CHAPTER-1

Introduction

1.1 Brief history of sulfoximine

Organosulfur compounds are important class of organic compounds and display various biological activities [1]. Among the different sulfur compounds (Figure 1.1), sulfoximines are relatively less explored in chemistry. The history of sulfoximine starts in late 1940s. Methionine sulfoximine (**2**) was the first known compound in sulfoximine family that obtained during the process of wheat flour bleaching using nitrogen chloride (also known as "agene") [2]. Basically, methionine (**1**), an amino acid that present in wheat flour was converted into methionine sulfoximine by the treatment of nitrogen chloride. Methionine sulfoximine was identified as a toxic compound causing "canine hysteria" in dogs. In chemistry perspective, sulfoximines are aza analogues sulfones where chirality is created at the sulfur atom by the introduction of the nitrogen atom on sulfur.

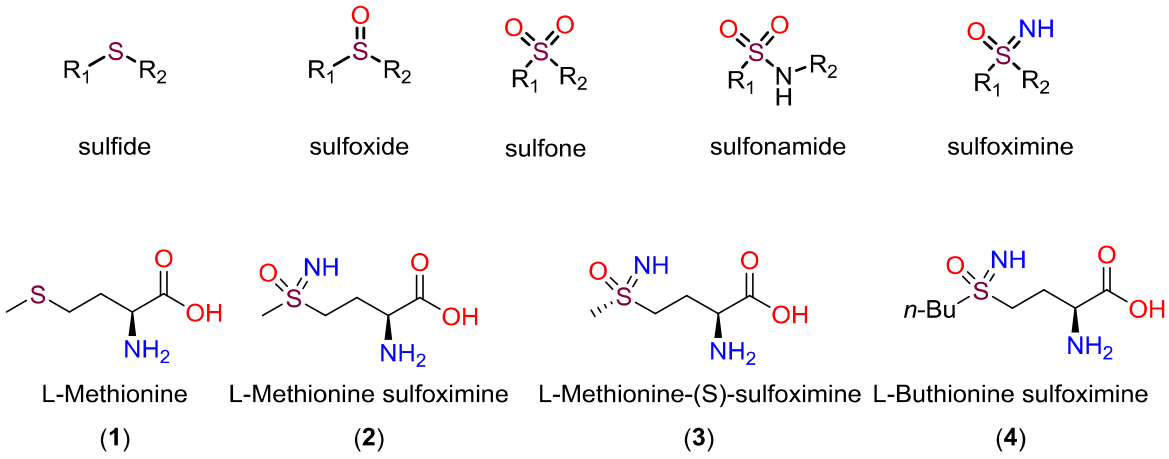


Figure 1.1: Structures of L-methionine and related compounds.

Methionine sulfoximine exists in four stereoisomeric forms in which L-methionine-(S)-sulfoximine (MSO) (**3**) was found to be the more biologically active compound. MSO inhibits both glutamine synthetase and γ-glutamylcysteine synthetase enzymes [3]. The analogue of MSO, buthionine sulfoximine (BSO, **4**) displays specific and competitive

inhibitor activity against the γ-glutamylcysteine synthetase enzyme [4]. These basic studies triggered the interest of scientists to shed light on the synthesis and applications of various sulfoximine derivatives in drug discovery [5].

1.2 Structure and properties of sulfoximines

Sulfoximines are stable compounds in which sulfur atom exists in tetrahedral geometry with sp^3 configuration [6]. Chirality is created at sulfoximine when sulfur is attached with two dissimilar carbon groups. The α-carbon of sulfoximine can be functionalized relatively under mild conditions due to the presence of acidic proton. In contrast to sulfone, sulfoximine possesses a mild basic *NH*- group which can be functionalized easily to obtain diverse compounds (Figure **1.2**).

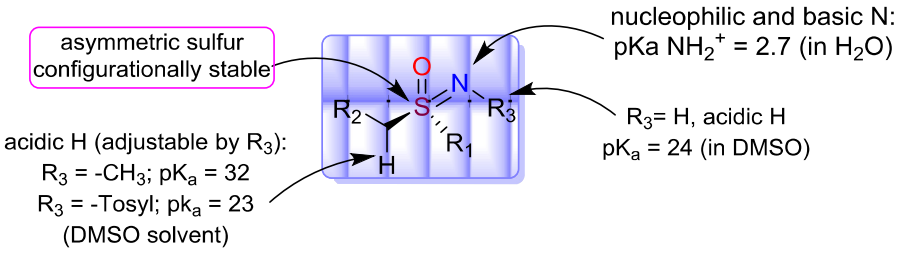


Figure 1.2: Characteristic of sulfoximine towards its versatility.

