Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds
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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, sulfilimines (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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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. 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 sulfinyl compounds, which are also prepared in a stereoselective manner, e.g., sulfinamides, sulfinimines, sulfinates and thiosulfinates, sulfoximes, sulfonimidamides, and sulfinimidates.

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. Recent reviews show the utility of various sulfur derivatives in organic synthesis. 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.

Chiral organosulfur derivatives are found in natural systems such as methionine sulfoxide, S-adenosyl methionine, allisin, or leinamycin (Figure 2). Synthetic sulfinyl compounds often 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 antulcer drugs or modafinil 3 (Figure 2). Recently, the better synthetic availability of sulfoximes (as exemplified by roniciclib 4), sulfinimidamides, and sulfinimidates has led to the increased interest in their possible application in drug design. These analogues of sulfones and sulfinamides, 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 Mikolajczyk, Józef Drabowicz, and Piotr Kielbasiński, was printed in 1997 and contains chapters devoted to various types of sulfoxides, sulfonic acid derivatives,11 and sulfoximes.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 sulfoximes15 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. 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 substitution): sulfinic halides, sulfinimides and sulfinmines (N-sulfinylimines), sulfinates, and thiosulfinates (also thiosulfonic acids and their salts are chiral, although they are prone to slow decomposition and rarely prepared17,18). Among their counterparts in which the place of lone electron pair is taken by a =NR’ fragment, sulfoximes require two different carbon groups for chirality, while derivatives of sulfinimidic acids are chiral by definition (Figure 3). Salts with three organic groups attached to sulfiny 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 Rice and co-workers. A mechanism of racemization
of thiosulfonates caused by nucleophiles or catalyzed by acids was analyzed as well as kinetics of alkaline hydrolysis of aryl thiosulfonates and thiosulfonates.\textsuperscript{23–25} It was shown that the presence of a bulky substituent at sulfur increases the stability of thiosulfonates, and most work was done for tert-butyl derivative (see section 5). Various factors affecting racemization were summarized in a chapter written by Mikolajczyk and Drabowicz.\textsuperscript{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 sulfinyl 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, sulfinyl halides, sulfenic acid derivatives: sulfenes, sulfenamides), trisubstituted, and tetrasubstituted organosulfur compounds (Scheme 1). In conversions involving the first group to the 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).\textsuperscript{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.\textsuperscript{30} Similarly, reduction of sulfones has never emerged as a convenient route to sulfoxides.\textsuperscript{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 enantiomeric 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).\textsuperscript{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.\textsuperscript{33–35} 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.\textsuperscript{33} Several articles were devoted to asymmetric oxidations, including sulfoxidations, with a focus on environmentally benign methods.\textsuperscript{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 sulfinyl compounds: sulfoxides, disulfides, and sulfenylamines.\textsuperscript{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.\textsuperscript{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. Attempts with new chiral stoichiometric oxidants (N-chloramine derivatives) were not very encouraging (up to 23% ee). 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. 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 the design and synthesis of a chiral tetraol containing two tartrate moieties, which was found superior in the enantioselective oxidation of alkyl aryl sulfoxides in comparison with the original Kagan’s system (Scheme 2).

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

In a series of publications, Cardelliccio and co-workers thoroughly studied oxidation of sulfoxides by titanium/(S,S)- or (R,R)-hydrobenzoin (HB, 6) catalytic system. Through a combination of experimental and theoretical work, they found that benzyl aryl sulfoxides 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)$_2$]$^{2+}$ with substrate and TBHP. However, they found that for aryl benzyl or aryl phenacetyl sulfoxides 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). Again, this 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 pyridylmethylthiobenzimidazoles led to enantiopure proton pump inhibitors. Also, other groups prepared various enantiomerically enriched sulfoxides using chiral tetradeinate and tridentate Ti(IV) complexes as catalysts. An interesting dinuclear system based on 8-quino lignol-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).

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

Sulfoxides 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. Manganese was used in combination of salen or another tetradeinate, N4 ligand 8; the latter, with carboxylic acid 9 as additive and H$_2$O$_2$ as oxidant, allowed highly enantioselective, gram-scale preparation of various sulfoxides also in the flow system (Scheme 5).

Scheme 5. Oxidation of Sulfoxides Catalyzed by Manganese Complex

salen-type Fe(III) complexes were also used in successful sulfoxidations with peroxides. 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). Optimized reaction conditions included slow addition of aqueous hydrogen peroxide and the use of lithium 4-dimethylaminobenzoate additive 12 and ethyl acetate as a...
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). Other derivatives (lansoprazole, pantoprazole, rabeprazole) were obtained in 75–87% yield and 83–98% ee.

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

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. 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. 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, non-specific interactions of both thioanisole and Cu complexes with the quadruplex.

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

Construction of supramolecular assemblies and metal–organic frameworks capable of selective oxidation of sulfides to sulfoxides was reported by several groups. Certain systems containing chiral subunits led to high enantioselectivities. In our previous review on stereoselective synthesis of sulfoxides, we expressed our expectation that organocatalytic sulfoxidation would attract growing attention. Since 2010, the

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

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

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 Ye

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. 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. 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, non-specific interactions of both thioanisole and Cu complexes with the quadruplex.
actual development has been not so impressive. However, promising results were obtained with flavin-derived catalysts and BINOL-based phosphoric acid derivatives. The latter allowed an enantioselective preparation of (R)-sulindac 20 (95% yield, 98% ee, Scheme 9). However, (R)-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.

