

Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds

Elżbieta Wojaczyńska* and Jacek Wojaczyński

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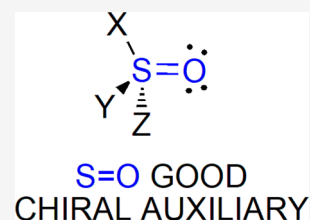


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ABSTRACT: Chiral sulfinyl compounds, sulfoxides, sulfoximines, sulfinamides, and other derivatives, play an important role in asymmetric synthesis as versatile auxiliaries, ligands, and catalysts. They are also recognized as pharmacophores found in already marketed and well-sold drugs (e.g., esomeprazole) and used in drug design. This review is devoted to the modern methods of preparation of sulfinyl derivatives in enantiopure or enantiomerically enriched form. Selected new approaches leading to racemic products for which the asymmetric variant can be developed in the future are mentioned as well.



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1. INTRODUCTION

In this review, we would like to focus on the recent achievements in the synthesis of chiral sulfinyl compounds. Their common feature, a stereogenic sulfur atom is connected to electronegative oxygen atom by a polar, partially dative bond, although in all structures in this review it is consistently shown as S=O moiety (Figure 1). We limit our discussion to organosulfur derivatives, i.e., compounds with at least one S–C bond. Consequently, sulfoximines (lacking S=O fragment), and sulfites or sulfates (no C–S bond present) will not be covered. Also sulfonyl compounds and sulfonyl derivatives will

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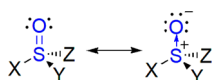


Figure 1. General formula of sulfinyl compounds showing resonance structures of sulfinyl group.

be only marginally mentioned as achiral starting materials or side products in the preparation of their sulfinyl counterparts.

We dare to undertake this topic encouraged by the good reception of our review published in the year 2010 on the enantioselective preparation of chiral sulfoxides.¹ Since then, hundreds of articles have appeared devoted to this group of compounds. Although chiral, enantiopure, or enantioenriched sulfoxides have been mainly prepared using previously developed methods, also new approaches to them have been described. This situation calls for a review which would include novel protocols and new interesting examples. The present paper is, however, not a simple update of our previous article as we have decided to extend our interest to other important groups of chiral sulfinyl compounds, which are also prepared in a stereoselective manner, e.g., sulfinamides, sulfinimines, sulfinates and thiosulfinates, sulfoximines, sulfonimidamides, and sulfonimidates.

These derivatives deserve attention due to their importance in modern synthetic, medicinal, and agricultural chemistry. The sulfinyl group is considered as a valuable chiral auxiliary, used in the stereoselective preparation of variety of useful chiral compounds. It is relatively easy to introduce and remove, configurationally stable, and capable of high asymmetric induction. As an example, *tert*-butane sulfinamide introduced by Ellman and co-workers finds numerous applications in the synthesis of enantiomerically pure amines and their derivatives, in many cases exhibiting significant biological activity.² Recent reviews show the utility of various sulfur derivatives in organic synthesis.^{3,4} Nonracemic sulfinyl compounds are also used in catalytic stereoselective reactions, both as ligands for transition metals and as chiral organocatalysts. Three important reviews published in the last five years deal with this emerging application of chiral sulfoxides and their analogues in asymmetric catalysis.^{5–7}

Chiral organosulfur derivatives are found in natural systems such as methionine sulfoxide, *S*-adenosyl methionine, allicin, or leinamycin **1** (Figure 2).⁸ Synthetic sulfinyl compounds often

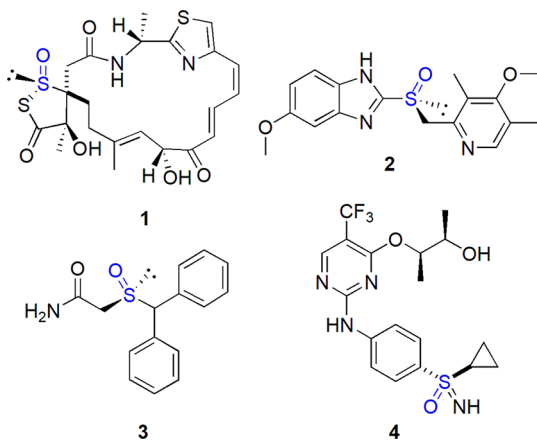


Figure 2. Examples of enantiomerically pure sulfinyl compounds exhibiting biological activity: leinamycin (**1**), esomeprazole (**2**), modafinil (**3**), roniciclib (**4**).

exhibit a significant biological activity. As a consequence, pharmaceutical and agrochemical industry manifest an increasing interest in these chemicals, part of which have been marketed as drugs, like esomeprazole **2** and its various derivatives used as antiulcer drugs or modafinil **3** (Figure 2). Recently, the better synthetic availability of sulfoximines (as exemplified by roniciclib **4**), sulfonimidamides, and sulfonimidates has led to the increased interest in their possible application in drug design.⁹ These analogues of sulfones and sulfonamides, well recognized pharmacophores, offer additional possibilities of structural modifications which may affect their interactions within natural systems. In this context, the development of efficient methods of stereoselective preparation of sulfinyl compounds is of special importance.

Articles describing methods of preparation of sulfoxides, but also of other sulfinyl compounds, are collected in several books. Among the most recent, the first one, entitled “*Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*”, written by Marian Mikołajczyk, Józef Drabowicz, and Piotr Kielbasiński, was printed in 1997 and contains chapters devoted to various types of sulfoxides,¹⁰ sulfinic acid derivatives,¹¹ and sulfoximines.¹² Eleven years later, a book edited by Takeshi Toru and Carsten Bolm was issued. From the point of view of the present review, chapters on synthesis and application of chiral sulfinates,¹³ sulfinamides,¹⁴ and sulfoximines¹⁵ are particularly important.

Important review articles and highlights underscoring the significance of particular groups of sulfinyl compounds will be introduced in respective sections. As we do not intend to repeat the material covered by them, only the most representative examples and the latest papers published up to the year 2019 will be discussed.

2. CHIRAL ORGANIC COMPOUNDS WITH A TETRAHEDRAL SULFUR STEREOCENTER

The study of stereochemistry of organic sulfur compounds has a long and rich history.¹⁶ We shall limit our discussion to tetrahedral sulfur, which can become a stereogenic center when three (a lone pair of electrons takes the part of fourth substituent) or four different groups are attached to it. If we take into account only the chirality arising from the presence of the sulfinyl group, among trisubstituted derivatives sulfoxides are chiral if two carbon groups are different. A whole family of chiral compounds can be regarded as derivatives of sulfinic acids, which themselves are achiral due to proton exchange (however, chirality can result from isotopic substitution¹⁷): sulfinic halides, sulfinamides and sulfinimines (*N*-sulfinylimines), sulfinates, and thiosulfinates (also thiosulfinic acids and their salts are chiral, although they are prone to slow decomposition and rarely prepared^{17,18}). Among their counterparts in which the place of lone electron pair is taken by a =NR' fragment, sulfoximines require two different carbon groups for chirality, while derivatives of sulfonimidic acids are chiral by definition (Figure 3). Salts with three organic groups attached to sulfur should be also mentioned.

Certainly, these derivatives differ in terms of chemical and configurational stability. Sulfinyl chlorides have been mainly prepared as reactive intermediates without bothering about enantiomeric purity, and their storage is problematic (a contact with moisture evolves gaseous HCl).^{19–21} Sulfinic acids are prone to disproportionation, yielding diaryl thiosulfinates and sulfonic acids.²² Stability of sulfinyl derivatives was extensively studied by Kice and co-workers. A mechanism of racemization

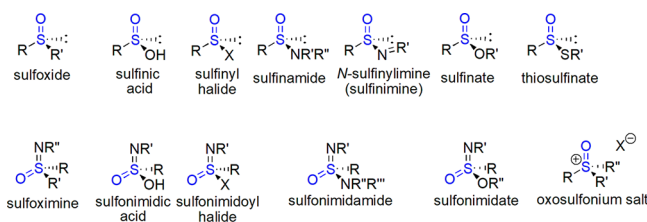


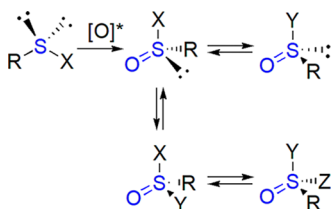
Figure 3. Main classes of chiral sulfinyl compounds. R, R', R'', R''' = alkyl or aryl, but when attached to N then also H; X = F, Cl, Br, I.

of thiosulfates caused by nucleophiles or catalyzed by acids was analyzed as well as kinetics of alkaline hydrolysis of aryl thiosulfates and thiosulfonates.^{23–25} It was shown that the presence of a bulky substituent at sulfur increases the stability of thiosulfates, and most work was done for *tert*-butyl derivative (see section 5). Various factors affecting racemization were summarized in a chapter written by Mikołajczyk and Drabowicz.²⁶

Several types of methods to prepare chiral sulfinyl compounds can be distinguished, taking into account which bond is formed in the course of reaction. Stereoselective oxidation of prochiral sulfur atom in sulfenyl compounds has been recognized as an efficient method of synthesis of nonracemic sulfoxides but is also of importance for other classes of organosulfur derivatives. Alternatively, one sulfinyl derivative can be converted into another, with concomitant formation of either sulfur–carbon or sulfur–heteroatom (N, O, S) bond.

In general, we can also consider possible transformations involving disubstituted (sulfides, disulfides, thiols, sulfenyl halides, sulfenic acid derivatives: sulfenates, sulfenamides), trisubstituted, and tetrasubstituted organosulfur compounds (Scheme 1). In conversions involving the first group to the

Scheme 1. Possible Interconversions of Sulfinyl Derivatives



members of the second and third one, chiral reactant or catalyst is necessary to yield optically active product (stereoselective formation of two new bonds constitutes a considerable challenge). Chirality transfer from another stereogenic center already present in the molecule is also possible in diastereoselective reactions.

Other transformations engaging chiral tri- or tetrasubstituted derivatives can be stereospecific, proceeding with either retention or inversion of configuration of sulfur atom. As proven by early experiments, substitution reactions, which typically make use of nucleophilic reagents, are in most cases associated with inversion, while conversions connected with change of coordination number keep the arrangement of substituents (the fourth one takes place of the lone pair or vice versa, see also section 9.1).^{27–29}

Kinetic resolution can be engaged in certain cases to increase the optical purity of desired products or to resolve racemic mixtures. Certain interconversions, like sulfonamide into

sulfinylimine and vice versa, do not proceed at a stereogenic sulfur atom (this is also true for modifications within substituents, although certain reaction conditions may favor racemization). One should not forget about desymmetrization of achiral (e.g., *meso*) compounds, also resulting from modification of substituents.

Not all possible conversions can be treated as useful preparative methods. Yield and stereoselectivity are the main criteria, but economic and environmental aspects should be also taken into account. Procedures should be possibly general, operationally simple, and with the number of steps minimized. Last but not least, they should start from cheap and easily available materials. Therefore, deamidation of sulfoximines, which proceeds with retention of configuration, is not regarded as a practical synthetic route to enantiomerically pure sulfoxides.³⁰ Similarly, reduction of sulfones has never emerged as a convenient route to sulfoxides.^{31,32}

The subsequent sections will be devoted to the synthesis of particular groups of sulfinyl compounds, mainly in enantiomerically pure or enriched form. However, certain procedures leading to racemic mixtures will be also presented as at least part of them can be adapted to give single stereoisomeric products.

3. PREPARATION OF CHIRAL, NONRACEMIC SULFOXIDES

Our review on stereoselective preparation of chiral sulfoxides covered mainly literature from the years 2000–2008 (although referred also to classical papers).¹ In recent years, several other review articles devoted to this group of organosulfur compounds have been published, differing in their scope, size, and general message as well as topicality. Three important papers concerning application of chiral sulfoxides in asymmetric catalysis have already been mentioned in the Introduction.^{5–7} A general review by Maguire and co-workers on the synthesis of enantioenriched sulfoxides, with a special attention paid to kinetic resolution, was published in 2011.³³ Several articles were devoted to asymmetric oxidations, including sulfoxidations, with a focus on environmentally benign methods.^{34–36} A first part of a paper in which Franklin Davis described his “adventures in sulfur–nitrogen chemistry” (using his own words) described the preparation and use of chiral oxaziridine derivatives (known as Davis reagents) in enantioselective oxidation of sulfenyl compounds: sulfides, disulfides, and sulfenylimines.³⁷ In 2018, a review by Han et al. was published, presenting the developments in the preparation of optically active sulfoxides in the years 2011–2016.³⁸ An important issue of correct determination of stereochemical outcome of synthetic reactions has been discussed in detail. The problem is connected with self-disproportionation of enantiomers (SDE), the effect of change of enantiomeric composition during the purification process.

We do not intend to present once more the details of all methods used for preparation of chiral, enantiomerically pure, or enantiomerically enriched sulfoxides. Their description can be found in previous reviews. In this section, we shall focus on the main tendencies that could be observed in field in the past decade.

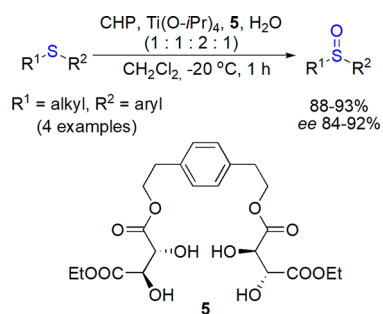
3.1. Chemical Methods

3.1.1. S=O Bond Formation. Enantioselective sulfoxidation remains the principal method of preparation of chiral, nonracemic sulfoxides. From the economical point of view,

catalytic oxidation systems are preferred, although Davis' oxaziridines are also used.³⁹ Attempts with new chiral stoichiometric oxidants (*N*-chloramine derivatives) were not very encouraging (up to 23% *ee*).⁴⁰ Consequently, transition metal catalysts (in particular, titanium- and vanadium-based) are commonly used.

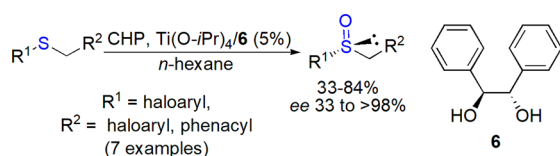
The long puzzling origin of the Kagan/Modena oxidation system based on Ti(IV) complexes of diethyl tartrate and *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP) was studied by Corey's group.⁴¹ DFT calculations were applied to compare geometries and energies of possible isomeric helical complexes formed in the course of reaction: the more stable *P* diastereomer was shown to preferentially yield one of the enantiomers of sulfoxide. This analysis led to design and synthesis of a chiral tetraol containing two tartrate moieties **5**, which was found superior in the enantioselective oxidation of alkyl aryl sulfides in comparison with the original Kagan's system (Scheme 2).

Scheme 2. Enantioselective Oxidation of Sulfides Catalyzed by Ti(IV) Complex with Chiral Tetraol **5**⁴¹



In a series of publications, Cardelliccio and co-workers thoroughly studied oxidation of sulfides by titanium(*S,S*)- or (*R,R*)-hydrobenzoin (HB, **6**) catalytic system.⁴²⁻⁴⁷ Through a combination of experimental and theoretical work, they found that benzyl aryl sulfides were particularly efficiently oxidized by TBHP (yields up to 92%, *ee* 84 to >98%), which was rationalized by different interactions in diastereomeric octahedral adducts formed by [Ti(HB)₂]⁴⁺ with substrate and TBHP.⁴²⁻⁴⁴ However, they found that for aryl benzyl or aryl phenacyl sulfides containing fluorinated substituents, *tert*-butyl hydroperoxide was relatively inefficient but could be replaced with CHP, which resulted in satisfactory yields and much improved enantioselectivity (Scheme 3).⁴⁵⁻⁴⁸ Again, this

Scheme 3. Enantioselective Oxidation Catalyzed by Titanium/*S,S*-Hydrobenzoin⁴⁸

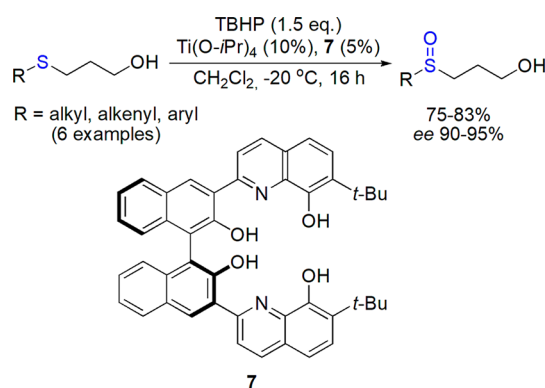


observation was explained by the calculated degeneracy of the octahedral diastereomers formed when TBHP was applied, while in the case of CHP, additional interactions stabilized mainly one of complexes leading preferentially to one enantiomer.

