrates with *ortho*- and *meta*-substitution could also provide the required alkyne sulfoxides with yields up to 81%.

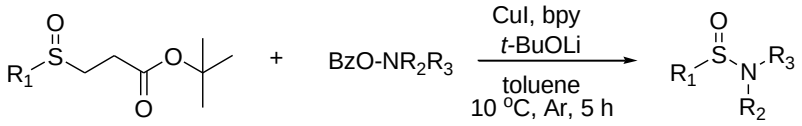
Under the conditions of this reaction, increasing the temperature and prolonging the reaction time could also provide heteroaryl alkyl sulfoxides with pretty good yields, such as alkynopyridine sulfoxides, alkyl thiophene sulfoxides, alkyl furyl sulfoxides and the like. At higher temperatures, β-sulfinyl esters with both primary and secondary alkyl moieties had a good substrate scope.

When EBX reagents were changed to TBDPS-EBX (TBDPS = *tert*-butyldiphenylsilyl) and tBu-EBX (tBu = *tert*-butyl), both could be used as effective alkyne transfer reagents. However, the target product was not obtained when using $C_{14}H_{29}$-EBX and Ph-EBX as reagents.

In short, they developed a new method for synthesizing alkynylaryl sulfoxides, alkynoaryl sulfoxides and alkynoalkyl sulfoxides with moderate to excellent yields. This practical way to synthesize alkyne sulfoxides is expected to facilitate the application of valuable alkyne sulfoxides as building blocks in organic synthesis.

4. Synthesis of Sulfinamides from β-Sulfinyl Esters

In 2018, Dai's group developed a method to construct sulfinamides via the copper-catalyzed electrophilic amination of sulfenate anions with N-benzoyloxyamines as an amination reagent (Scheme 18) [33]. This process was characterized by the capture of in situ generated sulfenate anions from β-sulfinyl esters under mild conditions.



Scheme 18. Reaction of β-sulfinyl esters with amination reagents to synthesize sulfinamides.

When using β-sulfinyl esters with different structures, it was found that regardless of whether there was an electron-absorbing substituent or an electron-donating substituent on the aromatic ring, the corresponding negative sulfinyl ion could be effectively released. Methyl-substituted β-sulfinyl esters on the aromatic ring could give the target products with excellent yields, while the yields of *ortho*-methyl-substituted β-sulfinyl esters were significantly reduced, which suggests that steric hindrance had a negative effect on the reaction. The 2-naphthyl sulfenate anion precursor was also suitable for this reaction, efficiently providing the required sulfinamide.

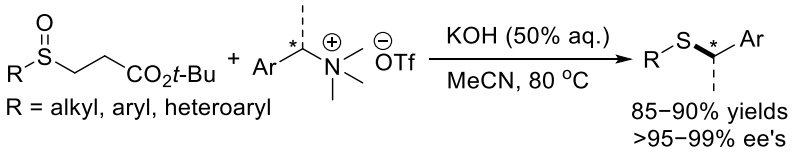
In addition to the aromatic structure, the aliphatic structure of β-sulfinyl esters is also suitable for this reaction. β-Sulfinyl esters with linear alkyl and cyclic alkyl structures could be smoothly converted into the corresponding products. When N-benzoyloxyamines with different substituents were used as the reaction substrates, amino electrophiles without a cyclic structure could react to form the desired sulfinamides.

Interestingly, when using pyrrole-derived amination reagents, an increased amount of the base was required to facilitate the complete conversion of β-sulfinyl esters. Amino electrophiles with cyclic structures, whether a six-membered ring or a seven-membered cyclic amination reagent, readily participated in the reaction and provided the target products with good yields. Therefore, this reaction protocol directly provides a variety of aryl and alkyl sulfinamides with moderate to good yields.

At the same time, this method has the advantage of an easily scaled-up synthesis and can replace unstable sulfinyl halides or thioesters in the synthesis of sulfinamides. Unfortunately, this method is not yet able to synthesize chiral sulfinamides.

5. Synthesis of Chiral Thioethers via Deoxidative Coupling Reaction of β-Sulfinyl Esters

Our research group recently discovered an unusual deoxidative coupling reaction of β-sulfinyl esters with benzylic trimethylammonium salts promoted by the strong base KOH (Scheme 19) [34], and various thioethers were produced. Enantiomerically enriched chiral quaternary ammonium salts synthesized from chiral amines afforded highly enantiomerically pure chiral benzyl thioethers (>95–99% ee). It seems that this reaction occurs via an S_N2-type nucleophilic substitution process, since the chiral benzyl thioethers obtained had configurations opposite to those of the enantiomerically enriched amines.



Scheme 19. Reaction of β-sulfinyl esters with amination reagents to synthesize sulfinamides.

6. Conclusions and Outlook

β-Sulfinyl esters prepared via the in situ formation of sulfenate anions under the action of alkali as a nucleophile, under catalysis by transition metals, can react with a variety of electrophiles. Among them, the most reported is the formation of sulfoxides, some of which were chiral sulfoxides synthesized with high enantiomeric purity. This has important practical significance, because a variety of important chiral drugs have structures of chiral sulfoxide moieties. Therefore, this synthetic method could provide another way to synthesize chiral drugs.

It is foreseeable that negative sulfinyl ions generated in situ by β-sulfinyl esters can react with carbocation species to synthesize chiral sulfoxides in the presence of chiral catalysts. This means that with a suitable chiral catalyst, sulfenate anions can also react with a variety of electrophiles, such as positively charged nitrogen, oxygen, phosphorus and sulfur species, to form various chiral sulfinyl-containing chiral compounds.

The reaction of β-sulfinyl esters with positively charged nitrogen species to produce sulfinamides has been reported; however, chiral products have not yet been obtained. Therefore, this area has yet to be vigorously developed.

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