The free *NH*-sulfoximines can act as a hydrogen donor (through the *NH*- group) and also an acceptor. The acid-base properties of sulfoximine compounds can be significantly harnessed by changing the nature of the substituent on the nitrogen atom. Sulfoximine group possesses slightly more electron-withdrawing nature when compared with sulfone groups. Furthermore, sulfoximines are usually soluble in polar protic solvents (e.g. water and alcohols) when compare to their sulfone analogues due to special solvation effect around the sulfoximine functionality. These unique properties of sulfoximine group (e.g. structural diversity, metabolic stability, promising physicochemical properties, hydrogen bonding, etc.) have attracted the scientists to investigate the sulfoximine as valuable "pharmacophore" in

drug discovery. Some of the recent developments in sulfoximine based drug discovery are described below.

1.3 Biological applications of sulfoximines (drugs and drug-like molecules)

Sulfoximines have been rarely noticed in medicinal chemistry and drug discovery till recent. Sulfoxaflor (**5**) was the first clinically used sulfoximine-based insecticide, got approved in 2013. Sulfoxaflor has a broad spectrum of insecticidal activity compared to other insecticides [7]. After the entry of sulfoxaflor, many research groups actively involved in the design, synthesis and biological activity of sulfoximine based compounds for therapeutic applications [5]. Towards this end, in the search for new antiasthmatic agents, suloxifen (**6**) was developed [8]. This compound was found to be effective both orally and parenterally with high potentials. Although there are no commercially available drugs bearing sulfoximine group for human diseases, some sulfoximine compounds are in different phases of clinical trials. In particular, replacement of different functional groups such as sulfonamide, sulfone, amidine, acid and alcohol moieties with sulfoximine functional group in the existing pharmacophores or lead compounds is being explored. As a result of these investigations, sulfoximine based glucokinase–glucokinase regulatory protein (GKRP) disruptor (**7**) has been developed for the diabetic treatment [9]. Similarly, roniciclib (**8**) [10], BAY 1143572 (**9**) [11] and AZD 6738 (**10**) [12] have been the developed as the kinase inhibitors in the cancer treatment (Figure **1.3**) [10-12].

The compound GKRP disruptor (**7**) was developed as an antidiabetic agent based on the previous lead compound AMG 3969 (Figure **1.4**). The replacement of trifluoromethanol group with sulfoximine retains the activity with favorable pharmacokinetic profile such as low clearance and good oral bioavailability.

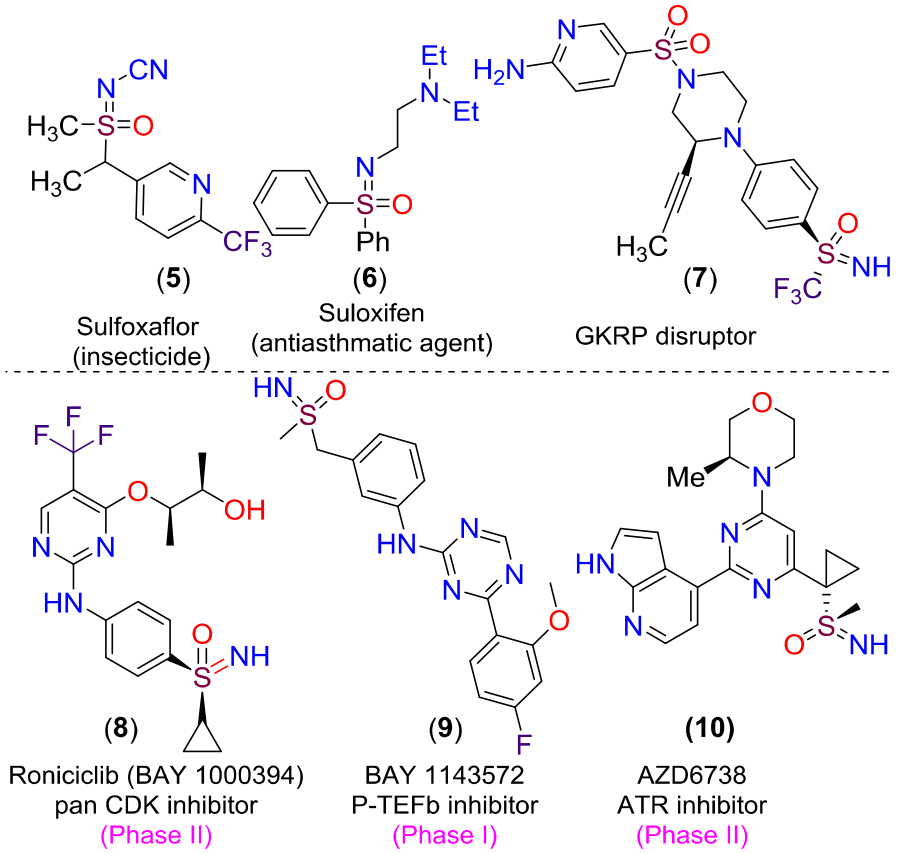


Figure 1.3: Biologically relevant sulfoximine compounds.