Talsi and Bryliakov explored titanium complexes with salan derivatives; oxidation of pyridylmethylthioimidazoles led

to enantiopure proton pump inhibitors.⁴⁹⁻⁵² Also, other groups prepared various enantiomerically enriched sulfoxides using chiral tetradenate and tridentate Ti(IV) complexes as catalysts.⁵³⁻⁵⁶ An interesting dinuclear system based on 8-quinolinol-derived ligand **7**, which was found efficient in epoxidation of a variety of homoallylic alcohols, was checked in sulfoxidation by Bhadra et al. (Scheme 4).⁵⁷ γ -Hydroxypropyl

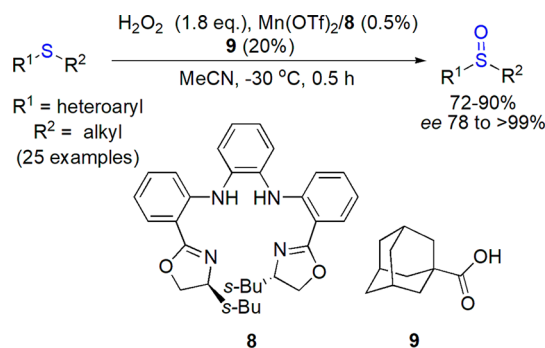
Scheme 4. Oxidation of Hydroxypropyl Sulfides with a Catalytic System Based on Dinuclear Titanium Complex with Chiral Ligand **7** Described by Bhadra et al.⁵⁷



sulfides were converted to the corresponding sulfoxides (difficult to prepare by other routes) in high yield and with *ee* values up to 95%; the presence and placement of hydroxyl group was found crucial for the observed stereochemical outcome.

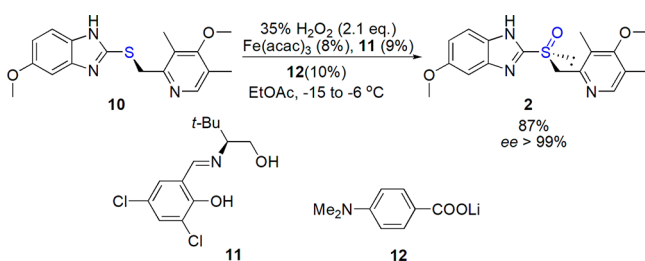
Modified Schiff bases were introduced by several research groups as chiral tridentate ligands for vanadium(IV), typically applied as VO(acac)₂ in a two-phase system with hydrogen peroxide as oxidant.⁵⁸⁻⁶⁴ Manganese was used in combination of salen^{65,66} or another tetradenate, N4 ligand **8**; the latter, with carboxylic acid **9** as additive and H₂O₂ as oxidant, allowed highly enantioselective, gram-scale preparation of various sulfoxides also in the flow system (Scheme 5).⁶⁷⁻⁶⁹ Chiral

Scheme 5. Oxidation of Sulfides Catalyzed by Manganese Complex⁶⁹



salen-type Fe(III) complexes were also used in successful sulfoxidations with peroxides.^{70,71} Nishiguchi et al. applied iron(III) complex with a Schiff base **11** in preparation of proton pump inhibitors and received esomeprazole **2** in 87% yield (12% of sulfone was formed) and >99% *ee* (Scheme 6).⁷² Optimized reaction conditions included slow addition of aqueous hydrogen peroxide and the use of lithium 4-dimethylaminobenzoate additive **12** and ethyl acetate as a

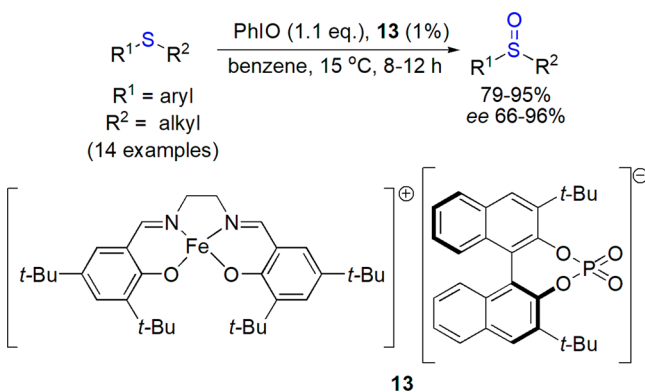
Scheme 6. Synthesis of Esomeprazole 2 Catalyzed by Fe(III)-Chiral Schiff Base Complex⁷²



solvent. Both ligand and carboxylate could be prepared in situ, and the reaction was conducted on a kilogram scale (up to 4.66 kg of sulfide **10**). Other derivatives (lansoprazole, pantoprazole, rabeprazole) were obtained in 75–87% yield and 83–98% *ee*.

A new concept of asymmetric counteranion-directed catalysis (ACDC)⁷³ was tested by Liao and List; the catalyst **13** consisted of an achiral iron(III) cationic complex and an enantiopure phosphate counteranion.⁷⁴ High yields and enantioselectivities were noted, setting the new record for salen-Fe systems (Scheme 7).

Scheme 7. Chiral Anion as the Source of Asymmetric Induction in Sulfoxidation Catalyzed by Achiral Cationic Fe(III) Complex⁷⁴



The best effects of asymmetric induction (up to 97% *ee*) were also achieved in the category of copper-Schiff base catalysts described by Maguire and co-workers.⁷⁵ The first use of nucleic acid-bound copper(II) complex with bipyridine in sulfoxidation of thioanisole by aqueous hydrogen peroxide was reported by Cheng et al.^{76,77} A transfer of chirality for G-quadruplex DNA to the product was observed with the enantiomeric excess up to 56% (99% conversion). CD and fluorescence quenching measurements showed that the limited stereoselectivity may result from relatively weak, nonspecific interactions of both thioanisole and Cu complexes with the quadruplex.

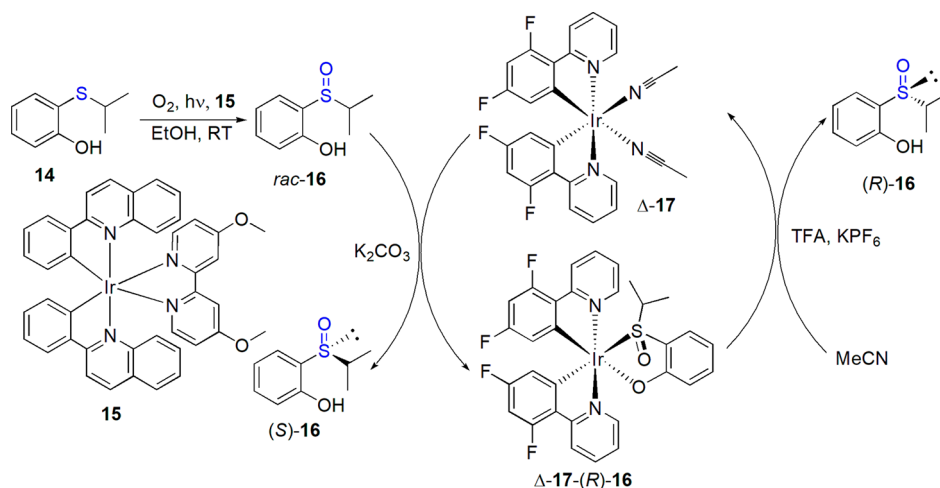
Molybdenum(VI) complexes of chiral Schiff bases^{78,79} or imidazolium-based zwitterionic dicarboxylic acid derived from L-valine^{80,81} were also used in asymmetric oxidation of sulfides, albeit with moderate or low enantioselectivity, which could be improved by kinetic resolution.⁸⁰

Chirality of coordination compounds can result not only from the presence of appropriate ligands but also from a stereogenic center located on the central ion. In possible catalytic conversions, this core is usually directly engaged in the catalytic action, and it is not surprising that chiral-at-metal complexes have already found application in various asymmetric transformations.^{82,83} Ye and co-workers explored the strategy based on the use of such octahedral ruthenium(II) or iridium(III) complexes with 2,2'-bipyridyl or 2-phenylpyridyl ligands, capable of catalyzing enantioselective oxidation of sulfides by *m*-CPBA but also of preferential coordination of one enantiomer of sulfoxide (dynamic thermodynamic resolution).^{84–87} Enantiomeric excess of up to 99% was reached for various derivatives, including modafinil acid and its analogues. Photooxidation of hydroxysulfides catalyzed by iridium complex of 2-phenylquinoline connected with coordination-based resolution of enantiomers was reported by Li and Ye in 2019 (Scheme 8).⁸⁸

Construction of supramolecular assemblies and metal-organic frameworks capable of selective oxidation of sulfides to sulfoxides was reported by several groups.^{89–93} Certain systems containing chiral subunits led to high enantioselectivities.⁹¹

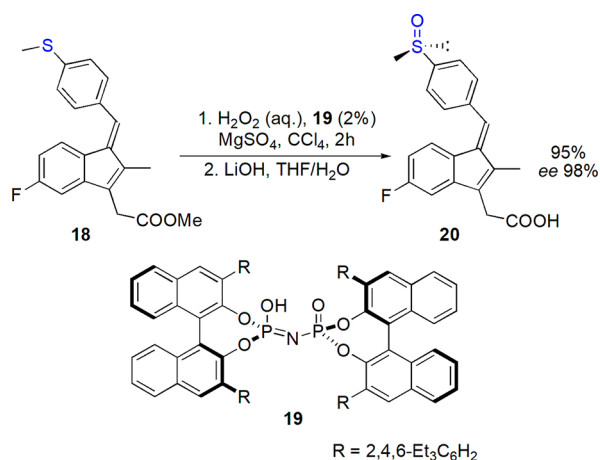
In our previous review on stereoselective synthesis of sulfoxides, we expressed our expectation that organocatalytic sulfoxidation would attract growing attention.¹ Since 2010, the

Scheme 8. One-Pot Photooxidation of Sulfide 14 Catalyzed by Iridium Complex 15 Coupled with Resolution of Sulfoxide 16 by Chiral-at-Metal complex Δ-17 Described by Li and Ye⁸⁸



actual development has been not so impressive.^{94–96} However, promising results were obtained with flavin-derived catalysts^{97,98} and BINOL-based phosphoric acid derivatives.^{99–101} The latter allowed an enantioselective preparation of (*R*)-sulindac **20** (95% yield, 98% *ee*, Scheme 9). However, (*R*)-

Scheme 9. Enantioselective Preparation of *R*-Sulindac with a Chiral Confined Brønsted Acid⁹⁹



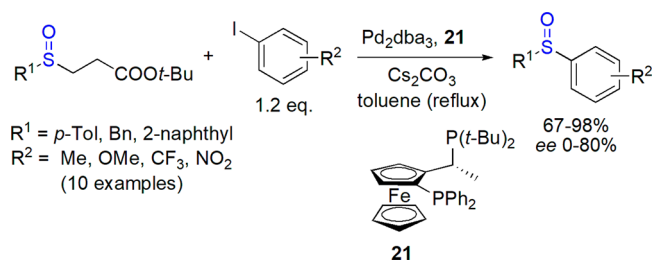
modafinil was identified as a more difficult goal, and organocatalyzed oxidation of its parent sulfide with hydrogen peroxide solution was performed with up to 26% *ee*.¹⁰²

3.1.2. S–C Bond Formation. Preparation of sulfoxides in Friedel–Crafts-type reactions dates back to the 1974 paper of Olah and Nishimura.¹⁰³ Among recent applications, sulfonylation of indoles through electrophilic substitution with arylsulfinic acids described by Miao et al. is worth mentioning, as it was performed in water at room temperature without any additives.¹⁰⁴ Another green Friedel–Crafts sulfonylation of aromatic compounds with sulfinic esters was carried out in ionic liquid and accelerated by ultrasound irradiation.¹⁰⁵ Sulfinamides were applied in a similar, visible light-accelerated transformation of heteroaromatic substrates.¹⁰⁶ A lack of source of chiral induction in all above reactions resulted in formation of racemic products.

In recent years, a considerable progress in the enantioselective synthesis of sulfoxides has been connected mainly with the development of methods based on the reactions of sulfenate anions with electrophiles. In 2004, structure, methods of generation, and reactions of sulfenic acid anions were reviewed by O'Donnell and Schwan.¹⁰⁷ In the following years, efficient routes to these underexplored intermediates were introduced and their subsequent arylations catalyzed by transition metal complexes were described. Perrio and co-workers identified β -sulfinyl esters as versatile precursors of a sulfenate anion.¹⁰⁸ Various bases (NaHMDS, KHMDS, NaH, LDA, *n*-BuLi, *t*-BuOK) were efficient in its generation, and reaction with benzyl or alkyl halides led to expected sulfoxides in up to 95% yield. To obtain enantioenriched products, the authors added enantiopure sparteine to the system and observed a weak asymmetric induction (*ee* up to 29%). The same method of generation of sulfenate anion from β -sulfinyl esters was used by Madec, Poli, and co-workers, who connected it with palladium-catalyzed allylic alkylation¹⁰⁹ and arylation.¹¹⁰ Enantioenriched aryl–aryl and aryl–benzyl sulfoxides were prepared by this group by applying palladium catalyst with a chiral ligand.¹¹¹ Josiphos-type derivatives

appeared most efficient in this role (Scheme 10). A pseudodimino process of palladium-catalyzed arylation of

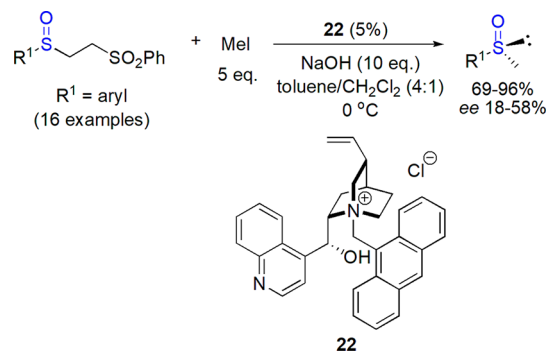
Scheme 10. Stereoselective Preparation of Sulfoxides via Palladium-Catalyzed Arylation of Sulfenate Anion with Josiphos-Type Ligand¹¹¹



anions obtained from allylic sulfoxides was also described.¹¹² The achievements by Poli, Madec, and co-workers in the field were summarized in a short review published in 2010.¹¹³

Perrio's group focused their attention on a diverse approach involving the use of phase-transfer reagents serving both as catalysts and chirality source.^{114,115} *Cinchona* alkaloid-based ammonium salt was found optimal for this task; it was applied in a two-phase system (aqueous NaOH/toluene–dichloromethane mixture), sulfinyl sulfone served as a starting material, and methyl iodide as an electrophile. The yields were high (up to 96%), but the enantioselectivity was moderate (up to 58% *ee*, Scheme 11).

Scheme 11. Chiral Phase-Transfer Catalyst **22 in Synthesis of Aryl Methyl Sulfoxides¹¹⁴**

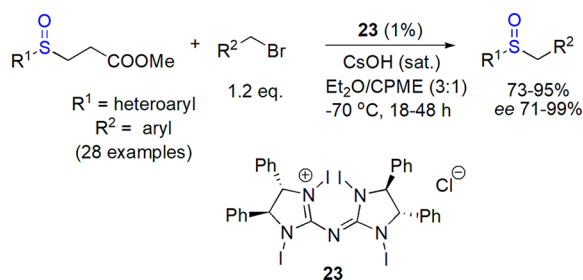


An improvement of methodology based on chiral phase-transfer catalyst was introduced by Zong et al., who described a highly enantioselective alkylation of sulfenate anions bearing heteroaryl substituents in the presence of novel halogenated chiral pentanidium salts (Scheme 12).¹¹⁶ The reaction was performed in cyclopentyl methyl ether or diethyl ether and concentrated aqueous cesium hydroxide; yields and enantioselectivities, particularly for benzyl derivatives, were high (up to 99% *ee*).

Another report from Perrio's group explored a possibility of sulfenate anion generation by pyrolysis of *tert*-butyl sulfoxides followed by the action of K₃PO₄ as a base and palladium-catalyzed coupling with aryl halides or triflates.¹¹⁷ Induction of chirality in this process was only studied with a planar-chiral racemic substrate, for which 50% *de* was observed.

Also other research teams contributed to the development of chiral sulfinate methodology. Schwan and co-workers investigated mainly diastereoselective alkylations.^{118,119} Nolan and

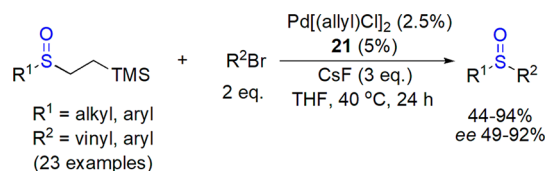
Scheme 12. Use of Iodinated Pentanidium Salt **23** as Phase-Transfer Agent for Preparation of Optically Active Benzyl Heteroaryl Sulfoxides¹¹⁶



co-workers published their improvement to the existing methodology, which suffered from the limited availability of activated sulfoxides required for anion generation and the need of using aryl iodides.¹²⁰ To overcome these drawbacks, they applied palladium complexed with *N*-heterocyclic carbene (NHC) as a precatalyst and observed a direct *S*-arylation of nonactivated aryl sulfoxides by aryl chlorides and bromides. The reaction was not performed in the asymmetric variant.