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. Among recent applications, sulfinylation of indoles through electrophilic substitution with arylsulfonic acids described by Miao et al. is worth mentioning, as it was performed in water at room temperature without any additives. Another green Friedel–Crafts sulfinylation of aromatic compounds with sulfonic esters was carried out in ionic liquid and accelerated by ultrasound irradiation. Sulfinamides were applied in a similar, visible light-accelerated transformation of heteroaromatic substrates. 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. In the following years, efficient routes to these underexplored intermediates were introduced and their subsequent arylation catalyzed by transition metal complexes were described. Perrio and co-workers identified β-sulfinyl esters as versatile precursors of a sulfenate anion. Various bases (NaHMDS, KHMD5, 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 enantipure 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 alkylation and arylation. Enantioenriched aryl−arylated and aryl−benzyl sulfoxides were prepared by this group by applying palladium catalyst with a chiral ligand. Josiphos-type derivatives appeared most efficient in this role (Scheme 10). A pseudodinomin process of palladium-catalyzed arylation of anions obtained from allylic sulfoxides was also described. The achievements by Poli, Madec, and co-workers in the field were summarized in a short review published in 2010.

Perrio’s group focused their attention on a diverse approach involving the use of phase-transfer reagents serving both as catalysts and chirality source. 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).

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). 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. 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 sulfinamide methodology. Schwand and co-workers investigated mainly diastereoselective alkylations.
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. 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. Later on, they concentrated their efforts on finding mild conditions for generation of sulenate. In their preparation of enantioenriched aryl sulfoxides, sodium tert-butoxide was chosen as a base, and the chiral catalyst was formed in situ from Pd(dba)$_3$ and [Pd(allyl)Cl]$_2$ as a palladium source. Nineteen sulfoxides were prepared, including these bearing heteroaryl moieties. Cs$_2$CO$_3$ was used as a base, Pd$_2$(dba)$_3$ and [Pd(allyl)Cl]$_2$ as a palladium source were sometimes added as additives. The reaction was not performed in the asymmetric variant.

Scheme 13. Enantioselective Reaction of Sulenate Anions with Aryl and Alkenyl Bromides

Although palladium-catalyzed reactions of sulenate anions were commonly performed, protocols in which this noble metal was not used were described as well. A CuBr$_2$-catalyzed reaction of sulenate 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. Transition metal-free arylation reactions 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.

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 sulenate anions. Aryl or alkyl sulenate 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 sulenate anions.

Synthetic methods based on reactions of sulenate 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 efficiently), these routes should be treated as an interesting alternative to purely chemical systems.

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; in 2018, sulfoxidations with biological systems were also summarized.

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. However, the use of isolated enzymes for enantioselective oxidation of sulfoxides in the past decade was
also described by several groups.\textsuperscript{141–144} Examples include monoxygenases, 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 protein\textsuperscript{145} or bovine serum albumin.\textsuperscript{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%).\textsuperscript{148} Among the latest biocatalytically stereoselective preparations of sulfoxides, asymmetric sulfoxidation of 1-thiochromanone-4-one derivatives by cytochrome P450-BM3 monooxygenase was described by Reetz and co-workers (Scheme 15).\textsuperscript{149} Directed evolution allowed increasing of the stereoselectivity (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.\textsuperscript{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).\textsuperscript{151–153}

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.\textsuperscript{1,13} 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 sulfenates with chiral oxidants (e.g., peroxocamphoric acid\textsuperscript{154} or catalytic oxidation systems (Kagan’s method\textsuperscript{155}) were not particularly encouraging (maximum ee of 36% was reached).

Diastereoselective oxidation of benzenesulfenates bearing a phosphonate group at the ortho-position leading to the corresponding sulfinates was investigated by Vazeaux, Drabowicz, and their co-workers.\textsuperscript{156} Starting sulfenates 27 were obtained in the reaction of chiral alcohols with sulfenyl chloride 26 (in turn prepared from thioliol 25, Scheme 17). Menthol 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-tolysulfinates by transesterification.\textsuperscript{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.\textsuperscript{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 \textit{Cinchona} alkaloids, and the method extended over other (mainly benzyl) alcohols (Scheme 18).\textsuperscript{159} Simultaneously, highly enantioselective preparation of aresulfinates from racemic sulfinyl chlorides and achiral alcohols assisted by \textit{Cinchona} alkaloids was reported by Shibata, Toru, and co-workers (up to 99% ee).\textsuperscript{160,161}

A variety of chiral alcohols have already found use in diastereoselective preparation of sulfinates. Menthol 29 has often been applied;\textsuperscript{162} Andersen’s method of stereoselective synthesis of sulfoxides is based on the crystalline (1R,2S,5S,R,S,−)−menthyl p-toluenesulfinate.\textsuperscript{163} Diacetone-
\textit{d}-glucose (DAG), a sugar-derived alcohol 33, was also identified as a particularly useful auxiliary (both are commercially available).\textsuperscript{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
sulfinates in the presence of strong acids was shown to proceed with a predominant inversion of configuration.\textsuperscript{165} (S)-N,N-Diethyl p-toluene sulfinamide was first prepared from the corresponding menthyl sulinate and Et\textsubscript{2}NMgBr. 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 sulfinates 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 sulinate and acid used (up to 40% ee).\textsuperscript{166,167}

The stereochemistry of conversion of sulfinamides to sulfinates was later found to be more complex.\textsuperscript{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.\textsuperscript{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 sulinate esters was introduced by Jacobsen et al.\textsuperscript{170} A mixed anhydride was prepared from sodium sulinate 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.\textsuperscript{171} A double activation was provided by Lewis acid (bismuth(III) triflate) and Brønsted acid (CCl\textsubscript{3}COOH). Asymmetric variant of these two protocols was not proposed.