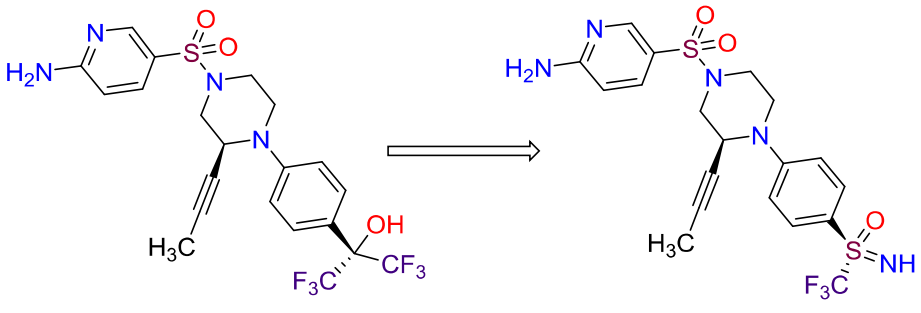
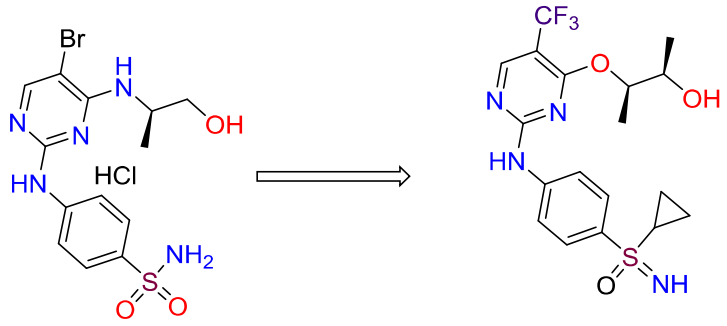


Figure 1.4: Structure of lead compound AMG 3969 and clinical candidate GKRP disruptor.

The compound roniciclib (BAY 1000394) was developed as a pan CDK inhibitor by envisioning the structure of lead compound named ZK 304709 (Figure **1.5**). Roniciclib (**8**) displayed high aqueous solubility (i.e. 182 mgL^{-1}) and broad range of antiproliferative

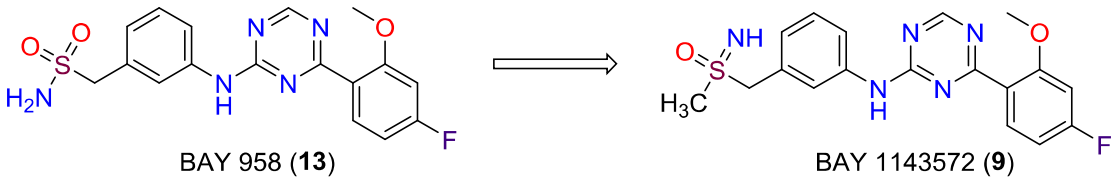
activity for various tumors of diverse genetic backgrounds when compared with ZK 304709 (**12**).



ZK 304709 (**12**) BAY 1000394 (**8**)

Figure 1.5: Structure of lead compound ZK 304709 and clinical candidate BAY1000394.

Along with CDKs, there is positive transcription elongation factor-b (P-TEFb), plays an important role in the cancer treatment. In this regard, BAY 1143572 has been demonstrated as a dual inhibitor for pan CDK and P-TEFb by replacing the sulfonamide groups to sulfoximine in the lead compound BAY 958 (Figure **1.6**). The compound BAY 1143572 exhibited the most promising overall profile with respect to potency, kinase selectivity, high aqueous solubility (479 mg/L), etc. in animal models when compared with BAY 958.



BAY 958 (**13**) BAY 1143572 (**9**)

Figure 1.6: Structure of lead compound BAY 958 and clinical candidate BAY 1143572.