Walsh and co-workers studied palladium-catalyzed arylations of benzylic sulfoxides.^{121,122} Later on, they concentrated their efforts on finding mild conditions for generation of sulfenate.^{123,124} In their preparation of enantioenriched aryl-aryl sulfoxides, sodium *tert*-butoxide was chosen as a base, and the chiral catalyst was formed in situ from Pd(dba)₂ and enantiopure ferrocene-based bis-phosphine **21**.¹²⁵ Nineteen sulfoxides were prepared, including these bearing heteroaryl groups, in 73–98% yield and 70–95% *ee*. An elegant route to two enantiomers of 3-quinolino 6-quinolino sulfoxide was proposed using the same catalytic system and regioisomeric starting materials. As an extension of their studies, Walsh and co-workers described the use of CsF to generate sulfenate anions and their Pd-catalyzed reaction with alkenyl and aryl bromides (Scheme 13).¹²⁶ Ferrocene-based chiral phosphine

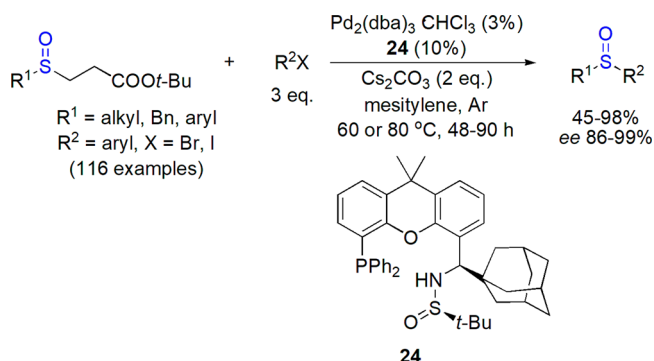
Scheme 13. Enantioselective Reaction of Sulfenate Anions with Aryl and Alkenyl Bromides¹²⁶



ligand **21** and [Pd(allyl)Cl]₂ as a palladium source were efficient in the process affording various enantioenriched (49–92% *ee*) sulfoxides in 44–94% yield.

Aryl-aryl, but also alkyl- and benzyl-aryl sulfoxides were enantioselectively prepared by Zhang and co-workers via arylation of sulfenate anions catalyzed by palladium complexes.¹²⁷ Among various chiral phosphine ligands tested, optimum results were obtained for a new xanthene-based phosphine derivative (*R,R*_S)-**24** bearing 1-adamantyl and sulfonamide moieties. Cs₂CO₃ was used as a base, Pd₂(dba)₃·CHCl₃ as a palladium source, and mesitylene as a solvent (Scheme 14). The versatility of the system was demonstrated by the synthesis of over 100 different sulfoxides, including sulindac, in most cases with enantiomeric excess higher than 90%. A possibility of scaling-up of the protocol was also shown.

Scheme 14. Palladium-Catalyzed Preparation of Sulfoxides Reported by Zhang and Co-workers¹²⁷



Although palladium-catalyzed reactions of sulfenate anions were commonly performed, protocols in which this noble metal was not used were described as well. A CuBr₂-catalyzed reaction of sulfenate anions generated from sulfoxide ester by cesium carbonate with benzyl radicals formed from arenes by *tert*-butyl perbenzoate was developed by Bolm and co-workers.¹²⁸ Transition metal-free arylations were also reported by this group; they obtained racemic aryl-aryl and alkyl-aryl sulfoxides from β-sulfinyl ester and diphenyliodonium triflate with KOH as a base in a water-toluene biphasic system at room temperature.¹²⁹

In a search for the cheaper methodology for sulfoxide synthesis under milder conditions, Zhang's group developed a transition metal-free protocol of arylation of sulfenate anions.¹³⁰ Aryl or alkyl sulfenate anions were generated at room temperature and reacted with diaryliodonium salts. A variety of aryl-aryl and alkyl-aryl sulfoxides were prepared in 62–91% yield. A possibility of scaling-up the reaction was demonstrated; however, it was not applied in the enantioselective preparation of sulfoxides. Racemic alkynyl sulfoxides were prepared by Waser and co-workers in an efficient metal-free method using ethynyl benziodoxolone (EBX) reagents to trap sulfenate anions.¹³¹

Synthetic methods based on reactions of sulfenate anions allow for the preparation of a variety of chiral sulfoxides, and in many cases yields and enantioselectivities are excellent. Despite of certain drawbacks (alkyl-alkyl sulfoxides cannot be prepared directly), these routes should be treated as an important alternative way of C–S bond formation for Andersen's method based on nucleophilic substitution.

3.2. Biological Preparations

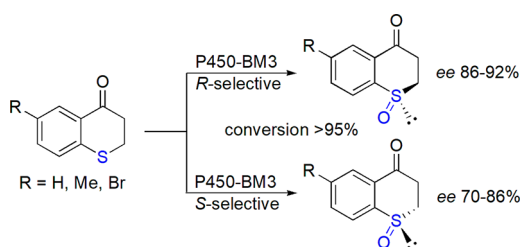
Biotechnological methods of preparation of chiral sulfoxides provide an interesting alternative to purely chemical systems. In most cases, oxidation with enzymes results in high enantioselectivity and turnover number. Possible drawbacks are connected mainly with sensitivity of biocatalysts and, sometimes, their wide substrate scope. A longer discussion can be found in our previous review;¹ in 2018, sulfoxidations with biological systems were also summarized.¹³²

Two main approaches to enzymatic synthesis of optically active sulfoxides can be distinguished. Whole-cell preparations are operationally simpler and do not require addition of cofactors, although the nature of active catalytic species is not certain. Not surprisingly, the majority of recent reports in this area concern the use of bacteria or fungi for sulfoxidation.^{133–140} However, the use of isolated enzymes for enantioselective oxidation of sulfides in the past decade was

also described by several groups.^{141–144} Examples include monooxygenases, dioxygenase, and peroxidase.

Several research groups reported on the enantioselective oxidation of sulfides catalyzed by appropriately modified enzymes into which metal cofactors were introduced. Such artificial metalloenzymes were based on normally redox-innocent transport protein¹⁴⁵ or bovine serum albumin.^{146,147} In another approach, appropriately designed mutations in the heme pocket of dye-decolorizing peroxidase resulted in introduction of its ability to catalyze oxidation of sulfides with high conversion and enantioselectivity (both up to 99%).¹⁴⁸ Among the latest biocatalytic stereoselective preparations of sulfoxides, asymmetric sulfoxidation of 1-thiochroman-4-one derivatives by cytochrome P450-BM3 monooxygenase was described by Reetz and co-workers (Scheme 15).¹⁴⁹ Directed evolution allowed increasing of the stereo-

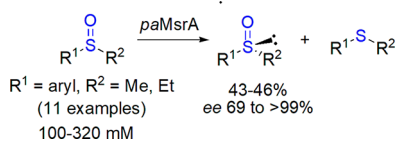
Scheme 15. Sulfoxidation of Thiochromanone Derivatives by Cytochrome P450-BM3 Variants Obtained through Directed Evolution¹⁴⁹



selectivity (*ee* increased from 50% for the wild-type enzyme to 86–93%) and even to reversing of the stereochemical preference.

Enzymes can be used also for the reductive resolution of racemic sulfoxides. Electrochemical regeneration of DMSO reductase applied in such a process was described by Chen et al.¹⁵⁰ Methionine reductase was also exploited by Chen and co-workers; newly identified homologues tolerated various substrates at high concentration and led to ca. 50% yield (maximum value for resolution) and >99% *ee* (Scheme 16).^{151–153}

Scheme 16. Reductive Resolution of Alkyl Aryl Sulfoxides by Methionine Reductase *paMsrA*¹⁵³



4. STEREOSELECTIVE SYNTHESIS OF SULFINATES

Esters of sulfinic acid $RS(O)OR'$ have been treated mainly as valuable synthetic intermediates for other sulfinyl derivatives. A relatively easy preparation of these configurationally stable derivatives bearing a chiral R' fragment followed by separation of diastereomers allows their transformation into enantiomerically pure sulfoxides and other derivatives. Methods of preparation and major applications of sulfinates were reviewed in book chapters.^{11,13} Consequently, in this section, only a short overview of older contributions will be presented, with the stress on the possible diverse synthetic routes.

4.1. S=O Bond Formation

Stereoselective sulfoxidation as the method of preparation of optically active sulfinates has not gained popularity in comparison to other approaches, which make use of more available starting materials, are operationally simpler and more efficient. The attempts of enantioselective reactions of sulfinates with chiral oxidants (e.g., peroxocamphoric acid¹⁵⁴) or catalytic oxidation systems (Kagan's method¹⁵⁵) were not particularly encouraging (maximum *ee* of 36% was reached).

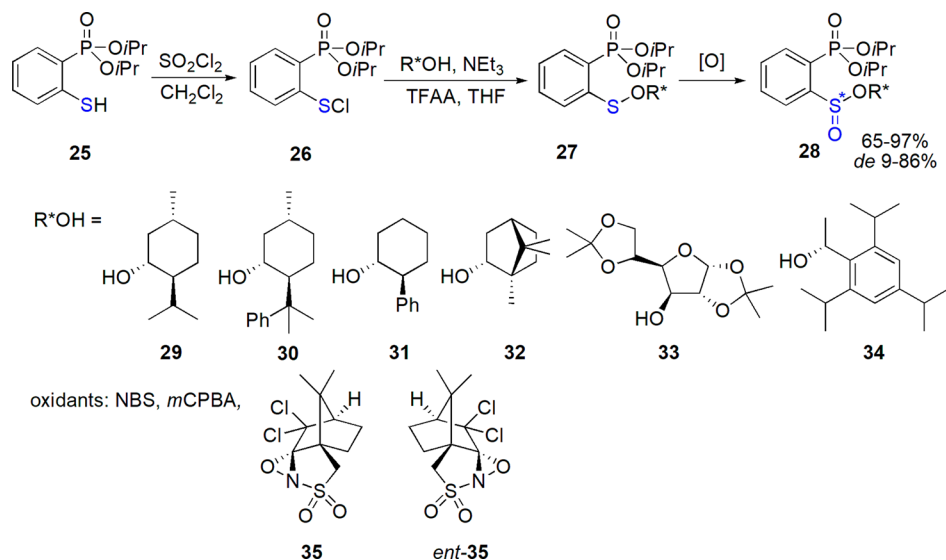
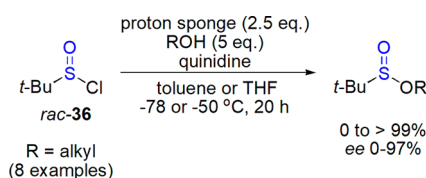
Diastereoselective oxidation of benzenesulfinates bearing a phosphonate group at the *ortho*-position leading to the corresponding sulfinates was investigated by Vazeaux, Drabowicz, and their co-workers.¹⁵⁶ Starting sulfinates **27** were obtained in the reaction of chiral alcohols with sulfinyl chloride **26** (in turn prepared from thiol **25**, Scheme 17). Menthyl derivatives were oxidized with tested oxidants with high yield and variable diastereoselectivity (up to 76% *de* for NBS), and the direction of asymmetric induction could be changed if the appropriate enantiomer of chiral oxaziridine was applied. Among other chiral alcohols, 8-phenylmenthol **30** and *trans*-2-phenylcyclohexanol **31** led to reasonable results (also for (*R*)-Greene's alcohol **34**, and one of enantiomers of Davis' oxaziridine **35** 86% *de* was noted, while for the other enantiomer *ent*-**35** *de* = 9% and a reversed stereochemical preference was found).

4.2. S–O Bond Formation

The first successful preparation of optically active sulfinates was achieved by Phillips in 1925, who obtained alkyl *p*-tolylsulfinates by transesterification.¹⁵⁷ Since that time, numerous protocols have been described with chirality transfer from reactants (diastereoselective preparations) or auxiliaries used (enantioselective synthesis). The latter methods often utilized chiral tertiary amines, which were used in the reaction of racemic sulfinyl chlorides and achiral alcohols. As an example, preparation of sulfinates through enantioselective dynamic kinetic resolution of racemic *tert*-butanesulfinyl chloride was achieved by Ellman and co-workers.¹⁵⁸ This compound was subjected to the reaction with benzyl alcohol in the presence of proton sponge and a chiral base (*N*-methyl imidazole-containing octapeptide) led to the best results (99% yield, 80% *ee*, for only 0.5% of the catalyst). This catalyst was later replaced by relatively cheap and available *Cinchona* alkaloids, and the method extended over other (mainly benzyl) alcohols (Scheme 18).¹⁵⁹ Simultaneously, highly enantioselective preparation of arenesulfinates from racemic sulfinyl chlorides and achiral alcohols assisted by *Cinchona* alkaloids was reported by Shibata, Toru, and co-workers (up to 99% *ee*).^{160,161}

A variety of chiral alcohols have already found use in diastereoselective preparation of sulfinates. Menthol **29** has often been applied;¹⁶² Andersen's method of stereoselective synthesis of sulfoxides is based on the crystalline (1*R*,2*S*,5*R*,5*S*)-(-) menthyl *p*-toluenesulfinate.¹⁶³ Diacetone- α -D-glucose (DAG), a sugar-derived alcohol **33**, was also identified as a particularly useful auxiliary (both are commercially available).¹⁶⁴ Cholesterol, ephedrine, and various sugar alcohols including cyclodextrin should be also mentioned.

Mikołajczyk, Drabowicz, and co-workers thoroughly analyzed the stereospecificity of substitution at a stereogenic sulfur atom. Conversion of enantiomerically enriched sulfinamides to

Scheme 17. Diastereoselective Oxidation of Sulfenates Bearing a Phosphonate Group¹⁵⁶Scheme 18. Enantioselective Preparation of Sulfonates from Racemic Sulfinyl Chlorides in the Presence of Quinidine¹⁵⁹

sulfonates in the presence of strong acids was shown to proceed with a predominant inversion of configuration.¹⁶⁵ (*S*)-*N,N*-Diethyl *p*-toluene sulfinamide was first prepared from the corresponding menthyl sulfinate and Et_2NMgBr . Its reactions with alcohols were found to proceed with medium to excellent stereospecificity, dependent mainly on the structure of alcohols; a complete inversion was observed for primary ones, and the steric hindrance exerted by secondary and tertiary alcohols resulted in partial racemization. Also, transesterification of sulfonates with 2-propanol in the presence of strong acids was primarily shown to proceed with a predominant inversion of configuration, with stereochemical outcome dependent on both sulfinate and acid used (up to 40% *ee*).^{166,167}

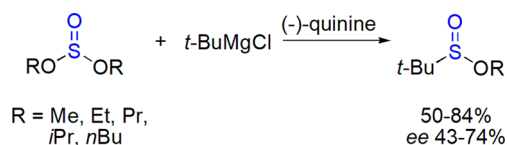
The stereochemistry of conversion of sulfinamides to sulfinate esters was later found to be more complex.¹⁶⁸ Bujnicki et al. investigated the effect of substituents of sulfinamide and the structure of alcohol and found that in certain cases a predominant retention of configuration was observed.¹⁶⁹ It was associated with a combination of sterically hindered alcohol and a bulky leaving amine fragment. Moreover, the stereochemical preference could be changed by addition of inorganic salt to the system while solvent change did not affect much the stereoselectivity. Analysis of reaction kinetics allowed the authors to propose a mechanism of the reaction involving addition, leading to sulfurane intermediates capable of pseudorotation (forced by steric factors).

A novel approach to the preparation of sulfinate esters was introduced by Jacobsen et al.¹⁷⁰ A mixed anhydride was prepared from sodium sulfinate and trimethylacetyl chloride, and reacted with various primary and secondary alcohols in the presence of trimethylamine. Esters were formed in 57–82% yield. Sulfination of nonactivated alcohols with the use of

sulfonyl isocyanides was achieved by Ji et al.¹⁷¹ A double activation was provided by Lewis acid (bismuth(III) triflate) and Brønsted acid (CCl_3COOH). Asymmetric variant of these two protocols was not proposed.

4.3. S–C Bond Formation

Reactions of sulfites and chlorosulfites with organometallic reagents also provided sulfonates with a variable yield and stereoselectivity. Optically active *tert*-butyl sulfonates were prepared from symmetrical dialkyl sulfites and *tert*-butylmagnesium chloride in the presence of chiral amines (the optimal results, *ee* up to 74%, were obtained for *Cinchona* alkaloids, bearing also a hydroxyl group; Scheme 19).¹⁷² An appropriate

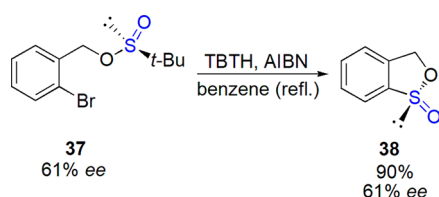
Scheme 19. Preparation of Optically Active Sulfonates from Dialkyl Sulfites in the Presence of Quinine¹⁷²

choice of the auxiliary allowed to prepare both optical antipodes of the product. An alternative method based on a kinetic resolution upon reaction of racemic thiosulfonates with Grignard reagents and quinine was also developed; it allowed preparation of nonracemic sulfonates with nonbulky alkyl or aryl substituents with *ee* up to 33%.