### 4.3. S−C Bond Formation

Reactions of sulfinates and chlorosulfinates with organometallic reagents also provided sulfinates with a variable yield and stereoselectivity. Optically active tert-butyl sulfinates were prepared from symmetrical dialkyl sulfinates and tert-butyl magnesium 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).\textsuperscript{172} An appropriate 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 thiosulfinates with Grignard reagents and quinine was also developed; it allowed preparation of nonracemic sulfinates with nonbulky alkyl or aryl substituents with ee up to 33%.

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

An interesting homolytic substitution process in which certain sulfinates under radical conditions (Bu\textsubscript{3}SnH, AIBN, heating in benzene) underwent an intramolecular cyclization to give cyclic esters (sultines) was reported by Coulomb et al.\textsuperscript{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.
5. SYNTHESIS OF OPTICALLY ACTIVE THIOSULFINATES

Thioesters of thiosulfinic acid (or disulfide S-oxides) belong to chiral sulfynyl compounds containing 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. Preparation of tert-Butane tert-Butyl Thiosulfinate Developed by Ellman and Co-workers

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 sulfynyl compounds: sulfinimides, sulfoxides, sulfinates, and others.27

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 Sagine and Favaro. In 1965, Rice and co-workers described an asymmetric oxidation of aryl disulfides to thiosulfinates.181 The use of chiral peroxyxandamic 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-sulfonyleoxaziridines 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/Ti(O-Pr)4/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 H2O2 and the use of cosolvent with low miscibility with water (CHCl3 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-butylsalcylaldehyde (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-butylsulfinamide 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 form 3,5-di-tert-butylsalicylaldehyde and aminoalcohols were applied. Also para-tolyl disulfide was oxidized by H2O2 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 monoxygenase 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 Monooxygenase
connected to tert-butyl substituent was noted for the unsymmetrical substrate, p-tolyl tert-butyl disulfide. Bovine serum albumin was tested as a chiral auxiliary in oxidation of disulfides; desired products were formed, but stereoselectivity was unsatisfactory. Instead, an oxidation system based on chiral fructose-derived dioxirane was applied, which led to high conversion and ee up to 75%.

Also, Boyd et al. described oxidation of 1,2-disulfides using enzymatic methods. While acyclic substrates failed to give expected thiosulfates under conditions used, 1,2-dithiane was converted into S-oxide quantitatively and with 96% ee by chloroperoxidase (CPO) and H₂O₂ (Scheme 23).

Scheme 23. Oxidation of Cyclic Disulfides by Chloroperoxidase

Other tested systems: cyclohexanone monoxygenase and whole cells expressing arene dioxygenases were inefficient in this transformation. CPO catalyzed oxidation of a bicyclic substrate in 59% yield and 47% ee (Scheme 23); in both cases, configuration of the main isomer was established as S. A possibility of stereoselective deoxygenation of racemic dithiane-derived thiosulfate by dimethyl sulfoxide reductase (DMSOR) to yield enantioenriched residual substrate (95% ee, S isomer) was demonstrated as well.

5.2. S−S Bond Formation and Other Preparations

Drabowicz and Mikolajczyk explored various possibilities for preparation of nonracemic thiosulfates from other sulfinyl derivatives. Thermal decomposition of di-tert-butyl sulfoxide in the presence of equimolar amount of enantiopure chiral amines led to the formation of nonracemic tert-butyl tert-butane thiosulfinate (Scheme 24). Although enantiomeric excess was low (1−26%, the latter value for quinine as inducer of chirality), both enantiomers of thiosulfate could be prepared, and amines could be recovered after the reaction. Other thiosulfates could not be prepared with this method, which was attributed to their instability under the conditions used.

Chiral amines were also applied as chiral inducers in the condensation of sulfinyl chlorides with thiols. (−)-N,N-Dimethylamphetamine and (+)-N,N-dimethylfenchylamine allowed preparation of six enantioenriched (S)-thiosulfates (Scheme 25). A reaction of tert-butyl thiol with arylsulfonic acids in the presence of chiral carbodiimide led to the corresponding thiosulfinate in up to 2% ee.

Scheme 25. Synthesis of Enantioenriched Thiosulfates from Sulfinyl Chlorides and Thiols

Nonracemic thiosulfates were also prepared by Drabowicz and Mikolajczyk by treatment of enantiomerically enriched sulfinamides with thiols in the presence of trifluoroacetic acid. The reaction took place with predominant inversion of configuration, with stereoselectivity in the range of 30 to >80%, dependent mainly on the structure of thiols.

tert-Butane tert-butyl thiosulfinate was obtained by Liao et al. by resolution of racemate using inclusion crystallization with (R)-binol, yielding both enantiomers with high enantiomeric purity (ee > 99%).

6. STEREOSELECTIVE PREPARATION OF SULFINAMIDES AND SULFINIMINES

Trisubstituted sulfinyl compounds of the general formula R¹S(O)NR²R³ (sulfinamides) or R²S(O)N=CR¹R³ (sulfinimines/N-sulfinylamines) belong to most important chiral auxiliaries in asymmetric synthesis, used in preparation of a great variety of optically active heteroorganic compounds containing a nitrogen atom. Primary (R² = R¹ = H), secondary (R² = alkyl, aryl, R¹ = H), and tertiary amides can be prepared; the appropriate choice of R¹−R³ groups results in modification of their properties, e.g., basicity and nucleophilicity of the nitrogen atom, which may influence the course of asymmetric reactions.