Ataxia telangiectasia and rad3-related (ATR) is a serine/threonine-protein kinase is being considered as an attractive target on cancer cells for the treatment of cancer. The lead compound AZ 20 was identified as a potent inhibitor of ATR. However it's lower aqueous solubility (10 µM @pH 7.4) and high risk for drug-drug interaction (DDI) made it incurious

for further developments. Replacement of sulfone group with sulfoximine leads to the development of AZD 6738 which showed better activity and high aqueous solubility when compared with AZ 20 (Figure **1.7**).

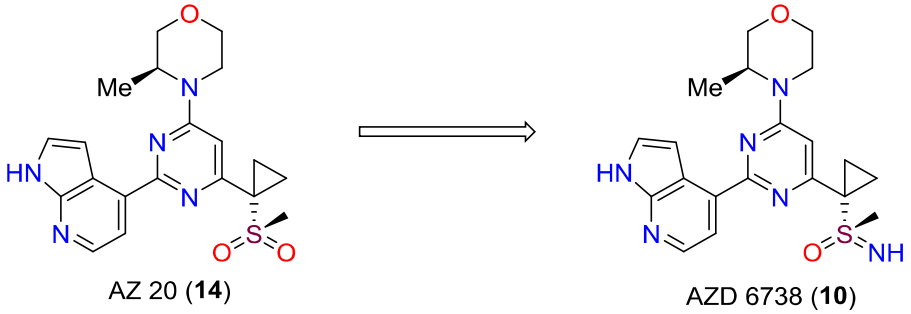


Figure 1.7: Structure of lead compound AZ 20 and clinical candidate AZD 6738.

Calcitrol (**15**) is an active form of vitamin D (i.e. the natural hormone 1α, 25-dihydroxyvitamin D_3), plays an important role with respect to anti-proliferative and growth regulatory factors of normal and neoplastic cells.

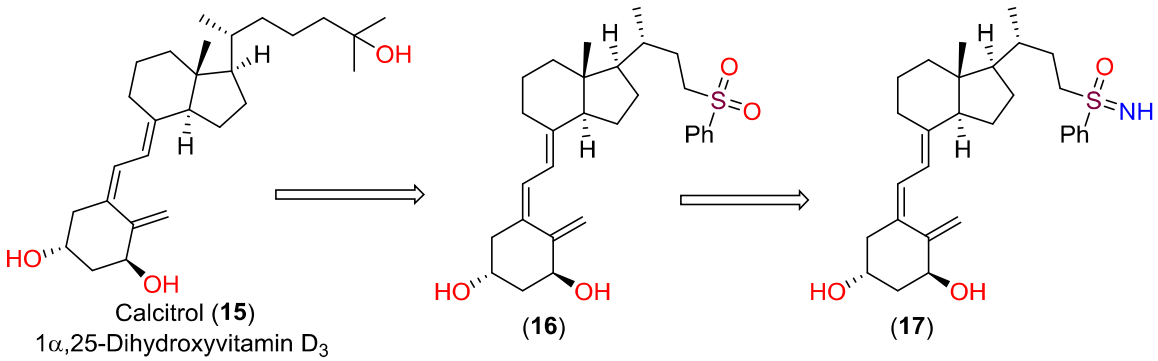


Figure 1.8: Structure of natural compound calcitrol and its sulfone and sulfoximine analogues.

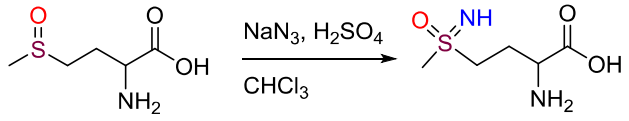
Cytochrome P450C24 (CYP24) hydroxylase enzyme catalyze the hydroxylation reaction which is responsible for the degradation of the calcitrol. A synthetic sulfone and sulfoximine analogues of calcitrol, **16** and **17** are potent like calcitrol that inhibits human cytochrome CYP24 hydroxylase enzyme (Figure **1.8**). Indeed, sulfoximine analogue (**17**)

showed 4-fold, less calcemic and high inhibitory selectivity for CYP24 when compared with (**16**) [13].

In addition to all these, asparagine synthetase inhibitors, antimalarial agents, antibacterial agents, antidiabetic agents, antiretroviral (HIV) agents, CYP24 hydroxylase inhibitors, proline-rich tyrosine kinase 2 (PYK2) inhibitors, factor Xa inhibitors and bromodomain and extraterminal domain (bet) inhibitors have been developed with sulfoximine functional groups [5]. However, two main reasons one can assume for the rare existence of sulfoximines in drug discovery, (i) safety issues due to the use of sodium azide (explosive nature) as a source of imine during the synthesis of sulfoximine and (ii) lack of understanding on the sulfoximine functional group. In the last decade, new and safe methods were developed for the synthesis of sulfoximines which led to an increased interest in sulfoximines based drug discovery.