The use of chiral sulfites leading to diastereomeric mixtures of sulfinate products was also described.^{173,174} Kagan's group converted the obtained, purified esters into enantiopure sulfoxides.¹⁷³

An interesting homolytic substitution process in which certain sulfonates under radical conditions (Bu_3SnH , AIBN, heating in benzene) underwent an intramolecular cyclization to give cyclic esters (sultines) was reported by Coulomb et al.¹⁷⁵ An optically enriched starting compound led to the product with a complete inversion of configuration (Scheme 20); the similar conclusion was drawn for the cyclization of chiral sulfinamides. When a new stereogenic center was created, a preference for *trans* configuration was observed

Scheme 20. Stereospecific Radical Cyclization of Enantiopure Sulfinamide¹⁷⁵



and two sultines were formed with a complete diastereoselectivity.

4.4. Other Methods

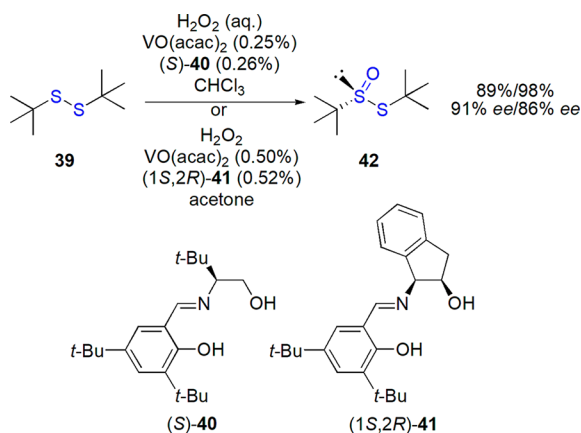
Formation of two bonds in one process was also reported. Sulfinates (but only racemic) were prepared using aerobic, copper-catalyzed reaction of thiols and alcohols.¹⁷⁶ Shyam et al. showed that also disulfides and thiosulfinates could be reacted with benzyl alcohol to give the desired ester, although in lower yield.

The racemic *O*-alkyl alkylsulfonates were resolved using formation of inclusion complexes with β -cyclodextrin.¹⁷⁷ The highest optical purity of 70% was achieved for complexed *O*-isopropyl methylsulfinate.

5. SYNTHESIS OF OPTICALLY ACTIVE THIOSULFINATES

Thioesters of thiosulfonic acid (or disulfide *S*-oxides) belong to chiral sulfinyl compounds exhibiting limited chemical and configurational stability (see section 2). As the increase of steric hindrance exerted by groups connected to sulfur atoms results in the stabilization, majority of studies focused on *tert*-butyl *tert*-butane thiosulfinate **42** (Scheme 21). High-yielding

Scheme 21. Preparation of *tert*-Butane *tert*-Butyl Thiosulfinate Developed by Ellman and Co-workers^{178,184–187}



and enantioselective methods have been developed for its preparation from a cheap and easily available *tert*-butyl disulfide **39**, and thus this thiosulfinate is regarded as a valuable starting material for the synthesis of other enantiopure sulfinyl compounds: sulfinamides, sulfoxides, sulfonates, and others.^{27,178}

Asymmetric sulfoxidation procedures are of particular importance, and they include chemical and enzymatic procedures. Other methods, although less significant and with limited practical use, should not be completely neglected.

5.1. S=O Bond Formation

5.1.1. Chemical Methods. The study on the synthesis of nonracemic disulfide monoxides started in 1960s with the works of Savige and Fava.^{154,179,180} In 1965, Kice and co-workers described an asymmetric oxidation of aryl disulfides to thiosulfinates.¹⁸¹ The use of chiral peroxycamphoric acid led to the optically active product in ca. 60% yield and very low enantioselectivity (ca. 3% ee based on the given specific rotation). Davis' 2-sulfonyloxaziridines were slightly more efficient (14% ee for oxidation of *tert*-butyl disulfide, but only 2% ee for *p*-tolyl derivative),¹⁸² and Kagan's system (*t*-BuOOH/ $\text{Ti}(\text{O-}i\text{Pr})_4/\text{DET}$) allowed to increase the enantiomeric excess to 52%.¹⁵⁵

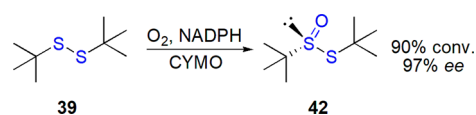
Further improvement was possible after introduction of vanadium Schiff base catalysts. In 1997, Ellman and co-workers developed an enantioselective method of preparation of *tert*-butane *tert*-butyl thiosulfinate **42** by oxidation of the corresponding disulfide **39** with hydrogen peroxide in a biphasic system in the presence of chiral vanadium complex (Schiff base **40** introduced by Bolm and Bienewald¹⁸³ was used, Scheme 21).^{178,184} In subsequent studies, it was proven that slow addition of 30% aqueous H_2O_2 and the use of cosolvent with low miscibility with water (CHCl_3 was found optimal) were of importance for the observed stereoselectivity (up to 91% ee was reached), which is otherwise limited by a nonenantioselective oxidation.¹⁸⁵ Later, change of chiral ligand to the one derived from *cis*-1-aminoindan-2-ol and 3,5-di-*tert*-butylsalicylaldehyde (**41**) allowed to exchange the two-phase solvent system to acetone, and to apply the protocol on a kilogram scale (99% conversion, 85–86% ee).^{186,187} The product could be purified by a simple crystallization and obtained in both enantiomeric forms, depending on configuration of the Schiff base.¹⁸⁷

An enantiopure analogue of *tert*-butylsulfonamide attached to a polystyrene support was also prepared in Ellman's group using a dynamic resolution methodology.¹⁸⁸ Its utility in the enantioselective synthesis of chiral amines and alkaloids was demonstrated.

Other chiral Schiff bases were tested by Ma et al. in vanadium-catalyzed enantioselective oxidation of disulfides by hydrogen peroxide.¹⁸⁹ *tert*-Butane *tert*-butyl thiosulfinate was obtained in 30–93% yield and 4–88% ee when ligands derived from 3,5-di-*tert*-butylsalicylaldehyde and aminoalcohols were applied. Also *para*-tolyl disulfide was oxidized by H_2O_2 under these conditions, albeit in lower yield and enantioselectivity (ee < 40%). Both esterified and reduced derivatives of Schiff bases were found to be inefficient chiral inducers.

5.1.2. Enzymatic Methods. Cyclohexanone monooxygenase was applied by Colonna and co-workers in the asymmetric oxidation of disulfides.¹⁹⁰ An excellent enantioselectivity (97% ee and 90% conversion) was observed only for *tert*-butyl disulfide **37** (Scheme 22), while three other thiosulfinates were obtained in low yield and ee up to 70%, which was attributed to their lower stability and ease of racemization. A regioselective oxidation of sulfur atom

Scheme 22. Oxidation of *tert*-Butyl Disulfide by Cyclohexanone Monooxygenase¹⁹⁰

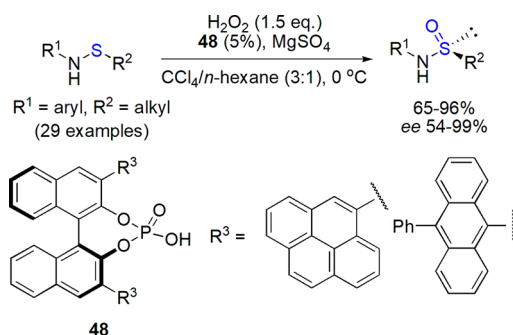


substitution. However, other synthetic routes to these compounds have been reported as well. Sulfinamides and *N*-sulfinylimines can be mutually interconverted without the change of configuration of sulfur; importantly, such conversions can be stereoselective if a new stereogenic center or double bond is formed.

6.1. S=O Bond Formation

Only a few examples of preparation of sulfinamides by oxidation of corresponding sulfenamides were reported. This approach is hindered by a limited scope of available substrates, although they can be prepared, e.g., from thiols, disulfides or sulfonyl halides.²⁰³ Among recent examples, a nonstereoselective oxidation of various sulfenamides by KF/*m*-CPBA system in acetonitrile–water at 0 °C in 82–94% yield was performed by Datta et al.²⁰⁴ The reaction was fast (5–20 min), and overoxidation products were not formed. A recent report by Tang and co-workers on enantioselective oxidation of sulfenamides with hydrogen peroxide mediated by a chiral binaphthyl-based phosphoric acid derivative showed the possibility of preparation of nonracemic sulfinamides via S=O bond formation (Scheme 26).²⁰⁵ Under optimized reaction

Scheme 26. Preparation of Optically Active Sulfinamides by Oxidation of Sulfenamides Catalyzed by Chiral Phosphoric Acid Derivative²⁰⁵

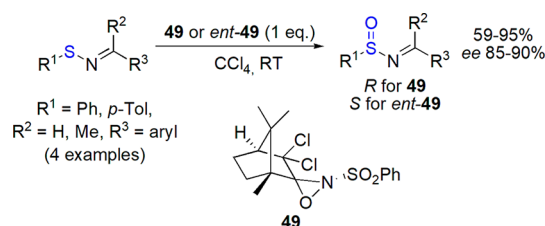


conditions (dichloromethane/35% aqueous H_2O_2 /5% of catalyst/ MgSO_4 additive/0 °C), overoxidation to sulfonamide was not observed, and various derivatives were isolated in 65–96% yield and with high enantioselectivity (in most cases 90–99% ee). A proposed mechanism involved activation of reactants by a catalyst through hydrogen bond formation, and the observed stereochemical outcome was substantiated with DFT calculations of transition states. The prepared sulfinamides were further converted into other compounds from this class (vide infra) and sulfoxides.²⁰⁵

Other attempts involving oxidation of sulfonyl derivatives formed from thiols or disulfides are worth mentioning. *N*-*tert*-Butanesulfinylphthalimide was prepared by treatment of the corresponding sulfonyl derivative (obtained from *N*-bromophthalimide and *tert*-butyl disulfide) with peroxyacetic acid.²⁰⁶ Ring opening under Lewis acid catalysis (samarium triflate was used) followed by the addition of ammonia yielded *tert*-butane sulfinamide. Unfortunately, all attempts to perform the process in a stereoselective manner were unsuccessful. Copper-catalyzed oxidative coupling of thiols or disulfides with amines was reported by Taniguchi.²⁰⁷ Reactions were carried out under air, and the presence of dioxygen was found necessary for the reasonable yield. Only achiral reactants and catalysts were tested.

N-Sulfinylimines were also prepared by enantioselective oxidation of sulfonylimines. In 1997, Davis and co-workers described the use of enantiopure oxaziridines **49** for this purpose and obtained the desired products in 59–95% yield and enantiomeric excess up to 90% (improved to >97% by crystallization, Scheme 27).²⁰⁸ Kagan's method was less efficient (80% yield, 13% ee). As preparation methods based on nucleophilic substitution were found more promising, this approach was abandoned.

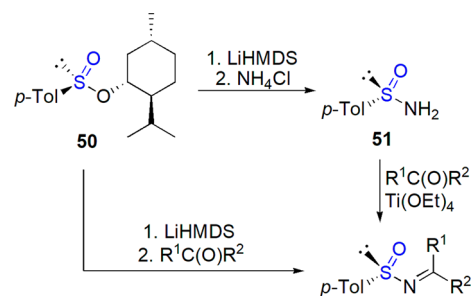
Scheme 27. Enantioselective Oxidation of Sulfonylimines with Oxaziridines²⁰⁸



6.2. S–N Bond Formation

Sulfinamides are conveniently obtained from other trisubstituted sulfonyl derivatives. Nonracemic sulfonates have been used in such conversions for over half of a century. In 1968, Colonna, Giovini, and Montanari prepared optically active *p*-toluenesulfinamides from the corresponding menthyl sulfinate and dialkylaminomagnesium bromides.²⁰⁹ The reaction proceeded with an inversion of configuration. Later on, this auxiliary introduced by Andersen,¹⁶³ now commercially available, was used in the synthesis of other sulfinamides, mainly with the use of lithium amides. Davis and co-workers reacting this sulfinate with lithium amide followed by addition of aldehyde or ketone obtained the corresponding *N*-sulfinylimine with high enantioselectivity (Scheme 28).^{208,210,211}

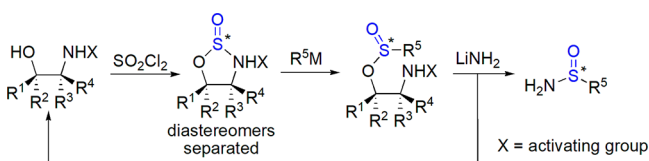
Scheme 28. Use of Menthyl Sulfinate in Stereoselective Preparation of Sulfinamides and Sulfinylimines³⁷



In 2002, Senanayake's group introduced a versatile and stereoselective method for the synthesis of sulfonyl compounds with the use of *N*-activated oxathiazolidine oxides (Scheme 29).^{212,213} Their subsequent reactions with organometallic compounds and lithium amide led to a variety of tertiary alkyl and aryl sulfinamides.¹⁵ Reaction of *N*-acylated 1,2,3-oxathiazolidine-2-oxide with Grignard compounds was also used to prepare chiral sulfinamides by Qin et al.²¹⁴

Nucleophilic substitution of enantioenriched *tert*-butane *tert*-butyl thiosulfinate (see Section 5.1) was established by Ellman and co-workers as a very convenient route to *tert*-butyl

Scheme 29. Senanayake's Approach to Chiral Sulfinamides¹⁵



sulfoxides and, in particular, *tert*-butanesulfinamide (lithium amide was used, Scheme 30).^{178,184,186,187} No racemization during this step was observed, and the product could be obtained in multigram amounts. Compound **52** was identified as a valuable precursor for a range of enantiomerically pure *tert*-butanesulfinyl derivatives and, after removal of sulfinyl auxiliary, chiral nitrogen-containing compounds. As an example, reaction with aldehydes provided *N*-sulfinylimines; Grignard addition and cleavage with acid yielded optically active branched amines.¹⁷⁸

Various enantiomerically pure aldimines were prepared in a one-step condensation of sulfinamide **52** with aldehydes in the presence of dehydrating agents.²¹⁵ Also, ketimines were formed with a significant *E/Z* preference from respective ketones when Ti(OEt)₄ was applied as a Lewis acid (Scheme 30).^{215,216} The procedure was later optimized, and tetrahydrofuran and cyclopentyl methyl ether (preferred in the case of more challenging ketones) were identified as optimal solvents.²¹⁷ The possibility of recovering the chiral auxiliary was investigated as well.²¹⁸ After the cleavage of imine with HCl, fast racemizing sulfinyl chloride was separated from chiral amine hydrochloride. The dynamic chiral resolution of this sulfinyl derivative treated with ethanol in the presence of quinine and proton sponge (both could be reused as well) in cyclopentyl methyl ether led to *tert*-butanesulfinamide in high yield and enantiomeric purity (up to 87% *ee*).