A chapter of “Chiral Sulfur Reagents” by Mikolajczyk, Drabowicz, and Kielbasinski presents methods of stereo-selective preparation of sulfinamides and N-sulfinylamines (named N-alkyldenesulfinamides throughout the chapter) and their synthetic applications published up to 1996. In their chapter from the book, edited by Toru and Bolm, Senanayake and co-workers covered the literature up to 2007, with a special focus of a general preparative route introduced in their laboratory. Ellman and co-workers published two review papers in which tert-butanesulfinamide was presented as a useful synthetic intermediate in asymmetric reactions. N-Sulfinylamines, the family of compounds of great synthetic importance, were the subject of the second part of article by Davis, who briefly described the synthesis of enantiothermically pure compounds from his group, more widely showing their great potential as chiral auxiliaries and reactants. In their papers published in 2002 and 2009, respectively, Ellman’s group and Ferreira and co-workers narrowed their topic to tert-butanesulfinimines: their enantioselective preparation, postsynthetic modification, and use in asymmetric transformations, mainly in the synthesis of chiral amines.

Typically, optically active sulfinamides are prepared from enantiothermically pure sulfinates, thiosulfates, or sulfinyl chlorides (the latter generated in situ) by a nucleophilic
substitution. However, other synthetic routes to these compounds have been reported as well. Sulfonamides and N-sulfinylamines 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 sulfonamides by oxidation of corresponding sulfenylamines were reported. This approach is hindered by a limited scope of available substrates, although they can be prepared, e.g., from thiols, disulfides or sulfenyl halides. Among recent examples, a nonstereoselective oxidation of various sulfenylamines by KF/m-CPBA in acetonitrile-water at 0 °C in 82–94% yield was performed by Datta et al. 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 sulfenylamines with hydrogen peroxide mediated by a chiral binaphthyl-based phosphoric acid derivative showed the possibility of preparation of nonracemic sulfonamides via S=O bond formation (Scheme 26). Under optimized reaction conditions (dichloromethane/35% aqueous H2O2/5% of catalyst/MgSO4 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 by DFT calculations of transition states. The prepared sulfonamides were further converted into other compounds from this class (vide infra) and sulfoxides.

Other attempts involving oxidation of sulfinyl derivatives formed from thiols or disulfides are worth mentioning. N-tert-Butanesulfinylphthalimide was prepared by treatment of the corresponding sulfinyl derivative (obtained from N-bromophthalimide and tert-butyl disulfide) with peroxyacetic acid. Ring opening under Lewis acid catalysis (samarium triflate was used) followed by the addition of ammonia yielded tert-butane sulfonamide. 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. 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-Sulfinylamines were also prepared by enantioselective oxidation of sulfinylamines. In 1997, Davis and co-workers described the use of enantiopure oxaziridines 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). 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.

### 6.2. S–N Bond Formation

Sulfonamides are conveniently obtained from other trisubstituted sulfinyl 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-toluensulfonamides from the corresponding menthyl sulinate and dialkylaminomagnesium bromides. The reaction proceeded with an inversion of configuration. Later on, this auxiliary introduced by Andersen, now commercially available, was used in the synthesis of other sulfonamides, mainly with the use of lithium amides. Davis and co-workers reacting this sulinate with lithium amide followed by addition of aldehyde or ketone obtained the corresponding N-sulfinylamine with high enantioselectivity (Scheme 28).

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

Nucleophilic substitution of enantioenriched tert-butyl tert-butyl thiosulfinate (see Section 5.1) was established by Ellman and co-workers as a very convenient route to tert-butyl...
sulfoxides and, in particular, tert-butanesulfinamide (lithium amide was used, Scheme 30).\textsuperscript{178,184,186,187} No racemization during this step was observed, and the product could be obtained in multigram amounts. Compound \textit{S2} 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.\textsuperscript{178}

Various enantiomerically pure aldimines were prepared in a one-step condensation of sulfinamide \textit{S2} with aldehydes in the presence of dehydrating agents.\textsuperscript{215} Also, ketimines were formed with a significant \textit{E}/\textit{Z} preference from respective ketones when \textit{Ti(OEt)}\textsubscript{4} was applied as a Lewis acid (Scheme 30).\textsuperscript{215,216} The procedure was later optimized, and tetrahydronorbornyl methyl ether (preferred in the case of more challenging ketones) were identified as optimal solvents.\textsuperscript{217} The possibility of recovering the chiral auxiliary was investigated as well.\textsuperscript{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 NaBH\textsubscript{4} could be performed to give sulfinamides (66–86% yield, 80–94 \textit{de}).\textsuperscript{219} Both enantiomers of amine were obtained with high ee, with configuration dependent on the choice of reducing agent (NaBH\textsubscript{4} vs \textit{i}-selectride).\textsuperscript{220} Addition of alkyl, aryl, alkenyl, and allyl carbanions to aldimes and ketimines was performed, and the resulting sulfinamides were cleaved by HCl in methanol, yielding a variety of enantioenriched branched amines.\textsuperscript{221}

Other examples of the use of tert-butylsulfinyl auxiliary in asymmetric synthesis by Ellman’s group included preparation of (among others) amino acids,\textsuperscript{222–224} amino alcohols,\textsuperscript{225–227} cyclic amines,\textsuperscript{234,228,229} unsaturated amines,\textsuperscript{2,230,231} nitrides,\textsuperscript{232} aminophosphonates,\textsuperscript{233} aminoboronates,\textsuperscript{234} and total synthesis of natural products.\textsuperscript{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.\textsuperscript{237} They were obtained in condensation of isocyanates or isothiocyanates with tert-butanesulfinamide and used in asymmetricaza-Henry reaction. High stereoselectivity was observed for derivatives also containing aminooindanol moiety. Other sulfinylureas were found efficient in enantioselective additions to nitroalkanes.\textsuperscript{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.\textsuperscript{243} Ellman’s group applied enantiopure tert-butanesulfinamide \textit{S2} to the preparation of chiral ligands. \textit{C}_{2}-Symmetric bis(N-sulfinylimine) derivatives and bis(sulfinyl)imidoamidine (SIAM) were tested in copper- and zinc-catalyzed asymmetric Diels–Alder reaction (up to 98% \textit{de} and up to 98% \textit{ee}),\textsuperscript{244} while \textit{N}-sulfinylimine ligands bearing phosphine moiety were used in palladium-catalyzed allylic alkylation (yielding up to 96% \textit{ee}),\textsuperscript{245} and iridium-catalyzed hydrogenation of stilbenes (up to 94% \textit{ee}).\textsuperscript{246}