1.4 Synthesis of sulfoximines

Chemical synthesis of sulfoximine (i.e. methionine sulfoximine) was first reported by Bentley *et al.* in 1950 *via* imination of sulfoxide using sodium azide in the presence of sulfuric acid (Scheme **1.1**) [14].

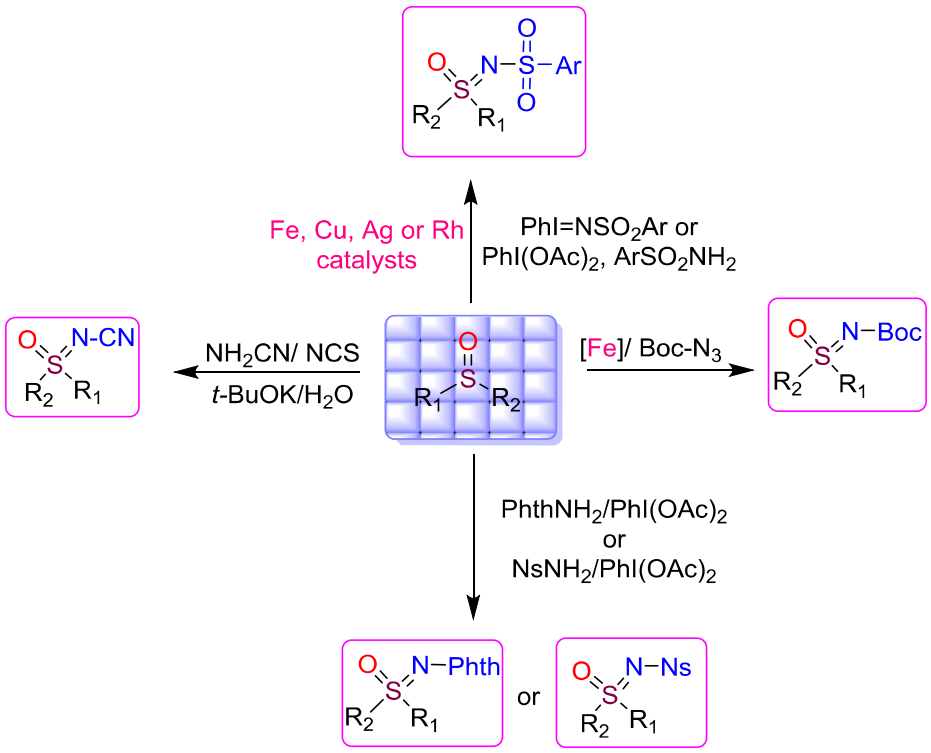


DL-Methionine sulfoxide Methionine sulfoximine (**A**)

Scheme 1.1: Synthesis of methionine sulfoximine (**A**).

Later, various safer methods were developed for the preparation of *N*-protected sulfoximines as well as *NH*-sulfoximines. Synthesis of *N*-protected sulfoximines was demonstrated from sulfoxides under different reaction conditions (Scheme **1.2**). The

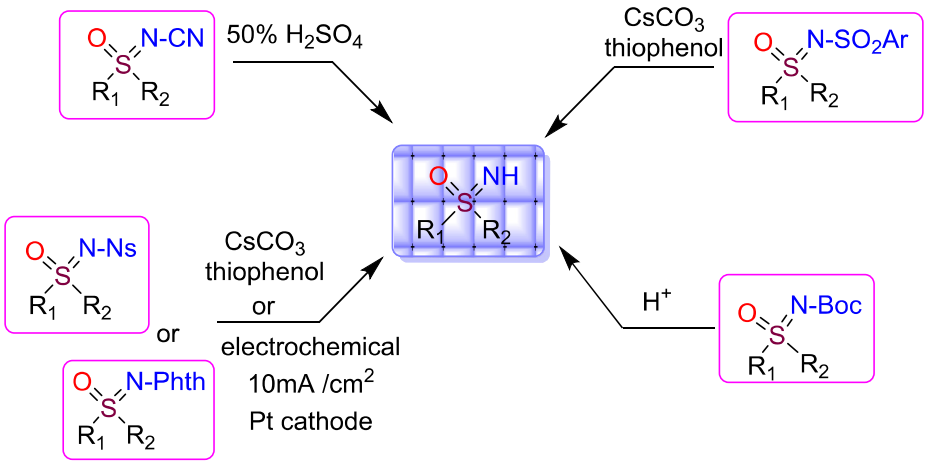
treatment of sulfoxide with iminating reagent such as (tosylimino)-phenyl-λ^3-iodane in the presence of transition metal catalysts (e.g. Cu, Rh, Fe, etc.) provided *N*-tosyl sulfoximines in good yields [15]. Alternatively, iron catalyzed imination of sulfoxides with *N*-*tert*.butyloxycorbonyl azide (Boc-azide) was explored for the preparation of *N*-Boc sulfoximines [16].