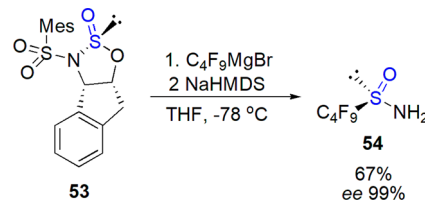
Alternatively, reduction of ketimines with NaBH₄ could be performed to give sulfinamides (66–86% yield, 80–94% *de*).²¹⁹ Both enantiomers of amine were obtained with high *ee*, with configuration dependent on the choice of reducing agent (NaBH₄ vs L-selectride).²²⁰ Addition of alkyl, aryl, alkenyl, and allyl carbanions to aldimines and ketimines was performed, and the resulting sulfinamides were cleaved by HCl in methanol, yielding a variety of enantioenriched branched amines.²²¹ Other examples of the use of *tert*-butylsulfinyl auxiliary in asymmetric synthesis by Ellman's group included preparation of (among others) amino acids,^{222–224} amino alcohols,^{225–227} cyclic amines,^{228,229} unsaturated amines,^{2,230,231} nitriles,²³² aminophosphonates,²³³ aminoboronates,²³⁴ and total synthesis of natural products.^{235,236}

Novel urea and thiourea organocatalysts bearing *N*-sulfinyl fragment as a chirality source and an acidifying agent were developed in Ellman's laboratory.²³⁷ They were obtained in condensation of isocyanates or isothiocyanates with *tert*-

butanesulfinamide and used in asymmetric aza-Henry reaction. High stereoselectivity was observed for derivatives also containing aminoindanol moiety. Other sulfinylureas were found efficient in enantioselective additions to nitroalkanes.^{238–242} Also enantiopure *N*-sulfinyl prolinamide was prepared via deprotonation of *tert*-butanesulfinamide and reaction with (*S*)-proline methyl ester, and its high efficiency in aldol reaction was demonstrated.²⁴³ Ellman's group applied enantiopure *tert*-butanesulfinamide **52** to the preparation of chiral ligands. C₂-Symmetric bis(*N*-sulfinylimine) derivatives and bis(sulfinyl)imidoamidine (SIAM) were tested in copper- and zinc-catalyzed asymmetric Diels–Alder reaction (up to 98% *de* and up to 98% *ee*),²⁴⁴ while *N*-sulfinylimine ligands bearing phosphine moiety were used in palladium-catalyzed allylic alkylation (yielding up to 96% *ee*),²⁴⁵ and iridium-catalyzed hydrogenation of stilbenes (up to 94% *ee*).²⁴⁶

Later, Ellman and co-workers developed an improved synthesis of more electrophilic perfluorobutanesulfinamide **54** accomplished with the use of Senanayake's 2-aminoindanol-derived sulfinyl transfer reagent²¹³ and a suitable Grignard reagent prepared from EtMgBr and C₄F₉I.^{247,248} The sulfinate intermediate was treated with amine nucleophiles; NaHMDS led to the highest yield. The sulfinamide could be prepared on a gram scale in 67% yield and 99% *ee* using this two-step sequence (Scheme 31). Its condensation with ethyl glyoxylate

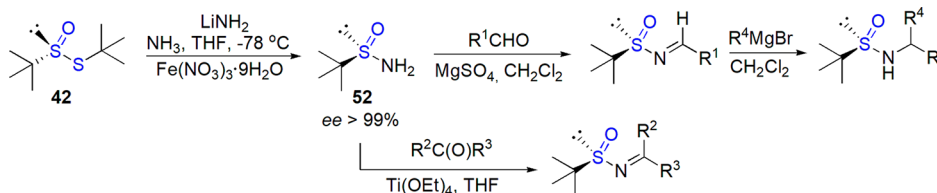
Scheme 31. Preparation of Perfluorobutanesulfinamide²⁴⁸

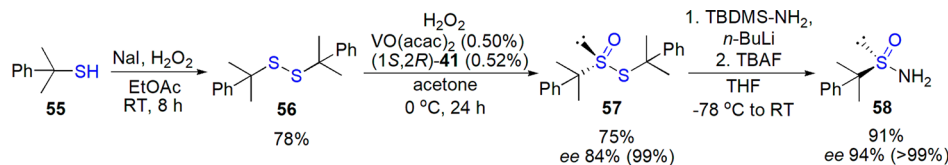


provided *N*-sulfinyl imine ester, which was used in asymmetric transformations (Rh(III)-catalyzed C–H bond functionalization, aza-Diels–Alder reaction).^{247,249}

An alternative for *tert*-butane sulfinamide for the application in asymmetric synthesis was introduced by Li and co-workers.²⁵⁰ The novel auxiliary combined properties of *para*-tolyl- (aromatic chromophore) and *tert*-butyl-substituted (stability) derivatives. (*R*)-2-Phenyl-2-propyl sulfinamide **58** was prepared in four steps starting from the respective thiol, with H₂O₂/VO(acac)₂/chiral Schiff base oxidation of disulfide as a key step for chiral induction (85% *ee* was further improved to >99% by washing with *n*-hexane, Scheme 32). This time, amidation of thiosulfinate was not straightforward and required the use of *tert*-butyldimethylsilyl amine (TBDMS-NH₂) followed by deprotection. Reaction of aldimines and ketimine derived from this sulfinamide with allylmagnesium bromide

Scheme 30. Preparation of Enantiomerically Pure *tert*-Butanesulfinamide and Its Transformations^{178,186,187}

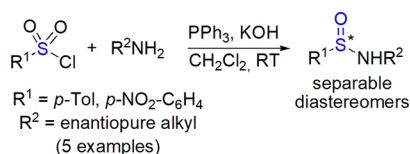


Scheme 32. Preparation of Sulfinamide 58 by Li and Co-workers²⁵⁰

proceeded with high diastereoselectivity, additionally increased by simple (group-assisted) purification.

Sulfinyl chlorides are less convenient in the stereoselective synthesis of sulfinamides due to their instability and configurational lability. However, several enantiopure arylsulfinamides were obtained by Zhu and Shi by a spontaneous crystallization of products of reaction of sulfinyl chlorides with (*R*)-*N*-benzyl-1-phenylethanamine.²⁵¹ (*R,S_s*)-Diastereomers were isolated from the reaction mixture as solids in ca. 30% yield, while mother liquor was enriched in (*R,R_s*) isomers (50–58% *de*) and could be separated by chromatography. Enantiopure sulfinates were prepared from the corresponding sulfinamides using methanol and boron trifluoride etherate and later converted to primary (*S_s*)-sulfinamides (which could not be obtained directly from tertiary counterparts).

A protocol for synthesis of sulfinamides from amines and sulfonyl chlorides reduced in situ with phosphine was developed by Harmata and co-workers.²⁵² The reaction showed broad substrate scope, although the use of chiral amines did not result in diastereoselection. We observed modest diastereoselectivity (up to 17% *de*) when we reacted tosyl and nosyl chlorides with enantiomerically pure amines (both commercially available and bicyclic derivatives prepared in our laboratory) under modified Harmata's conditions (Scheme 33).²⁵³ Products were isolated as single stereoisomers by chromatographic separation.

Scheme 33. Preparation of Chiral Epimeric Secondary Sulfinamides from Sulfonyl Chlorides and Enantiopure Amines²⁵³

Tang and co-workers converted *N*-phenyl *tert*-butane sulfinamide prepared by enantioselective oxidation of its sulfenyl counterpart (see section 6.1) into other derivatives (for which direct oxidation was not successful) via *N*-protection and nucleophilic substitution with primary amines.²⁰⁵ While yields were moderate (55–70%), almost complete inversion of configuration was observed (94–97% *ee*). Copper-catalyzed transamidations of primary sulfinamides with *O*-benzoylhydroxy-substituted secondary and primary amines were performed by Bolm and co-workers in 61–83% and 24–79% yield, respectively.²⁵⁴ The use of enantiomerically pure amines led to 1:1 mixtures of diastereomers, which were separated by column chromatography to yield enantiopure sulfinamides.

N-Bromosuccinimide was used by Wei and Sun to activate *tert*-butylsulfinyl group in sulfoxides.²⁵⁵ Reaction with nitrogen, oxygen, or carbon nucleophiles led to sulfinamides, sulfinates,

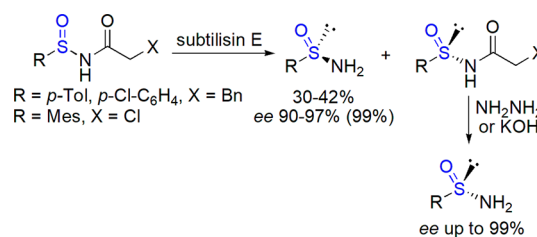
and other sulfoxides, respectively, generally in high yield. Only racemic compounds were prepared.

6.3. Dealkylation/Dearylation of Sulfoximines

Enantiopure sulfinamides were also obtained by dealkylation of sulfoximines with retention of configuration. First examples of this reactivity were reported in 1971. Schroeck and Johnson performed reduction with aluminum amalgam,²⁵⁶ Tsujihara et al.²⁵⁷ conducted pyrolysis of alkyl-substituted derivatives, and Williams et al. carried out tosylation.²⁵⁸ Schroeck and Johnson also observed a similar conversion (reductive elimination of $N(\text{CH}_3)_2$ or OPh group, respectively) of sulfonimidamides and sulfonimidates.²⁵⁶ More examples of stereoselective transformations of sulfoximines to sulfinamides caused by various triggers can be found in a recent review by Wiezorek et al. devoted to degradation of sulfoximines.³⁰ These reactions, though interesting for the study of stability and stereochemistry of involved derivatives, cannot be regarded as useful preparative routes for optically active sulfinamides.

6.4. Other Methods

Various methods based on transformation of substituents or involving rarely used sulfur reagents were described. A biocatalytic route to optically active sulfinamides was developed by Kazlauskas and co-workers.²⁵⁹ Hydrolysis of racemic *N*-chloroacetyl and *N*-dihydrocinnamoyl arylsulfinamides were catalyzed by subtilisin E overexpressed in *Bacillus subtilis*, providing mainly (*R*) primary sulfinamides (Scheme 34). Their (*S*) counterparts could be formed after non-

Scheme 34. Biocatalytic Deracemization of *N*-Acyl Sulfinamides²⁵⁹

enzymatic hydrolysis of unreacted acylated sulfinamides. Yields were moderate, but an excellent enantioselectivity was observed in most cases. Gram-scale resolutions were also performed, and synthetically useful auxiliaries were obtained with 95–99% *ee* (after recrystallization). Enantioselective *N*-arylation of racemic primary sulfinamides with aryl iodides catalyzed by chiral Cu(I) complexes was described by Liu et al.²⁶⁰ Under optimized conditions, substituted sulfinamides were obtained in variable yield (37–93%) and medium stereoselectivity (5–60% *ee*).

Inspired by the rapid development in the sulfenate anion application in the preparation of sulfoxides (see section 3.1.2), Dai and Zhang decided to study electrophilic amidation of these anions generated from β -sulfinyl esters.²⁶¹ Optimization

of reaction conditions revealed CuI/byby as the best catalytic system, lithium *tert*-butoxide as the most efficient base, with toluene as solvent. A variety of aliphatic and aromatic sulfinamides were prepared in 44–96% yield. The reaction could be performed in a gram scale; its asymmetric variant, however, was not described.

Wang et al. reported on a cross-coupling of arylboronic derivatives with aminosulfur trifluorides (DAST reagents) to afford diverse aromatic sulfinamides in yields up to 92%.²⁶² The use of enantiopure tocopherol-derived boronic acid resulted in the 1:1 mixture of epimers; all other compounds were racemic.

7. STEREOSELECTIVE SYNTHESIS OF SULFOXIMINES

About 60 years ago, Bentley and co-workers identified a novel sulfinyl compound from the treatment of protein with nitrogen trichloride.^{263–266} They were able to separate diastereomers of methionine sulfoximine and prepared other sulfoximines from sulfoxides using HN_3 .^{267,268} Since then, these stable monoaza analogues of sulfones have been recognized as valuable auxiliaries, ligands, and catalysts in asymmetric synthesis, building blocks in pseudopeptides and, in the recent years, also as drug candidates.

Sulfoximines share many properties with sulfoxides: they are chemically and (if chiral), also configurationally stable. They bear sulfinyl group capable of high induction of chirality. However, the presence of a nucleophilic imine nitrogen atom which can participate in hydrogen bonding or metal coordination makes them special.

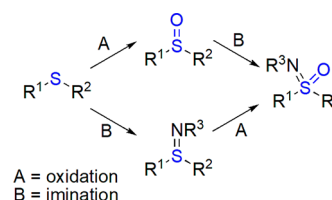
A recent growing interest in the synthesis and utilization of nonracemic sulfoximines prompted several research groups to write reviews, general, or focused on specific types, transformations, and applications. Bolm and co-workers prepared a chapter in the book on organosulfur chemistry.¹⁴ Articles by this group dealt with properties and applications of fluorinated derivatives,²⁶⁹ methods of sulfur atom imidation of sulfides and sulfoxides,²⁷⁰ and routes of degradation of sulfoximines.³⁰ The importance of these compounds in the area of drug discovery is highlighted in articles by Bolm's group²⁷¹ and Lücking et al.^{272,273} Harmata and Hong reviewed the chemistry of 2,1-benzothiazines, cyclic sulfoximines studied thoroughly by Harmata's group.²⁷⁴ Bull, Degennaro, and Luisi decided to highlight the progress made in preparation of *N*-unsubstituted derivatives.²⁷⁵ Two reviews written in Chinese on synthesis and applications of sulfoximines can be added to the list.^{276,277}

In this section we shall focus on showing diverse synthetic strategies and efficient routes to variously substituted derivatives. In their review published in 2000, Reggelin and Zur stated that the most chemistry of optically active sulfoximines emanated from several “key intermediates”, mainly *S*-methyl-*S*-phenyl-substituted compounds resolved through formation of diastereomeric salts with 10-camphor-sulfonic acid.^{278,279} Though resolutions (mainly kinetic) still remain important (see section 7.5), enantiomerically pure or enriched compounds can be now prepared using a variety of pathways developed in the recent years.

7.1. S=O Bond Formation

Typical preparations of sulfoximines start from prochiral sulfide. Oxidation and imidation steps can be performed in different sequence (Scheme 35). However, introduction of NH or NR fragment into a sulfoxide was recognized as more attractive strategy than the oxidative transformation of

Scheme 35. Possible Pathways for Preparation of Sulfoximines from Sulfides



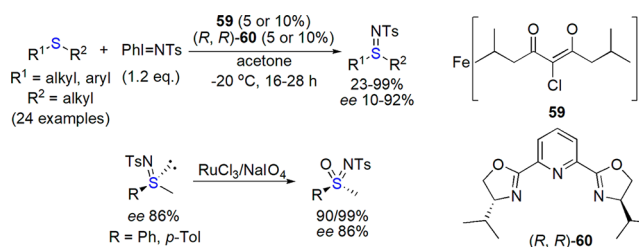
sulfilimines (sulfilimides). They are relatively stable toward oxidation, and access to sulfoximines requires strong oxidizing agents, such as potassium permanganate, alkaline hydrogen peroxide, etc.²⁸⁰ As far as we know, chiral oxidants have not been used for this transformation. However, chirality transfer is possible as sulfilimines can be obtained as single enantiomers.²⁸¹ Stereochemistry of oxidation of *N*-sulfonylsulfilimines with alkaline solution of KMnO_4 was studied by Kresze and Wustrow, who observed retention of configuration.²⁸² Long reaction times are sometimes required for this oxidant, and yields can be small (for instance, only 10% for oxidation of thiane-derived sulfilimine).²⁸³ However, permanganates are still chosen for certain preparations. For example, sulfilimines bearing perfluoroalkyl substituents were prepared from appropriate sulfoxides by treatment with nitriles; oxidation with KMnO_4 led to the corresponding racemic sulfoximines, either bearing *N*-acyl or *NH* fragment (depending on the environment).²⁸⁴

An improvement was introduced to the method of preparation of the crop protection agent sulfoxaflor (known also under trade name Isoclast active).²⁸⁵ The *N*-CN sulfilimine was prepared from pyridine sulfide treated with iodobenzene diacetate and H_2NCN in acetonitrile and then oxidized. Various oxidation methods were tested, including $\text{RuCl}_3/\text{NaIO}_4$ combination, but for practical and economic reasons, 40% aqueous NaMnO_4 was chosen. As the insecticide is used as a mixture of isomers (two stereogenic centers are present in the molecule), stereoselectivity of the reaction was not studied.

Various sulfoximines were also prepared by oxidation of sulfilimines with ruthenium tetroxide, generated in situ from NaIO_4 and substoichiometric amounts of RuO_2 .^{286,287}

Racemic *N*-cyanosulfilimines, prepared by Bolm and co-workers from sulfides and cyanogen amine, were easily oxidized with *m*-CPBA into corresponding sulfoximines, and the cyano group was cleaved by treatment with trifluoroacetic acid and methanolysis.²⁸⁸ Later on, the enantioselective sulfilimination of sulfides with $\text{PhI}=\text{NTs}$ catalyzed by transition-metal chiral complexes and bis-oxazoline ligands was studied (Scheme 36).²⁸⁹ The best results (yield reaching

Scheme 36. Enantioselective Imidation of Sulfides and Enantiospecific Oxidation of Sulfilimines²⁸⁹



99%, up to 82% *ee*) were noted for iron(III) acetylacetonates used as catalyst precursors. Oxidation of the obtained *N*-tosylsulfilimines with NaIO₄/RuCl₃ or *m*-CPBA led to optically active sulfoximines with high enantioselectivity, from which a protecting group could be easily removed.

A chiral *N*-mesyloxycarbamate caused a stereoselective amination of thioethers in the presence of a chiral dirhodium(II) carboxylate catalyst to yield the corresponding sulfilimines.^{290,291} The possibility of preparation of sulfoximine through oxidation of sulfilimine with NaIO₄ with RuCl₃ as a catalyst was demonstrated; removal of chiral auxiliary with zinc in acetic acid yielded *NH*-sulfilimine as a single enantiomer (94%). Lebel and co-workers also applied iron catalyst in a similar preparation.²⁹² Increase of yield was possible thanks to application of continuous flow technology. 1-Butylimidazole was used as a base to form 1-butylimidazolium mesylate as an ionic liquid byproduct.

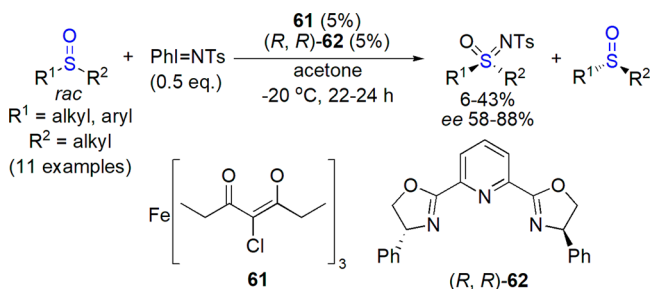
Alternatively, chlorination can be applied to increase oxidation state of sulfur atom. Furukawa, Oae, and co-workers found that alkaline hydrolysis of *N*-chlorinated sulfilimines resulted in formation of *NH*-sulfoximines in high yields (up to 95%).^{293,294} *N*-Chlorosuccinimide and sodium hypochlorite were used as chlorinating agents for *NH*-sulfilimine; both reaction steps were shown to proceed with a retention of configuration.