Later, Ellman and co-workers developed an improved synthesis of more electrophilic perfluorobutanesulfinamide \textit{S4} accomplished with the use of Senanayake’s 2-aminooindanol-derived sulfinyl transfer reagent\textsuperscript{213} and a suitable Grignard reagent prepared from EtMgBr and CF\textsubscript{3}I.\textsuperscript{247,248} The sulfinyl intermediate was treated with amine nucleophiles; NaHMDS led to the highest yield. The sulfinamide could be performed on a gram scale in 67% yield and 99% ee using this two-step sequence (Scheme 31). Its condensation with ethyl glyoxylate provided \textit{N}-sulfinyl imine ester, which was used in asymmetric transformations (Rh(III)-catalyzed C–H bond functionalization, aza-Diels–Alder reaction).\textsuperscript{247,249}

An alternative for tert-butane sulfinamide for the application in asymmetric synthesis was introduced by Li and coworkers.\textsuperscript{250} The novel auxiliary combined properties of para-tolyl- (aromatic chromophore) and tert-butyl-substituted (stability) derivatives. (R)-2-Phenyl-2-propyl sulfinamide \textit{S8} was prepared in four steps starting from the respective thiol, with H\textsubscript{2}O\textsubscript{2}/VO(acac)\textsubscript{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-NH\textsubscript{2}) followed by deprotection. Reaction of aldimines and ketimine derived from this sulfinamide with allylmagnesium bromide provided a range of new compounds that were used in further asymmetric transformations.
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-phenylethylamine.\textsuperscript{251} \((R,S)\)-Diastereomers were isolated from the reaction mixture as solids in ca. 30% yield, while mother liquor was enriched in \((R,R)\) 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 \((S)\)-sulfinamides (which could not be obtained directly form 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.\textsuperscript{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).\textsuperscript{253} Products were isolated as single stereoisomers by chromatographic separation.

**Scheme 33. Preparation of Chiral Epimeric Secondary Sulfinamides from Sulfonyl Chlorides and Enantiopure Amines**\textsuperscript{253}

Tang and co-workers converted N-phenyl tert-butane sulfinamide prepared by enantioselective oxidation of its sulfinyl counterpart (see section 6.1) into other derivatives (for which direct oxidation was not successful) via N-protection and nucleophilic substitution with primary amines.\textsuperscript{205} While yields were moderate (55–70%), almost complete inversion of configuration was observed (94–97% ee). Copper-catalyzed transimidations 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.\textsuperscript{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.\textsuperscript{255} Reaction with nitrogen, oxygen, or carbon nucleophiles led to sulfinamides, sulfonimidates, 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.\textsuperscript{256} Tsujihara et al.\textsuperscript{257} conducted pyrolysis of alkyl-substituted derivatives, and Williams et al. carried out tosylation.\textsuperscript{258} Schroeck and Johnson also observed a similar conversion (reductive elimination of \(\text{N}(\text{CH}_3)_2\) or OPh group, respectively) of sulfonimidamides and sulfonimidates.\textsuperscript{256} More examples of stereoselective transformations of sulfoximines to sulfinamides caused by various triggers can be found in a recent review by Wiestorek et al.\textsuperscript{259} 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.\textsuperscript{250} Hydrolysis of racemic N-chloroacetyl and N-dihydrocinnamoyl arylsulfinamides were catalyzed by subtilisin \(\text{E}\) overexpressed in \(\text{Bacillus subtilis}\), providing mainly \((R)\) primary sulfinamides (Scheme 34). Their \((S)\) counterparts could be formed after non-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(1) complexes was described by Liu et al.\textsuperscript{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 sulfinic 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 \(\beta\)-sulfinyl esters.\textsuperscript{261} Optimization

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**Scheme 32. Preparation of Sulfinamide 58 by Li and Co-workers**\textsuperscript{250}

**Scheme 34. Biocatalytic Deracemization of N-Acyl Sulfinamides**\textsuperscript{259}
of reaction conditions revealed Cul/bipy as the best catalytic system, lithium tert-butoxide as the most efficient base, with toluene as solvent. A variety of aliphatic and aromatic sulfinimides 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 sulfinimides 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.254–256 They were able to separate diastereomers of methionine sulfoximine and prepared other sulfoximines from sulfoxides using HNCl.257,258 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.266 Methods of sulfur atom imidation of sulfoxides and sulfoxides,270 and routes of degradation of sulfoximines.267 The importance of these compounds in the area of drug discovery is highlighted in articles by Bolm’s group.271 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, Reggadin 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-camphorsulfonic acid.278,279 Though resolutions (mainly kinetic) still resulted in the 1:1 mixture of epimers, all other compounds were racemic.