Scheme 1.2: Synthesis of *N*-protected sulfoximines.

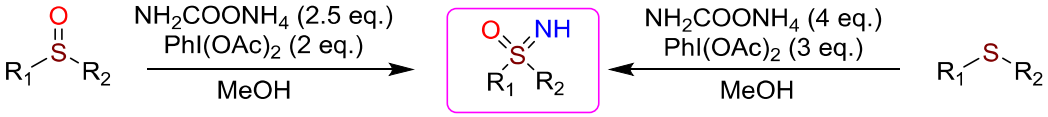
On the other hand, various metal-free methods were also demonstrated for preparation of *N*-protected sulfoximines. For instance, the reaction of sulfoxides with *p*-nitro benzenesulfonylamide ($NsNH_2$) or *N*-amino phthalimide (Phth-NH_2) in the presence of $PhI(OAc)_2$ provides *N*-(*p*-nitro) benzenesulfonylimido and *N*-phthalimido sulfoximines, respectively, in good yields [17]. Similarly, *N*-cyano sulfoximines were achieved from

sulfoxide in the presence of cyanamide (NC-NH_2), *N*-chlorosuccinimide (NCS) and potassium *tert*-butoxide (scheme **1.2**) [18]. Removal of these *N*-protecting groups under different conditions leads to *NH*-sulfoximines (Scheme **1.3**).



Scheme 1.3: Synthesis of *NH*- sulfoximine *via* deprotection.

Nevertheless, recently the direct preparations of *NH*-sulfoximines were presented from sulfoxides as well as from sulfides in a single step (Scheme **1.4**). For instance, the reaction of sulfoxides with ammonium carbamate in the presence of $PhI(OAc)_2$ provides quick access to *NH*-sulfoximines in excellent yields [19]. On the other hand, sulfide can be also transformed to *NH*-sulfoximines in a single step using excess amount of ammonium carbomate and $PhI(OAc)_2$ [20].



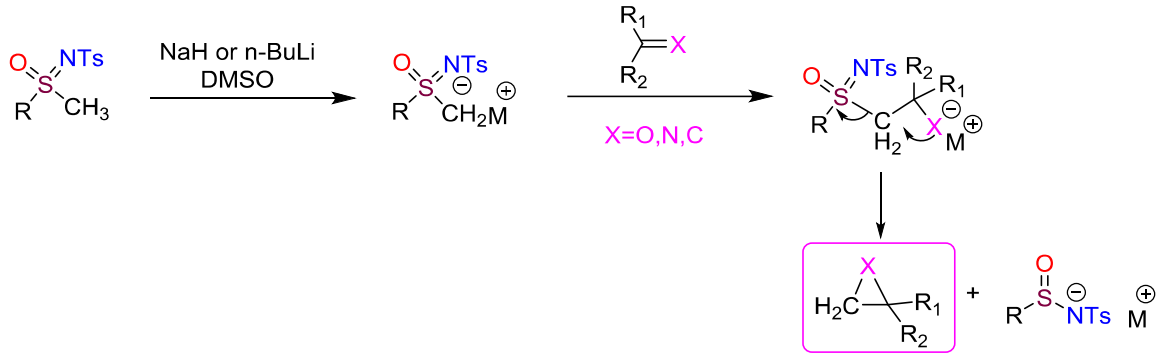
Scheme 1.4: Direct synthesis of *NH*- sulfoximine.

1.5 Applications of sulfoximines in organic synthesis

Besides the biological importance of sulfoximines, they were also explored in organic synthesis as reagents/chiral auxiliaries, ligands, directing groups, etc. Some of these synthetic applications are discussed below.