7.2. S=N Bond Formation

In a 2015 article by Bizet, Hendriks, and Bolm, methods for preparation of sulfoximines by imidation of sulfoxides (and sulfimides from sulfides) were comprehensively reviewed.²⁷⁰ Efficiency of various imidating agents: *N*-haloamides and similar compounds (chloramine T, MSH), aziridine derivatives, dioxazolones, azides, and iminoiodinanes was compared. Uncatalyzed reactions typically gave lower yields in comparison with protocols engaging metal complexes: copper, silver, rhodium, ruthenium, and iron. Most imidations of sulfoxides were performed with racemic reactants. However, several research groups checked the stereospecificity of the reaction using enantiopure or enantiomerically enriched sulfoxide as a starting material. In each case, a complete retention of configuration was observed. An interesting example of kinetic resolution from Bolm's laboratory is noteworthy: racemic sulfoxides were treated with PhI=NTs in the presence of Fe(acacCl)₃ **61** and a chiral bis-oxazoline ligand **62**, yielding sulfoximines with up to 88% *ee* (and up to 43% yield, Scheme 37).²⁹⁵

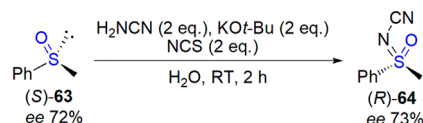
Among recent contributions from Bolm's laboratory, an efficient and stereospecific preparation of *N*-cyanosulfoximines from sulfoxides was described by Dannenberg et al.²⁹⁶

Scheme 37. Preparation of Optically Active Sulfoximines through Kinetic Resolution of Racemic Sulfoxides²⁹⁵



Optimized reaction conditions included the use of cyanamide (2 equiv), potassium *tert*-butoxide (2 equiv) as base, and *N*-chlorosuccinimide (2 equiv) as oxidant, the set of reactants that were efficient for the synthesis of *N*-cyanosulfilimines from sulfides.²⁸⁸ Reaction was performed in water at room temperature, with yields varying from 23 to 98%. Retention of configuration was observed for imination of a representative, enantioenriched sulfoxide (Scheme 38).

Scheme 38. Stereospecific Formation of *N*-Cyanosulfoximine from Sulfoxide²⁹⁶

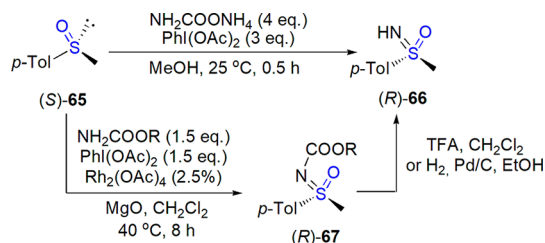


NH-Sulfoximines were synthesized in the reaction of sulfoxides and triflic acid salts of hydroxylamine catalyzed by Fe(II) complex.²⁹⁷ No attempt was made to perform the reaction with enantioenriched sulfoxide or chiral iron catalyst.

The significant increase of yield (up to 91%) of imination of sulfoxides with NaN₃ or TMSN₃ was observed by Gutmann et al. when concentrated sulfuric acid was replaced by a fuming one.²⁹⁸ The two-phase (H₂O/CH₂Cl₂) reaction could be performed under continuous flow conditions. However, the original optical purity of the reactant was not retained.

In 2015, Bull and co-workers described a rhodium-catalyzed transfer of carbamates to sulfoxides, yielding *N*-protected sulfoximines in good to excellent yields (54–98% under optimized conditions).²⁹⁹ BocNH₂ and PhI(OAc)₂ were used to generate BocN=IPh species in situ, Rh₂(OAc)₄ acted as a catalyst, and MgO served as a base. Carbamate protection allowed performing good-yielding Suzuki coupling with *S*-aryl substituents; on the other hand, Boc and Cbz groups were easily removed to afford *NH*-sulfoximines. As shown in one example, both *N*-transfer and deprotection proceeded with a complete retention of configuration (Scheme 39); other reactions were performed with racemic samples.

Scheme 39. Stereospecific Formation of Sulfoximine from Sulfoxide-Direct NH Transfer and Rh-Catalyzed Carbamate Transfer^{299,300}



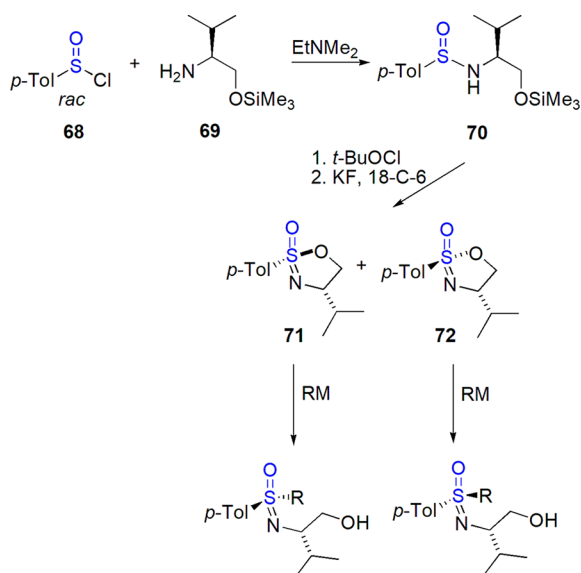
In the search of a convenient electrophilic nitrene source, Bull, Luisi, and co-workers tested ammonium salts for a direct NH transfer under metal-free conditions.³⁰⁰ The use of ammonium carbamate (4 equiv) and diacetoxyiodobenzene (3 equiv) in methanol at 25 °C resulted in fast formation of sulfoximines from the corresponding sulfoxides. The reaction showed a wide substrate scope. Stereochemical outcome of the process was checked for three enantioenriched sulfoxides, for which a complete retention of configuration was observed (an example is shown in Scheme 39).

Later, the same group reported the use of similar set of reactants for the one-pot preparation of sulfoximines from sulfides³⁰¹ and conversion of thiols to sulfones and sulfonimidates (vide infra).³⁰² The possibility of performing the synthesis in a flow reactor was demonstrated as well.³⁰³

7.3. S–C Bond Formation

Sulfoximines can be obtained from other tetrasubstituted sulfinyl derivatives: sulfonimidoyl halides, sulfonimidamides, and sulfonimidamides. Reggelin and co-workers developed a strategy based on preparation of two epimers of cyclic sulfonimidamide (71 and 72, see also section 9.1) and their reaction with organometallic reagents, which proceeded with an inversion of configuration (Scheme 40).³⁰⁴ This

Scheme 40. Sulfoximines Obtained from Epimeric Sulfonimidamides³⁰⁴

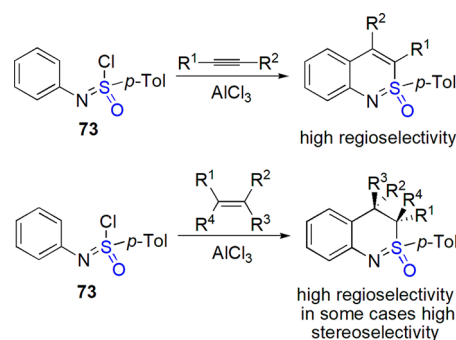


synthetic precursor was also applied in the preparation of the first bis(*NH*-sulfoximine) in a diastereomerically pure (but racemic) form.³⁰⁵ Epimers of the same sulfonimidamide were used in a one-pot synthesis of enantiopure cyclic oxathiazine *S*-oxides³⁰⁶ and other enantiopure sulfoximines.²⁷⁸

A synthesis based on the use of sulfonimidates was also reported in 2018.³⁰⁷ They were shown to react with a variety of organometallic (mainly Grignard) compounds in THF. Yields were moderate to high; as only racemic reactants were used, stereochemical aspects of the transformation were not discussed.

Harmata and co-workers concentrated their attention on the preparation of derivatives of cyclic sulfoximine, 2,1-benzothiazine, a compound which found numerous applications in asymmetric synthesis.²⁷⁴ Reaction of sulfonimidoyl chloride 73 with alkynes under Lewis acid catalysis afforded 2,1-benzothiazines in 46–75% yield (Scheme 38).³⁰⁸ These cyclic sulfoximines were also obtained when alkenes were used instead of alkynes, and good yield was in certain cases (for example, cyclohexene addition) accompanied by high diastereoselectivity (Scheme 41).³⁰⁹ Reaction of sulfonimidoyl chloride with mono-, di-, and trisubstituted olefins in the presence of AlCl_3 provided benzothiazines bearing two stereogenic centers with variable diastereoselectivity.³¹⁰ The

Scheme 41. Preparation of 2,1-Benzothiazines from Compound 73 and Alkynes or Alkenes^{308,309}

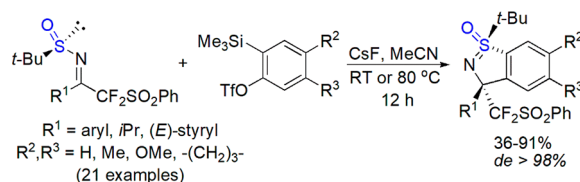


effect of alkene substitution on the reaction outcome was studied.

Also noncyclic sulfoximines were prepared from sulfonimidoyl chlorides or fluorides, as exemplified by the reaction of the latter with TMSCF_3 , leading to trifluoromethylated product.³¹¹ Diarylsulfoximines were prepared by Takata and co-workers from sulfonimidoyl chlorides (in turn obtained by treatment of sulfinyl chlorides with chloramine-T) and aromatic hydrocarbons catalyzed by Lewis acids.³¹²

Synthesis of sulfoximines can start from trisubstituted derivatives, sulfinamides, or imines derived therefrom. Enantiopure *N*-*tert*-butylsulfinylimines bearing fluorinated alkyl substituents were applied in a [3+2]-cycloaddition reaction with arynes, yielding cyclic sulfoximines with excellent diastereo- and enantioselectivity (the configuration of sulfur stereocenter was retained, Scheme 42).³¹³ A reverse process of conversion of cyclic sulfoximines into sulfonamides was investigated as well.

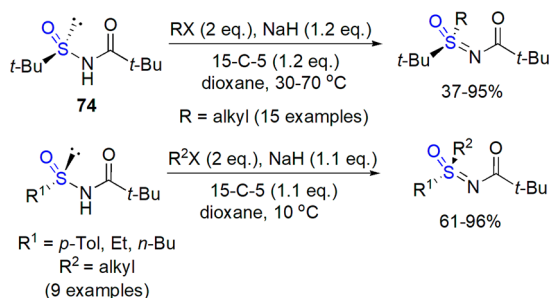
Scheme 42. [3+2]-Cycloaddition Leading to Cyclic Sulfoximines³¹³



Stockman and co-workers prepared a series of cyclic sulfoximines from nonracemic mesityl- or *tert*-butyl sulfinylimines via an aza-Darzens-type aziridination with 2-bromobut-2-enoic acid methyl ester; the formed vinyl aziridines spontaneously rearranged into diastereomerically pure products.³¹⁴ The reaction could be performed either with isolation of the aziridine intermediate or in a one-pot fashion, typically in higher yield.

In very recent reports by Aota et al, a stereospecific synthesis of sulfoximines by a *S*-selective alkylation or arylation of sulfinamides was described.^{315,316} Protection of nitrogen atom with a pivaloyl group and the proper choice of reaction conditions (2 equiv of alkyl iodide or bromide, 1.1–1.2 equiv of NaH, 1.1–1.2 equiv of 15-crown-5 in dioxane, 11–168 h) allowed preparation of sulfoximines in 31–96% (but in most cases >80%) yield with a retention of configuration (Scheme 43).³¹⁵ The protecting group could be removed by LiAlH_4 treatment. Interestingly, starting with *tert*-butyl sulfinamide opened the route to both enantiomers of various derivatives

Scheme 43. Alkylation of Pivaloyl-Protected Sulfinamides³¹⁵

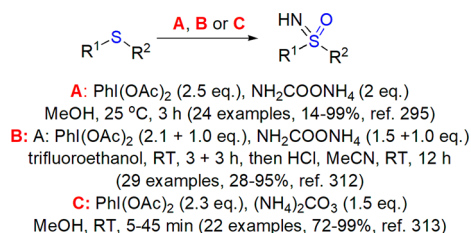


with two similar alkyl chains via *de-tert*-butylation of sulfoximine obtained in the first step with TFA followed by the second alkylation. The reaction was conducted on a gram scale as well. A similar strategy was used for CuI-catalyzed arylation of sulfinamides with arylidonium salts and *N,N*-dicyclohexylmethylamine in DMSO: conversion of *N*-pivaloyl *tert*-butane sulfinamide proceeded in 53–90% yield.³¹⁶ *De-tert*-butylation with potassium *tert*-butoxide (85%) and second arylation (68–91%) yielded the desired enantiopure diaryl sulfoximines. The same group described also a stereoselective preparation of five-membered cyclic sulfoximines by cyclization of optically pure *N*-propargylsulfinamides.³¹⁷

7.4. Formation of S=O and S=N Bonds

In 2017, three groups independently reported a convenient one-pot protocol for the synthesis of *NH*-sulfoximines from sulfides. Reactants which were found efficient for the conversion of sulfoxides to sulfoximines, diacetoxyiodobenzene (phenyliodine diacetate, PIDA), and ammonium carbamate were successfully applied by Bull, Luisi, and co-workers in nitrogen and oxygen transfer to sulfides (Scheme 44).³⁰¹

Scheme 44. Preparation of Sulfoximine from Sulfides^{301,319,320}



Preparation of *NH*-sulfoximines from sulfides treated with PIDA and H₂NCOONH₄ was also described by Reboul and co-workers,³¹⁸ and modified reaction conditions allowed extension of the methodology for derivatives bearing perfluoroalkyl substituents (Scheme 44).³¹⁹ A similar procedure, but with ammonium carbonate ((NH₄)₂CO₃) as the source of ammonia, was developed by Li and co-workers (Scheme 44).³²⁰ An asymmetric variant of this versatile, operationally simple method offering a broad substrate scope and performed under mild conditions (at room temperature under air) is of high demand, but it has not been announced yet.

The sulfoximation protocol was applied by Reboul's group in the last step of the synthesis of drug candidate atuvaciclib.³²¹ An attempted stereoselective synthesis via enantiomerically enriched sulfoxide resulted in (*S*)-enantiomer with only 20%

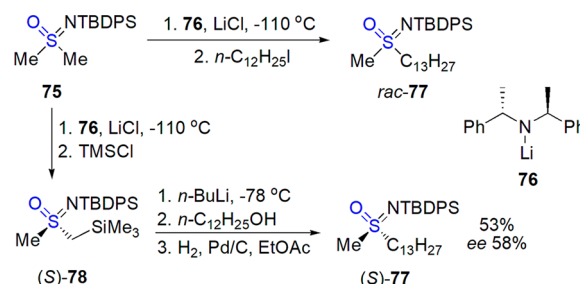
ee. The authors attributed this unsatisfactory result to the low enantioselectivity of sulfoxidation step for which Kagan's conditions were applied.

7.5. Desymmetrization of Achiral or Racemic Sulfoximines. Kinetic Resolution

Desymmetrization of *N*-trialkylsilyl dimethyl sulfoximines was performed by their treatment with chiral bases and reacting the resulting anion with electrophiles, thus yielding enantioenriched derivatives difficult to obtain by other methods.³²² Under optimized conditions, with chiral lithium amide prepared in situ, several electrophiles were tested with variable yield (6–86%) and enantioselectivity (18–70% *ee*).

The desymmetrization strategy was later used for the preparation of *S,S*-dialkyl sulfoximine 77, an optically active myristic acid analogue.³²³ However, a simple generation of anion from dimethyl derivative 75 followed by addition of dodecyl iodide resulted in a racemic product and a strategy was modified, finally yielding the desired sulfoximine with 58% *ee* (Scheme 45). The target compound was prepared in high

Scheme 45. Desymmetrization of Sulfoximine 75 Yielding Myristic Acid Derivative³²³



enantiomeric purity using enantioselective oxidation of 4-bromophenyl methyl sulfide (Kagan's method was applied), followed by a displacement of aryl group by Grignard reagent, iron-catalyzed imination, and deprotection of nitrogen atom.

Kinetic resolution of *NH*-sulfoximines utilizing their amidation with enals catalyzed by chiral *N*-heterocyclic carbene catalysts was described by Dong et al.³²⁴ A broad variety of aryl-substituted sulfoximines afforded amides with reasonable yield and excellent stereoselectivity (up to 59% yield, up to 96% *ee*), and unreacted sulfoximines in up to 56% yield and up to 99% *ee*; both enantiomeric forms of each product could be obtained). The reaction could be performed on a gram scale, which was demonstrated by the efficient preparation of sulfoximine further transformed into optically active Betrixaban analogue, an inhibitor of human Factor Xa.

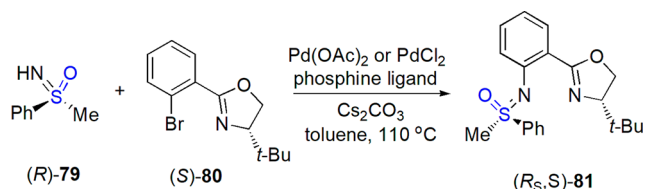
A stereodifferentiation of variety of sulfoximines upon annulation with diazo compounds catalyzed by rhodium(III) complex bearing a chiral Cp^x ligand was independently described by the groups of Li³²⁵ and Cramer.^{326,327} A possible inversion of stereoselectivity caused by the change of solvent or suitable additives was noticed.