7.1. S==O Bond Formation

Typical preparations of sulfoximines start from prochiral sulfoxide. 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 sulfilimes (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 sulfoximines can be obtained as single enantiomers.281 Stereochemistry of oxidation of N-sulfonylsulfilimines with alkaline solution of KMnO4 was studied by Kresze and Wustrow, who observed retention of configuration. Long reaction times are sometimes required for this oxidant, and yields can be small (for instance, only 10% for oxidation of thiane-derived sulfilimine).282 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 MnO2 led to the corresponding racemic sulfoximines, either bearing N-acyl or NH fragment (depending on the environment).283

An improvement was introduced to the method of preparation of the crop protection agent sulfoxaflor (known also under trade name Isoclast active).284 The N-CN sulfilimine was prepared from pyridine sulfoxide treated with iodosbenzene diacetate and H2NCN in acetonitrile and then oxidized. Various oxidation methods were tested, including RuCl3/NaIO4 combination, but for practical and economic reasons, 40% aqueous NaMnO4 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 sulfilimes with ruthenium tetroxide, generated in situ from NaIO4 and substoichiometric amounts of RuO2.285,286,287

Racemic N-cyanosulfilimines, prepared by Bolm and co-workers from sulfoxides 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 sulfilimide of sulfoxides with PhI==NTs catalyzed by transition-metal chiral complexes and bis-oxazoline ligands was studied (Scheme 36).289 The best results (yield reaching...
99%, up to 82% ee) were noted for iron(III) acetylacetones used as catalyst precursors. Oxidation of the obtained N-tosylsulfinilines 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-mesyoxy carbamate caused a stereoselective amination of thiocetals in the presence of a chiral dirhodium- (II) carboxylate catalyst to yield the corresponding sulfoximines. The possibility of preparation of sulfoximine through oxidation of sulfinilide with NaIO₄ with RuCl₃ as a catalyst was demonstrated; removal of chiral auxiliary with zinc in acetic acid yielded NH-sulfinilide as a single enantiomer (94%). Lebel and co-workers also applied iron catalyst in a similar preparation. 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 sulfinilides resulted in formation of NH-sulfoximines in high yields (up to 95%). N-Chlorosuccinimide and sodium hypochlorite were used as chlorinating agents for NH-sulfinilide; 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. Efficiency of various imidating agents: N-haloamides and similar compounds (chloramine T, MSH), aziridine derivatives, dioxazolones, azides, and iminodinonanes 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 enantioselectively enriched sulfoxide as a starting material. In each case, a complete retention of configuration was observed. An interesting example of kinetic resolution of racemic sulfoxides was described by Dannenberg et al.

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-cyanosulfinilides from sulfoxides. 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). NH-Sulfoximines were synthesized in the reaction of sulfoxides and triflic acid salts of hydroxylamine catalyzed by Fe(II) complex. 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. 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). 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 Saryl 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 38. Stereospecific Formation of N-Cyanosulfoximine from Sulfoxide

### Scheme 39. Stereospecific Formation of Sulfoximine from Sulfoxide-Direct NH Transfer and Rh-Catalyzed Carbamate Transfer

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. The use of ammonium carbamate (4 equiv) and diacetoxiodobenzene (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 sulfides \(^{301}\) 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: sulfonylmidoyl halides, sulfonylimidamidates, and sulfonylimidamides. Reggelin and co-workers developed a strategy based on preparation of two epimers of cyclic sulfonylimidamate (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 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 sulfonylimidamate were used in a one-pot synthesis of enantiopure cyclic oxathiazine S-oxides \(^{306}\) and other enantiopure sulfoximines. \(^{278}\)

A synthesis based on the use of sulfonylimidates 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 sulfonylimidoyl 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 sulfonylimidoyl chloride with mono-, di-, and trisubstituted olefins in the presence of \(\text{AlCl}_3\) provided benzothiazines bearing two stereogenic centers with variable diastereoselectivity. \(^{310}\) The effect of alkene substitution on the reaction outcome was studied.

Also noncyclic sulfoximines were prepared from sulfonylimidoyl chlorides or fluorides, as exemplified by the reaction of the latter with \(\text{TMSCF}_3\) leading to trifluoromethylated product. \(^{311}\) Diarylsulfoximines were prepared by Takata and co-workers from sulfonylimidoyl 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 sulfinamides was investigated as well.

### Scheme 40. Sulfoximines Obtained from Epimeric Sulfonylimidamidates

![Scheme 40. Sulfoximines Obtained from Epimeric Sulfonylimidamidates](image)

### Scheme 41. Preparation of 2,1-Benzothiazines from Compound 73 and Alkynes or Alkenes

![Scheme 41. Preparation of 2,1-Benzothiazines from Compound 73 and Alkynes or Alkenes](image)

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 alylation of sulfinamides was described. \(^{315,516}\) 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 \(\text{NaH}\), \(1.1–1.2\) 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 \(\text{LiAlH}_4\) treatment. Interestingly, starting with tert-butyl sulfinamide opened the route to both enantiomers of various derivatives.
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 aryliodonium salts and N,N-dicyclohexylmethylamine in DMSO: conversion of N-pivaloyl tert-butane sulfinamide proceeded in 53–90% yield. 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.

7.4. Formation of \( \text{S}=\text{O} \) and \( \text{S}=\text{N} \) 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 sulfides to sulfoximines, diazotioxidobenzene (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 Sulphides

Preparation of NH-sulfoximines from sulfides treated with PIDA and \( \text{H}_2\text{NCOONH}_4 \) was also described by Reboul and co-workers and modified reaction conditions allowed extension of the methodology for derivatives bearing perfluoroalkyl substituents (Scheme 44).319 A similar procedure, but with ammonium carbonate \( (\text{NH}_2\text{CO})_2\text{CO} \) 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 atucvecilbicil.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 enantiomer-enriched 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-diaryl 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 enantiomeric purity using enantioselective oxidation of 4-bromophenyl methyl sulfoxide (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* 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 substituent328–330). 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

Scheme 45. Desymmetrization of Sulfoximine 75 Yielding Myristic Acid Derivative323