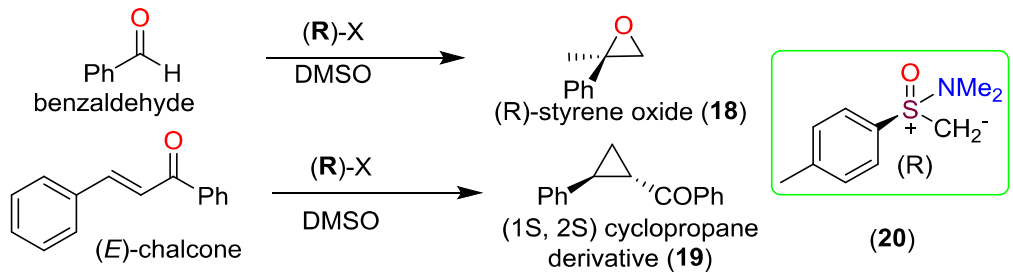
1.5.1 Sulfoximine as reagents and chiral auxiliaries

In 1973, Johnson *et al.* first demonstrated the applications of sulfoximine based ylides in organic synthesis. A number of *S,S*-dialkyl- and *S*-alkyl-*S*-aryl-*N*-(*p*-tolylsulfony1) sulfoximines were converted into corresponding ylides in the presence of a strong bases and treated with aldehydes, ketones, imines and enones to obtain epoxides, aziridines and cyclopropanes respectively in good yields [21].



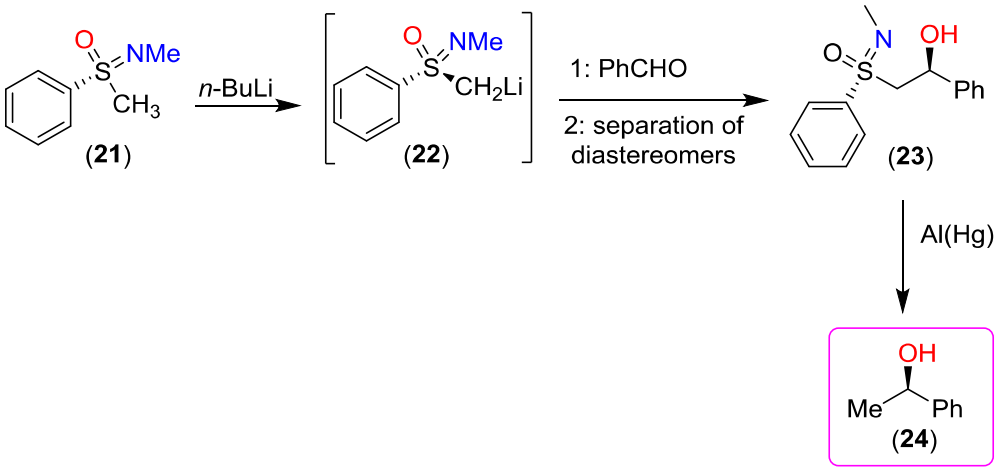
Scheme 1.5: Generation of sulfoximine ylide and its applications.

On the other hand, by choosing chiral sulfoximine ylides one can achieve asymmetric epoxidation, cyclopropanation, etc. For instance, reaction of chiral (R)-sulfoximine **20** with benzaldehyde and olefin provides epoxide and cyclopropane, respectively, with 20-35% optical purity [22].

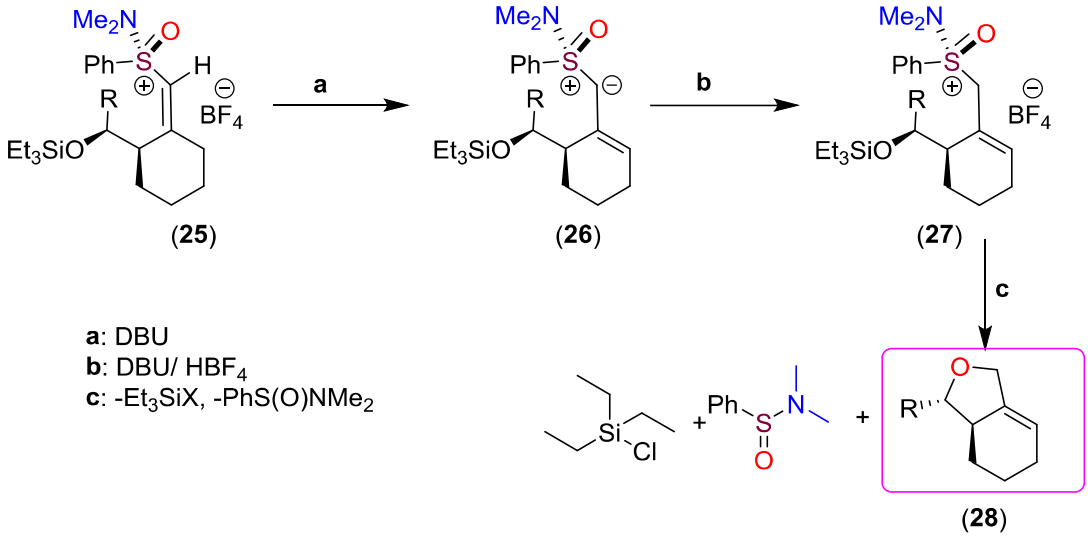


Scheme 1.6: Synthesis of chiral epoxide and cyclopropane.