7.6. Modifications of Sulfoximines

Typical modifications of optically active sulfoximines concern substitution of imine nitrogen atom (however, they were also introduced into pseudopeptides by Bolm and co-workers using reactions of *S*-methyl substituent^{328–330}). New attempts are usually performed with racemic substrates, but in many cases tests with enantiomerically pure compounds prove a retention of configuration of stereocenters. For example, in *N*-arylation

of various sulfoximines with aryl bromides catalyzed by palladium salts, Bolm and co-workers also used a chiral (*S*)-bromide and (*R*)-sulfoximine and obtained a single diastereomer, strongly supporting the hypothesis of complete retention of configuration of both stereogenic centers (Scheme 46).^{331,332}

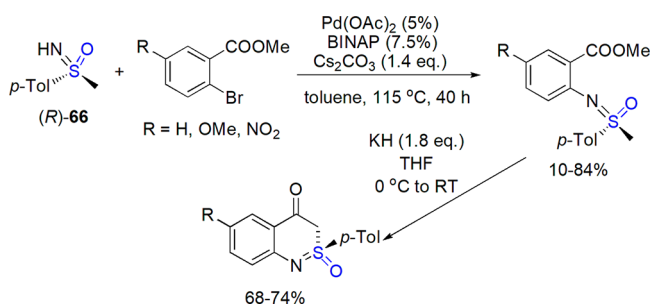
Scheme 46. Reaction between (*S*)-Aryl Bromide and (*R*)-Sulfoximine³³²



Palladium- and copper-catalyzed arylations of *NH*- or *N*-benzylsulfoximines developed in Bolm's laboratory allowed preparation of chiral ligands for asymmetric synthesis.^{333,334} This group obtained also chiral thiourea organocatalysts from (*S*)-*S*-methyl-*S*-phenylsulfoximine by a direct reaction with isothiocyanate.³³⁵ Protocols for preparation of *N*-alkyl (acylation and reduction with complexed boranes)³³⁶ and *N*-alkynyl derivatives (through the reaction with methoxy-(tosyloxy)iodobenzene) were described as well.^{337,338}

To avoid using stereochemically labile sulfonylimidoyl chlorides in the synthesis of enantiomerically pure benzothiazines, Harmata and Pavri adapted the *N*-arylation protocol developed by Bolm.^{331,339} The reaction between enantiopure *NH*-sulfoximine and *ortho*-bromobenzoates or analogous cinnamate derivative resulted in *N*-arylation; ring closure upon addition of a base such as sodium or potassium hydride yielded substituted 2,1-benzothiazines as single isomers (Scheme 47). The reaction could be performed in a one-pot

Scheme 47. Synthesis of 2,1-Benzothiazines from Enantiopure Sulfoximine (*R*)-66 Described by Harmata and Pavri³³⁹



version when *o*-bromobenzaldehydes were used as reactants. Benzothiazines were also obtained in the reaction of methyl phenylsulfoximine with *o*-bromocinnamates followed by base-induced cyclization.^{340,341} Products were formed as single stereoisomers in a highly stereospecific process.

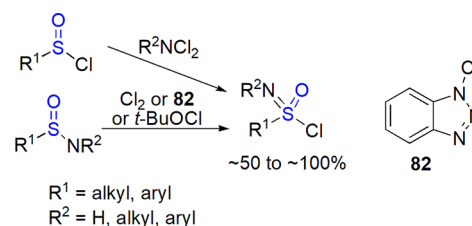
Harmata and co-workers described a palladium-catalyzed microwave-assisted reaction of aryl chlorides with *NH*-sulfoximine, which allowed preparation of a series of arylated sulfoximines and benzothiazines in good to excellent yields in a relatively short time.³⁴² When aryl dichlorides were used, under various reaction conditions, only products of mono-substitution were observed.³⁴³

8. SULFONIMIDOYL HALIDES

The title compounds, which can be regarded as halides of sulfonylimidic acid, are relatively unstable (at least chlorides and bromides), moisture-sensitive compounds prepared as intermediates in the synthesis of other tetrasubstituted sulfinyl derivatives. Their chemistry was reviewed by Levchenko and co-workers in 2000.³⁴⁴ Here, we present several papers devoted to the preparation of these compounds, but they will also appear in other sections, especially in the one concerning sulfonylimidamides.

Most frequently, sulfonylimidoyl chlorides are obtained from sulfinyl chlorides, sulfinamides, but also from other tetrasubstituted sulfinyl derivatives. Their first successful preparation was reported by Levchenko and Kirsanov in 1960.³⁴⁵ Johnson and co-workers developed a new method of preparation of these compounds by oxidation of sulfinamides with chlorine or *N*-chlorobenzotriazole **82**,^{346,347} later replaced by *tert*-butyl hypochlorite (Scheme 48).³⁴⁸ Retention of configuration

Scheme 48. Preparation of Sulfonylimidoyl Chlorides from Sulfinyl Chlorides or Sulfinamides^{346–349}



during this transformation was established (due to the priority rules, this means that when chlorine substituent takes place of lone pair of electrons, (*S*)-sulfinamide was converted to (*R*)-sulfonylimidoyl chloride).³⁴⁹ Stereospecific conversions of sulfonylimidoyl chloride to sulfinamide and sulfonylimidamides was associated with inversion of configuration.

Jones and Cram reported on the preparation of epimeric *N*-carbomethoxy-*p*-toluenesulfonylimidoyl chlorides using two methods and proved that also imination of sulfinyl chloride proceeds with retention of configuration.²⁸ A cycle of stereospecific transformations involving several sulfinyl derivatives was proposed.

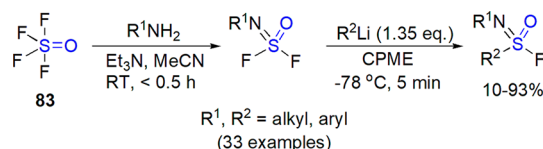
Roy investigated the possibility of preparation of sulfonylimidoyl chloride from other tetrasubstituted sulfinyl compounds.³⁵⁰ He reacted *N*-silylated sulfonylimidamides with phosphorus chlorides and observed formation of the corresponding chlorides under appropriate conditions. He also obtained the first detectable sulfonylimidoyl bromide. Correlation of configuration was not the part of the study.

Sulfonylimidoyl fluorides have been recognized as more stable analogues of their chloride counterparts, which makes them more convenient as reaction intermediates that can be isolated without the need of immediate use. Unfortunately, the stereochemical course of the reactions in which they were prepared was not studied. First, sulfonylimidoyl fluorides were prepared by Johnson and co-workers from the respective chlorides and diverse fluoride sources (NaF, KF, TBAF).³⁵¹ These derivatives were used in the synthesis of sulfoximines. Novel sulfonylimidoyl fluorides were prepared by van Leusen et al. by treatment of the corresponding chlorides with KF or KHF₂.³⁵² *N*-Tosyl derivatives exhibited shelf stability; partial resolution to enantiomers by crystallization was achieved for

one derivative. Fluorides were converted to the corresponding (racemic) isocyanides as well.

Selectfluor was found useful as a fluoride source in conversion of cyclic sulfoximine to the cyclic fluorinated 1-oxo-2H-1,2,4-benzothiadiazine derivative, which was characterized by X-ray study.³⁵³ Quite recently, Sharpless and co-workers applied thionyl tetrafluoride **83** in a two-step reaction; in the first step, primary amines were treated with SOF₄, which resulted in difluoride intermediate. Its reaction with alkyllithium yielded the desired products (Scheme 49).³⁵⁴

Scheme 49. Synthesis of Sulfonylimidoyl Fluorides from SOF₄ Reported by Sharpless and Co-workers³⁵⁴



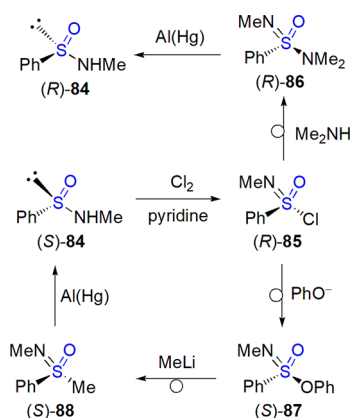
9. PREPARATION OF OPTICALLY ACTIVE SULFONIMIDATES

Similarly to sulfoximines and sulfonimidamides, sulfonimidates have been known for over half a century and recently rediscovered, mainly as intermediates in the synthesis of sulfoximines. To fulfill these roles, they are not always required in enantiomerically pure form, and thus certain preparative methods rather neglect the fate of stereogenic center. Possible applications of these compounds are limited by their observed slow conversion to corresponding sulfonamides at elevated temperature.³⁵⁵

9.1. S–O Bond Formation

Typical preparations of sulfonimidates involve oxidative introduction of alkoxy group into sulfinamides. It is often, but not necessarily, realized in two steps. Already, in the 1970s, Johnson and co-workers prepared enantiopure sulfonimidates in a two-step procedure involving reaction of (*S*)-*N*-methylbenzenesulfonamide **84** with chlorine followed by treatment of obtained sulfonylimidoyl chloride **85** with sodium phenoxide (Scheme 50).²⁹ (*S*)-Sulfonimidate **87** was formed as a result of retention of configuration in the first step and inversion in the second one. Scheme 50 shows other possible

Scheme 50. Transformations of Sulfonamide (*S*)-84** through Chloride (*R*)-**85** to Sulfonimidamide (*R*)-**86**, Sulfonimidate (*S*)-**87**, and Sulfoximine (*S*)-**88****²⁹



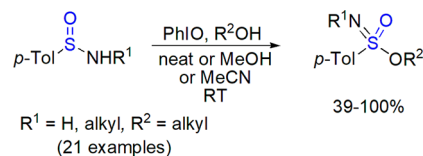
conversions involving also sulfonimidamide **86** and sulfoximine **88**, confirming that typically interconversions of tetrasubstituted derivatives are associated with the change of configuration, in contrast to those between three- and four-substituted chiral sulfinyl compounds.

In 1993, Roy reported a conversion of racemic *N*-silylated sulfonylimidoyl chlorides and bromides to the corresponding sulfonimidates in yields up to 78%.³⁵⁰ A quantitative desilylation with methanol resulted in *NH*-sulfonimidates.³⁵⁶ Thermally induced, Lewis acid-catalyzed polycondensation of these compounds as well as of certain silylated derivatives was observed, yielding poly(oxothiazene) polymers with an N=S backbone.

Sulfonamides bearing hydroxyl group in the *N*-substituent were shown to undergo cyclization to sulfonimidates. Reggelin and co-workers developed an efficient stereoselective synthesis of enantiomers of cyclic sulfonimidate that could be used as precursors for enantiopure sulfoximines (Scheme 40).^{304,357,358} The synthesis started from (*S*)-*O*-trimethylsilylvalinol and sodium salt of *p*-toluenesulfonic acid. The most efficient route included separation of epimeric sulfonamides by crystallization prior to the conversion of sulfonylimidoyl chlorides with *t*-BuOCl; a fast, DBU-induced cyclization appeared at -78°C , which precluded the loss of enantiomeric purity.³⁵⁷

Sulfonimidates were prepared by Malacria and co-workers through the reaction of sulfonamides with alcohols and iododisylbenzene (Scheme 51).³⁵⁹ The reaction proceeded

Scheme 51. Preparation of Sulfonimidates from Sulfonamides by Malacria and Co-workers^{359,360}



smoothly for primary alcohols serving also as solvents (71–94% yield after 1 h in room temperature). When the reaction was conducted in acetonitrile with 3 equiv of alcohols, yields were slightly lower (39–95%) due to the competitive oxidation to sulfonamide. Also, secondary sulfonamide was efficiently converted to the corresponding sulfonimidate in 52% yield. Stereospecificity of the transformation was checked with two enantiomerically pure sulfonamides, which yielded the corresponding products with 62 and 72% *ee*, mainly with retention of configuration.³⁶⁰ This observation was confirmed by the conversion of enantiopure sulfonamides bearing an additional stereogenic center: diastereomeric products were formed with 51–76 *de*. X-ray structure of the major isomer of resulting sulfonimidate proved that configuration of sulfur stereocenter was retained.

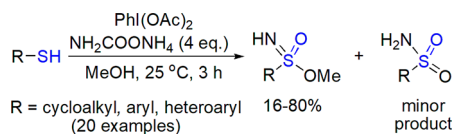
The above method was limited to *N*-alkyl derivatives. In 2006, Felim et al. reported the modified protocol which allowed preparation of *N*-aryl sulfonimidates, and better results were obtained when PhIO was replaced by more stable PhI(OAc)₂ (or its phenyl-substituted derivatives) with MgO as a base.³⁶¹

Similarly, a series of 27 sulfonimidates were prepared by oxidation of sulfonamides with PhIO in the presence of alcohols (15 min at room temperature, yields up to 93%).³⁰⁷ The resulting (racemic) compounds were further converted to sulfoximines (see section 7.4).

9.2. Other Methods

In a recent report of Luisi, Bull, and co-workers, thiols were reacted with ammonium carbamate and diacetoxyiodobenzene in methanol, yielding the corresponding sulfonamides or sulfonimidates, depending on reaction conditions (Scheme 52); shorter reaction time and an increase of the amount of

Scheme 52. Preparation of Sulfonimidates from Thiols³⁰²



ammonium carbamate resulted in higher yields of sulfonimide).³⁰² In this convenient one-pot protocol, a direct formation of both sulfur–oxygen and sulfur–nitrogen bonds was observed. Factors which would induce stereoselectivity of the process were not checked; all reactants, including a variety of thiols, were achiral, and chiral additives were not tested. A possibility of transformation of sulfonimide to sulfoximine was demonstrated by the reaction of electron-rich 4-methoxyphenyl sulfonimide with morpholine (80% yield, racemic).

10. STEREOSELECTIVE PREPARATION OF SULFONIMIDAMIDES

Sulfonimidamides belong to the group of intrinsically chiral sulfinyl compounds. Their story is very similar to other tetrasubstituted derivatives, sulfoximines and sulfonimidates; first prepared in the 1960s by Levchenko and co-workers, long forgotten, in the 21st century they have experienced an impressive revival.³⁶² It is connected with the discovery of their potential as biologically active substances, with possible pharmaceutical and agricultural applications³⁶³ but also as chiral auxiliaries for asymmetric synthesis. The progress in the synthesis of sulfonimidamides was reviewed in a 2018 article by Nandi and Arvidsson.³⁶² Since then, several new publications have been issued. They will be presented in this section, together with representative examples of important contributions to the field.

Enantiopure sulfonimidamides were obtained either from other optically active sulfinyl derivatives or by separation of obtained isomers by HPLC. As the access to the starting material with two sulfur–nitrogen bonds is limited, one of these connections is formed in most preparations. The majority of described transformations involve sulfinamides and sulfonamides, and other tetrasubstituted derivatives (sulfonimidoyl halides or sulfonimidates) may serve as intermediates. Various approaches can differ by the substitution of imine and amine nitrogen atoms in the final product; postsynthetic modifications can change this pattern without altering the configuration of stereogenic sulfur atom.

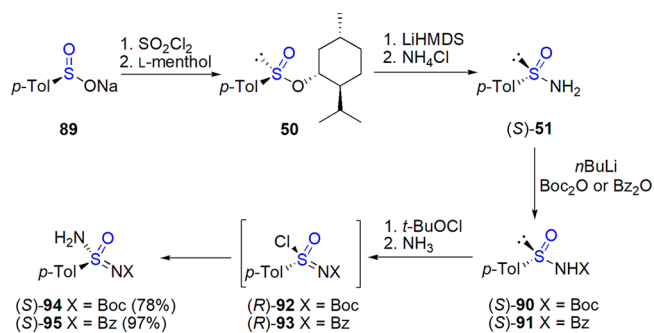
10.1. Preparation of Sulfonimidamides from Sulfinamides

The first synthesis of optically active sulfonimidamide was reported by Johnson and co-workers.³⁴⁹ Chlorination of sulfinamide (S)-84 followed by reaction with dimethylamine resulted in product (R)-86 in 56% overall yield with inversion of configuration (Scheme 50).