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Chem. Rev. 2020, 120, 4578–4611
of various sulfoximines with aryl bromides catalyzed by palladium salts, Bolm and co-workers also used a chiral (S)-bromide and (R)-sulfoxime 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)-Sulfoxime

\[
\text{HN}^+ \text{S}^- + \text{Ph}^+ \text{Br}^- \rightarrow \text{HN}^+ \text{S}^- \text{Ph} \]

Palladium- and copper-catalyzed arylations of NH- or N-benzylsulfoximines developed in Bolm’s laboratory allowed preparation of chiral ligands for asymmetric synthesis.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 sulfinimidoyl chlorides in the synthesis of enantiothermically pure benzothiazines, Harmata and Pavri adapted the N-arylation protocol developed by Bolm.331,339 The reaction between enantiopure NH-sulfoximine and ortho-bromobenzene 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 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 monosubstitution were observed.343

8. SULFONIMIDOYL HALIDES

The title compounds, which can be regarded as halides of sulfinimidic 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 sulfinimidamides.

Most frequently, sulfinimidoyl 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.346 Later replaced by tert-butyl hypochlorite (Scheme 48).348 Retention of configuration 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)-sulfinimidoyl chloride).349 Stereospecific conversions of sulfinimidoyl chloride to sulfinimide and sulfinimidamides was associated with inversion of configuration.

Jones and Cram reported on the preparation of epimeric N-carbomethoxy-p-toluensulfinimidoyl 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 sulfinimidoyl chloride from other tetrasubstituted sulfinyl compounds.350 He reacted N-silylated sulfinamides with phosphorus chlorides and observed formation of the corresponding chlorides under appropriate conditions. He also obtained the first detectable sulfinimidoyl bromide. Correlation of configuration was not the part of the study.

Sulfinimidoyl 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, sulfinimidoyl 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 sulfinimidoyl fluorides were prepared by van Leusen et al. by treatment of the corresponding chlorides withKF 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.335 Quite recently, Sharpless and co-workers applied thionyl tetrafluoride 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 Sulfonimidoyl Fluorides from SOF₄ Reported by Sharpless and Co-workers354

| R¹, R² = alkyl, aryl (33 examples) |
|-----------------------------------|
| F⁻ | S=F | O⁻ |
| 83   |

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 enantioselectively 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 sulfoximides at elevated temperature.335

9.1. S—O Bond Formation

Typical preparations of sulfonimidates involve oxidative introduction of alkoxy group into sulfoximides. 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-methylbenzenesulfinamide 84 with chlorine followed by treatment of obtained sulfonimidoyl chloride 85 with sodium phenoxy (Scheme 50).359 (S)-Sulfinamide 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 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 sulfonimidoyl chlorides and bromides to the corresponding sulfonimidates in yields up to 78%.350 A quantitative desilylation with methanol resulted in NF-sulfonylaminates.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.

Sulfinamides 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 sulfonimide that could be used as precursors for enantiopure sulfoximines (Scheme 40).304,357,358 The synthesis started from (S)-O-trimethylsilylvinil and sodium salt of p-toluenesulfonic acid. The most efficient route included separation of epimeric sulfinimides by crystallization prior to the conversion of sulfonimidoyl 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 sulfinimides with alcohols and iodosylbenzene (Scheme 51).359 The reaction proceeded 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 sulfinamide. Also, secondary sulfinamide was efficiently converted to the corresponding sulfonimide in 52% yield. Stereospecificity of the transformation was checked with two enantiomerically pure sulfinimides, which yielded the corresponding products with 62 and 73% ee, mainly with retention of configuration.360 This observation was confirmed by the conversion of enantiopure sulfinimides bearing an additional stereogenic center: diastereomeric products were formed with S1—76 de. X-ray structure of the major isomer of resulting sulfonimide 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 sulfinimidates, 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.

Similarly, a series of 27 sulfinimidates were prepared by oxidation of sulfinamides with PhIO in the presence of alcohols (15 min at room temperature, yields up to 93%).360 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 sulfonimidamides, depending on reaction conditions (Scheme 52; shorter reaction time and an increase of the amount of ammonium carbamate resulted in higher yields of sulfonimida-4te).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 connection with immediate transformation of transient sulfonimido-4yl chlorides by the amine nucleophile into the respective racemic sulfonimidamides in 50–97%.364 Two enantiopure N-benzyol- and N-tert-butyloxy carbonyl-protected sulfonimidamides were efficiently prepared in several steps starting from the commercially available sodium 4-toluenesulfinate 89 (Scheme 53).365 Its conversion to enantiopure sulfonamide was achieved using menthol auxiliary. Oxidative chlorination of this sulfonamide with tert-butyl hypochlorite followed by reaction of transient (R)-sulfonimido-4yl 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 sulfonimides with t-BuOCl followed by the reaction with amine or bisamine.366 Alternatively, a reaction of N-benzyol-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-arylsulfonimidamides with N-benzylo derivatives of secondary amines (piperidine, piperazine, or morpholine) catalyzed by CuBr was also reported by Bolm and co-workers.354 Chiral amines were not tested, and racemic products were obtained in 35–96% yield.

Oehlrich and co-workers described a synthesis of sulfonimida-4mes bearing a CF3 substituent from the corresponding sulfonimidamides. 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 sulfonil 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 dipetides containing sulfonimidamides as mimics for transition states for metalloproteases and aspartic acid.369 Sulfonil phthalimide prepared by oxidation of the respective sulfenyl derivative with m-CPBA was first treated with i-phenylalanine methyl ester to afford a separable mixture of diastereomers. Sulfonimide was then reacted with chlorine, followed by substitution of chloride

Scheme 52. Preparation of Sulfonimidates from Thiols302

Scheme 53. Preparation of Enantiopure Sulfonimidamides from Sodium Sulfinate365
with ammonia, which yielded a sulfonimidamide with a free NH$_2$ 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, Lücking’s group applied ammonium carbamate combined with Phi(OAc)$_2$ for NH transfer to tertiary sulfanimidates. 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 Sulfanamides

\[
\text{H}_2\text{NCOONH}_4 (4 \text{ eq.}) + \text{Phi(OAc)}_2 (3 \text{ eq.}) \rightarrow \text{HN} \quad \text{R}^1 \quad \text{NR}^2 \text{R}^3 \rightarrow \text{HN} \quad \text{R}^1 \quad \text{NR}^2 \text{R}^3 \\
\text{MeOH} \quad 25^\circ \text{C}, 0.5-2 \text{ h} \quad 17.95\%
\]

\( \text{R}^1 = \text{aryl, heteroaryl, alkyl, R}^2, \text{R}^3 = \text{alkyl (25 examples)} \)

10.2. Preparation of Sulfonimidamides from Sulfonamides

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

Yields varied from 20 to 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 Ph$_3$P=Cl, followed by the reaction with enantiopure amine esters. Diastereomers formed in ca. 2:1 ratio were separated by column chromatography. Alternatively, a removal of N-tert-butylphenylamyl (TBDDS) 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. 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. These compounds were obtained as racemates from sulfides, disulfides, thials, 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 (1S,2R)-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 O$_2$ atmosphere. 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. 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. 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.

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).

Relatively stable sulfonimidamides 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 sulfanamides, a rarely used starting material, prepared from disulphides and amines. A one-pot formation of $\equiv$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 NH$_2$COONH$_4$ 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 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.
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. Three methods were developed for deprotection of morpholine-substituted and imine-protected sulfonimidamidates under acidic, nucleophilic, and basic conditions. An efficient palladium-catalyzed amination of imine nitrogen with aryl halides was also described. Arvidsson and co-workers reported also copper-catalyzed arylation using aryl boronic acids (a similar reaction was independently described by Battula et al.), and N-acylation with aryl or heteroaryl halides and carbon monoxide released in situ from Mo(CO)₆ in the presence of palladium catalyst, DBU, and triethylamine. Recently, N-trifluoromethylthiolated sulfonimidamides were prepared and their cytotoxicity activity studied.

Microwave-assisted, copper-catalyzed N-arylation of sulfonimidamides was also described by Malacria and co-workers. Even though hydroxyproline was used as ligand, the obtained products were racemic. The same team converted sulfonimidamides bearing NH₃ group into nitrenes by the reaction with PhIO; these nitrogen-transfer agents were trapped by sulfides, sulfoxides, or olefins in the presence of Cu(II) salt. 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 azidination.

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 =NH group. 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. Enantiopure derivatives were tested in asymmetric reactions. Novel organocatalysts were obtained in good yield from protected (S)-proline and two enantiomers of N-tosylsulfonimidamide. 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 iodide complexes, the latter found efficient in asymmetric hydrogenation of enamides (70−92% ee).

Kinetic resolution of racemic sulfonimidamides was described by Liang et al., who applied these compounds for amination of benzylc C−H bonds catalyzed by a chiral Rh(II) complex. A strong matched effect was observed between (S)-enantiomers of sulfinyl compound and the catalyst. The reaction of various benzylc substrates with racemic sulfonimidamide and Ph(OCOR-Bu), in the presence of (S)-form of rhodium complex resulted in formation of (1R,S)-product in 56−77% yield, 88−99% de, and 97−99% ee, accompanied by recovery of unreacted substrate with (R) 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 steroespecific 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 organosulfin 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. 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

The authors declare no competing financial interest.

Biographies

Elżbieta Wojaczynska received her M.Sc. Eng. degree in organic chemistry from the Wrocław University of Science and Technology in 1997. Her doctoral thesis on the enantioselective synthesis and application of chiral sulfoxides was completed under the supervision of Prof. Jacek Skarzewski in 2001. Her research at the Wrocław University of Science and Technology concentrates on the synthesis of new chiral building blocks and novel chiral ligands and catalysts for asymmetric synthesis and biomedical applications.

Jacek Wojaczynski 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 = benzyol
CHP = cumene hydroperoxide
CMPE = cyclopentyl methyl ether
CPO = chloroperoxidase
Cp^8 = chiral cyclopentadienyl ligand
CMYO = cyclohexanone monoxygenase
DABCO = 1,4-diazabicyclo[2.2.2]octane
DABSO = DABCO-bis(sulfur dioxide)
DAG = diacetone-β-glucose
DAST = diethylamino-sulfur trifluoride
dba = dibenzylideneacetone
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DET = diethyl tartrate
DMC = dimethyl carbonate
DMSOR = dimethyl sulfoxide reductase
EBX = ethyl benzidoxolone
HB = hydrobenzoin
HOBT = 1-hydroxybenzotriazole
Josiphos = chiral diphosphine, ferrocene-based ligand
KHMD = 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
pMsa = methionine sulfoxide reductase A obtained from Pseudomonas alcaliphila
PIDA = phenylidine diacetate, Ph(OAc)_2
SIAM = bis(sulfinyl)midoamidine
SIAPhos = phosphorylated sulfonimidamides
TBAF = tetrabutylammonium fluoride
TBDS-NH_3 = tert-butylidimethylsilyl amine
TBDDS = N-tert-butylidiphenylsilyl
TBHP = tert-butyl hydroperoxide
TBTH = tributyltin hydride
TFAA = trifluoroacetic acid anhydride
TMS = trimethylsilyl
Tt = trityl, triphenylmethyl

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