More recently, conversion of sulfinamides to sulfonimidamides was studied by Bolm's group. Garcia Mancheño and Bolm investigated chlorination of *p*-tolylsulfinamides con-

nected with immediate transformation of transient sulfonimidoyl chlorides by the amine nucleophile into the respective racemic sulfonimidamides in 50–97%.³⁶⁴ Two enantiopure *N*-benzoyl- and *N*-*tert*-butyloxycarbonyl-protected sulfonimidamides were efficiently prepared in several steps starting from the commercially available sodium 4-toluenesulfinate 89 (Scheme 53).³⁶⁵ Its conversion to enantiopure sulfinamide

Scheme 53. Preparation of Enantiopure Sulfonimidamides from Sodium Sulfinate³⁶⁵



(S)-51 was achieved using menthol auxiliary. Oxidative chlorination of this sulfinamide with *tert*-butyl hypochlorite followed by reaction of transient (*R*)-sulfonimidoyl chlorides 92 and 93 with aqueous ammonia resulted in formation of enantiopure *N*-substituted (*S*)-sulfonimidamides 94 and 95 in 78% and 97% yield, respectively. Their configuration was confirmed by X-ray diffraction measurement. Amino-functionalized sulfonimidamides were prepared by oxidative chlorination of sulfinamides with *t*-BuOCl followed by the reaction with amine or bisamine.³⁶⁶ Alternatively, a reaction of *N*-benzoyl-protected sulfonimidamide with aziridinium salts obtained from aminoalcohols was performed. In the first case, enantiopure reactants were used and products were obtained as single stereoisomers, while the second method afforded separable mixtures of diastereomers. Applied in copper-catalyzed asymmetric Henry reaction, they led to product formation in reasonable yields and up to 95% *ee*.

A direct amination of *N*-arylsulfinamides with *N*-benzoyl derivatives of secondary amines (piperidine, piperazine, or morpholine) catalyzed by CuBr was also reported by Bolm and co-workers.²⁵⁴ Chiral amines were not tested, and racemic products were obtained in 35–96% yield.

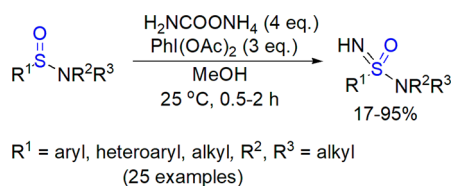
Oehlich and co-workers described a synthesis of sulfonimidamides bearing a CF₃ substituent from the corresponding sulfinamides. Their oxidative fluorination by the action of NCS and TBAF led to sulfonimidoyl fluoride intermediates, more stable as compared to their chloride counterparts; a subsequent reaction with amines led to the desired sulfinyl derivatives.³⁶⁷ Trifluoromethylated sulfonimidamides were also prepared by the same group from a bench-stable solid sulfoximine precursor. In both cases, the process could be conducted in a flow reactor. Unfortunately, stereoselectivity of the substitution was not the issue that deserved attention.³⁶⁸

Cathers and Schloss reported on the synthesis of dipeptides containing sulfonimidamides as mimics for transition states for metalloproteases and aspartic acid.³⁶⁹ Sulfinyl phthalimide prepared by oxidation of the respective sulfenyl derivative with *m*-CPBA was first treated with *L*-phenylalanine methyl ester to afford a separable mixture of diastereomers. Sulfinamide was then reacted with chlorine, followed by substitution of chloride

with ammonia, which yielded a sulfonimidamide with a free NH₂ group. Two more derivatives contained glycine benzyl ester and leucine methyl ester, the latter converted upon the crystallization attempt into a cyclic sulfonimidamide. The configuration of sulfur stereocenter in these compounds was, however, not studied.

Inspired by the work of Bull, Luisi, and co-workers,³⁰⁰ Lücking's group applied ammonium carbamate combined with PhI(OAc)₂ for NH transfer to tertiary sulfinamides.³⁷⁰ NH-sulfonimidamides were formed in good yields (Scheme 54) and, as suggested by one experiment with enantiomerically enriched substrate, also in a stereospecific manner (though configuration of the product was not established).

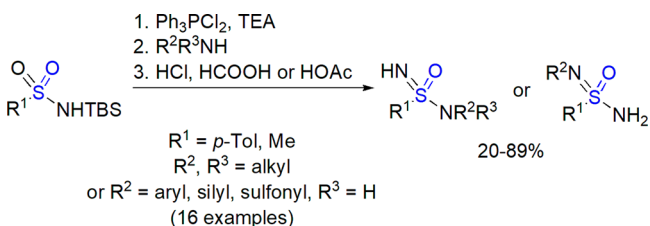
Scheme 54. Synthesis of Sulfonimidamides from Tertiary Sulfinamides³⁷⁰



10.2. Preparation of Sulfonimidamides from Sulfonamides

Sulfonamides can be also converted to sulfonimidamides by a formal replacement of =O by a =NR fragment. Typically, sulfonimidoyl chlorides serve as intermediates of such preparations, as exemplified by the synthesis described by Chen and Gibson (Scheme 55).³⁷¹ Yields varied from 20 to

Scheme 55. Preparation of Sulfonimidamides from Sulfonamides³⁷¹



89%; enantiomerically pure derivatives were obtained only by chiral HPLC separation of a racemic sample. Sulfonimidamide derivatives of amino acids were prepared by chlorination of sulfonamides with Ph₃PCl₂, followed by the reaction with enantiopure amino acid esters.³⁷² Diastereomers formed in ca. 2:1 ratio were separated by column chromatography. Alternatively, a removal of *N*-*tert*-butyldiphenylsilyl (TBDPS) protecting group was performed yielding five-membered cyclic sulfonimidamides; preparative HPLC led to individual stereoisomers, and configuration of one of them was established by X-ray study.

A novel approach to the synthesis of sulfonimidamides was recently proposed by Grygorenko and co-workers who prepared a stable and versatile imidosulfuric diamide from the corresponding sulfonamide and used it in reactions with amines.³⁷³ A variety of sulfonimidamides were obtained in 83–94% yield, but only as racemates because no attempt was directed toward enantioselective variant of the reaction.

10.3. Other Preparations

Toth et al. prepared a series of sulfonimidamide–urea conjugates and evaluated their biological activity.³⁷⁴ These compounds were obtained as racemates from sulfides, disulfides, thiols, or sodium sulfinates, which were converted into the corresponding *N*-sulfinyl thioureas; their oxidative chlorination with *t*-butyl hypochlorite followed by amination afforded the target compounds. The use of (1*S*,2*R*)-norephedrine in the last step yielded a mixture of epimers which were separated to give enantiopure derivatives.

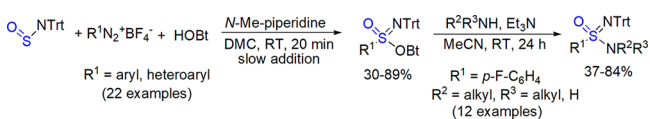
Sulfonimidamides were also obtained from unprotected sulfoximines in a copper-catalyzed dealkylation/amination process in which *S*-methyl or *S*-benzyl substituent was replaced by amines under O₂ atmosphere.³⁷⁵ Yields were in certain cases high, however, the use of optically active sulfoximine resulted in racemic product.

Willis and co-workers developed a one-pot protocol using sulfinylamines, in particular a stable sulfinyltritylamine, as a starting point for sulfonimidamide synthesis.³⁷⁶ Three steps: treatment with organometallic compound, chlorination, and the reaction with amine led to the protected sulfonimidamides in 49–80% yield. The use of chiral amine led to separable mixture of diastereomers; other stereochemical aspects were not considered.

Enantiopure imidazolyl and 1,2,4-triazolyl sulfonimidoyl derivatives were prepared from sulfonimidoyl chlorides as reported by Kluge et al.³⁷⁷ Also, 1,2,3-triazole ring was introduced as a substituent of sulfur atom via click reaction of the corresponding azide by Nandi and Jesin.³⁷⁸

To overcome the drawbacks of previous methods (e.g., limited functional group tolerance), Bolm's group described a new one-pot approach, involving sulfonimidate formation from *N*-tritylsulfinylamine, 4-fluorophenyldiazonium tetrafluoroborate, and 1-hydroxybenzotriazole in the presence of a base (*N*-methylpiperidine was found optimal) in dimethyl carbonate chosen as solvent (Scheme 56).³⁷⁹ Relatively stable sulfonimi-

Scheme 56. Formation of Sulfonimidamides from *N*-Tritylsulfinylamine³⁷⁹



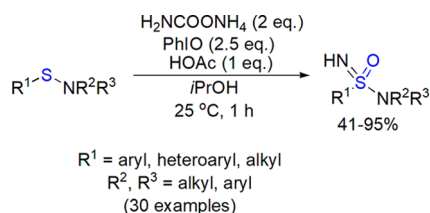
dates were converted to sulfonimidamides by the action of primary and secondary aliphatic amines. The method was found versatile, with high tolerance for various functional groups, although without any control of stereochemistry.

Bull, Luisi, and co-workers studied reaction of ammonium carbamate and iodosylbenzene with sulfenamides, a rarely used starting material, prepared from disulfides and amines.³⁸⁰ A one-pot formation of S=O and S–N bonds proceeded smoothly (45–95% yield after 1 h reaction in 2-propanol at 25 °C, with 2.5 equiv of PhIO as oxidant, 2.0 equiv of NH₂COONH₄, and 1.0 equiv of acetic acid additive, Scheme 57). The obtained racemic products could be further functionalized.

10.4. Modifications of Sulfonimidamides

Numerous modifications involving either imine or amine nitrogen atoms of prepared sulfonimidamide have been reported by several research groups. It is assumed that such reactions do not affect the sulfur stereocenter, and usually this

Scheme 57. One-Pot Preparation of Sulfonimidamides from Sulfenamides³⁸⁰



has not been checked or simply racemic mixtures have been used in these transformations. Apparently enantiopure final products are not necessary for certain applications. Several recent examples will be briefly described as the protocols can be easily adapted for synthesis of optically active compounds.

Arvidsson's group focused their attention on preparation of *NH* sulfonimidamides.³⁸¹ Three methods were developed for deprotection of morpholine-substituted and imine-protected sulfonimidamides under acidic, nucleophilic, and basic conditions. An efficient palladium-catalyzed arylation of imine nitrogen with aryl halides was also described. Arvidsson and co-workers reported also copper-catalyzed arylation using aryl boronic acids³⁸² (a similar reaction was independently described by Battula et al.³⁸³), and *N*-acylation with aryl or heteroaryl halides and carbon monoxide released in situ from $\text{Mo}(\text{CO})_6$ in the presence of palladium catalyst, DBU, and triethylamine.³⁸⁴ Recently, *N*-trifluoromethylthiolated sulfonimidamides were prepared and their cytotoxic activity studied.³⁸⁵

Microwave-assisted, copper-catalyzed *N*-arylation of sulfonimidamides was also described by Malacria and co-workers.³⁸⁶ Even though hydroxyproline was used as ligand, the obtained products were racemic. The same team converted sulfonimidamides bearing NH_2 group into nitrenes by the reaction with PhIO; these nitrogen-transfer agents were trapped by sulfides, sulfoxides, or olefins in the presence of $\text{Cu}(\text{II})$ salt.³⁸⁷ Reaction with enantiopure sulfoxide gave a mixture of separable diastereomers; otherwise diastereoselectivity was low in the case of sulfimide formation, while up to 50% *de* was noted for aziridination.

In 2018, 47 *N*-functionalized tertiary sulfonimidamides were prepared by Lücking and co-workers by arylation, alkylation, trifluoromethylation, cyanation, sulfonylation, alkoxy-carbonylation, and aminocarbonylation of the $=\text{NH}$ group.³⁸⁸ Their hydrolytic and metabolic stability were checked, indicating the potential of application in biological systems.

Modifications of sulfonimidamides were also introduced by Bolm and co-workers.^{389,390} Enantiopure derivatives were tested in asymmetric reactions. Novel organocatalysts were obtained in good yield from protected (*S*)-proline and two enantiomers of *N*-tosylsulfonimidamide.³⁹¹ High diastereo- and enantioselectivity was observed when these compounds were applied in solvent-free asymmetric aldol reaction. *N*-Phosphorylation of single enantiomers of sulfonimidamides resulted in novel phosphoramidites (SIAPhos), which were used to prepare neutral rhodium and iridium complexes, the latter found efficient in asymmetric hydrogenation of enamides (70–92% *ee*).³⁹²

Kinetic resolution of racemic sulfonimidamides was described by Liang et al., who applied these compounds for amination of benzylic C–H bonds catalyzed by a chiral $\text{Rh}(\text{II})$ complex.³⁹³ A strong matched effect was observed between

(*S*)-enantiomers of sulfinyl compound and the catalyst. The reaction of various benzylic substrates with racemic sulfonimidamide and $\text{PhI}(\text{OCOt-Bu})_2$ in the presence of (*S*)-form of rhodium complex resulted in formation of (*1R,S_S*) product in 56–77% yield, 88–99% *de*, and 97–99% *ee*, accompanied by recovery of unreacted substrate with (*R_S*) configuration.

11. SUMMARY

Undoubtedly, chiral sulfinyl compounds have proved their usefulness and versatility in modern stereoselective synthesis, serving as precursors, catalysts, and ligands in various preparations of important target molecules, mainly for biomedical applications. These derivatives, despite a common structural feature, constitute an omnifarious family. Consequently, certain methods of their preparation in enantiomerically pure form are similar, while part of synthetic routes remain applicable only for particular representatives. A possibility of mutual interconversions between various sulfinyl compounds is therefore worth emphasizing, because one precursor can be quite often transformed into other derivatives in a stereospecific manner without significant loss of optical purity (which can be in many cases improved by crystallization). More and more such chiral sulfinyl transfer agents have become easily available (in a short synthesis or from commercial sources), in both enantiomeric forms, and virtually any substitution pattern can be achieved. On the other hand, preparative methods based on catalytic enantioselective oxidation or imination of achiral organosulfur compounds involve chirality multiplication and are beneficial from the economic point of view. The possible disadvantages and difficulties (e.g., contamination by traces of toxic metals which can preclude biomedical applications) can be overcome if chiral organic molecules are applied as catalysts.

The development of synthetic methods is often inspired by the increased interest in a given family of compounds resulting from possible applications (both synthetic and biomedical). Quite often, a series of independent reports are published in a short period of time, followed by subsequent papers describing modifications and improvements. In the case of sulfinyl compounds, it can be observed that new approaches have been introduced mainly without much stress on stereochemical issues, which are included on the later stage. This raises hopes on further progress in the field, as asymmetric variants of newly introduced methods are needed. One recent example can be added to those cited in the previous sections. A one-pot synthesis of unsymmetrical sulfoxides was developed based on subsequent reactions of two organometallic reagents with DABSO (DABCO-bis(sulfur dioxide)) used as a source of sulfinyl group.³⁹⁴ A potential of this methodology and other protocols in which chiral sulfinyl compounds are obtained as racemic mixtures should serve as a driving force in future research in the field.

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Notes

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Biographies

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Jacek Wojaczyński graduated in chemistry from the Faculty of Mathematics, Physics and Chemistry of the University of Wrocław in 1993. Five years later, he defended his Ph.D. thesis on metalloporphyrin modifications at the Faculty of Chemistry of the same university (supervisor: Prof. L. Latos-Grażyński). He is a member of the Metalloporphyrin Chemistry Group at this faculty, and his research field includes oligoporphyrins, heme proteins, and degradation of oligopyrrolic macrocycles.

ABBREVIATIONS USED

15-C-5 = 15-crown-5, 1,4,7,10,13-pentaoxacyclopentadecane
 18-C-6 = 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane
 ACDC = asymmetric counteranion-directed catalysis
 AIBN = azobis(isobutyronitrile)
 BINOL = 1,1'-bi-2-naphthol
 Boc = *tert*-butoxycarbonyl
 Bz = benzoyl
 CHP = cumene hydroperoxide
 CPME = cyclopentyl methyl ether
 CPO = chloroperoxidase
 Cp^x = chiral cyclopentadienyl ligand
 CYMO = cyclohexanone monooxygenase
 DABCO = 1,4-diazabicyclo[2.2.2]octane
 DABSO = DABCO-bis(sulfur dioxide)
 DAG = diacetone-D-glucose
 DAST = diethylaminosulfur trifluoride
 dba = dibenzylideneacetone
 DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
 DET = diethyl tartrate
 DMC = dimethyl carbonate
 DMSOR = dimethyl sulfoxide reductase
 EBX = ethynyl benziodoxolone
 HB = hydrobenzoin
 HOBt = 1-hydroxybenzotriazole
 Josiphos = chiral diphosphine, ferrocene-based ligand
 KHMDS = potassium bis(trimethylsilyl)amide
 LDA = lithium diisopropylamide
 LiHMDS = lithium bis(trimethylsilyl)amide
m-CPBA = *meta*-chloroperbenzoic acid
 MSH = *O*-(mesitylsulfonyl)hydroxylamine

NaMDS = sodium bis(trimethylsilyl)amide
 NBS = *N*-bromosuccinimide
 NCS = *N*-chlorosuccinimide
 NHC = *N*-heterocyclic carbene
paMsrA = methionine sulfoxide reductase A obtained from *Pseudomonas alcaliphila*
 PIDA = phenyliodine diacetate, PhI(OAc)₂
 SIAM = bis(sulfinyl)imidoamidate
 SIAPhos = phosphorylated sulfonimidamides
 TBAF = tetrabutylammonium fluoride
 TBDMS-NH₂ = *tert*-butyldimethylsilyl amine
 TBDPS = *N-tert*-butyldiphenylsilyl
 TBHP = *tert*-butyl hydroperoxide
 TBTH = tributyltin hydride
 TFAA = trifluoroacetic acid anhydride
 TMS = trimethylsilyl
 Trt = trityl, triphenylmethyl

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