In addition, lithiated *N*-methyl sulfoximine compound have been employed as nucleophile for the additions reaction with carbonyl compounds. Initially, the nucleophile **22** is generated from **21** with *n*-butyllithium (Scheme **1.7**) which was added to benzaldehyde to afford β-hydroxysulfoximine **23**. Further, separation of diastereomers followed by reduction provides an optically pure (R)-phenylethanol **24** in good yield [23].

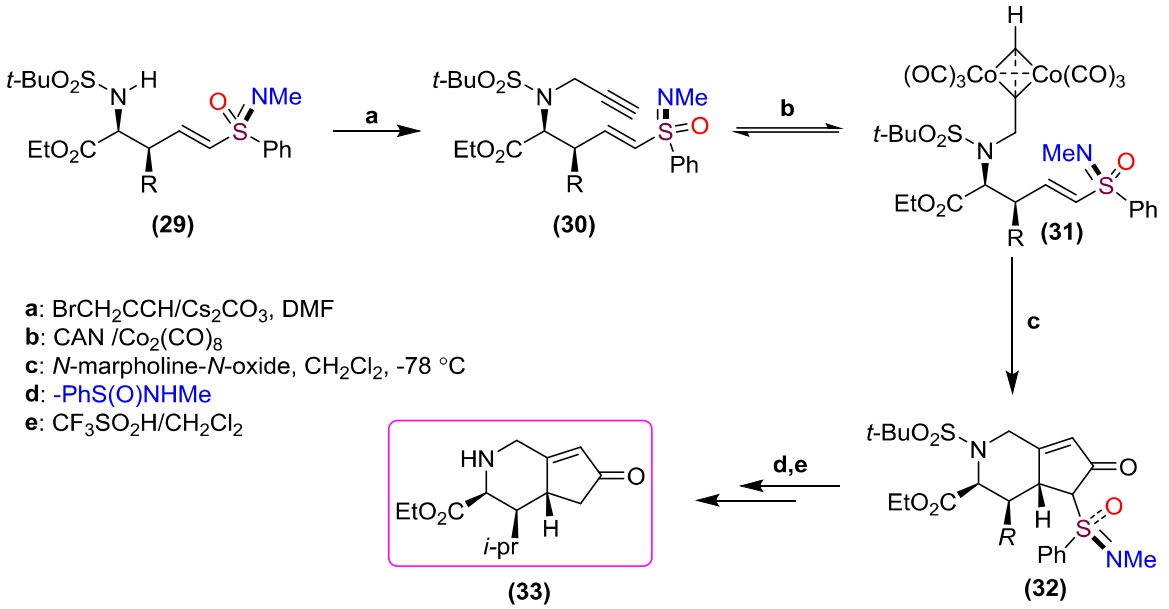


Scheme 1.7: Synthesis of (R)-phenylethanol.



Scheme 1.8: Asymmetric synthesis of unsaturated bicyclic tetrahydrofurans.

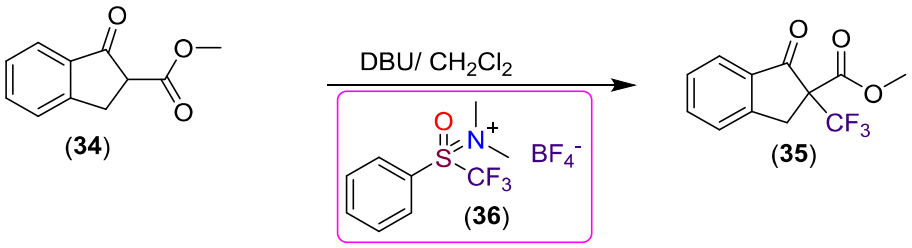
Bicyclic tetrahydrofuran skeleton is found in many natural products hence it has a great synthetic interest. In this regard, asymmetric synthesis of unsaturated bicyclic tetrahydrofurans was achieved using sulfoximine chiral auxiliary *via* intramolecular substitution reactions (Scheme **1.8**) [24]. Likewise, asymmetric synthesis of bicyclic amino acids using vinyl sulfoximines as chiral auxiliary was achieved as described in the Scheme **1.9** [25].



Scheme 1.9: Asymmetric synthesis of bicyclic amino acids.

1.5.2 Sulfoximine scaffold as trifluoromethylating agent:

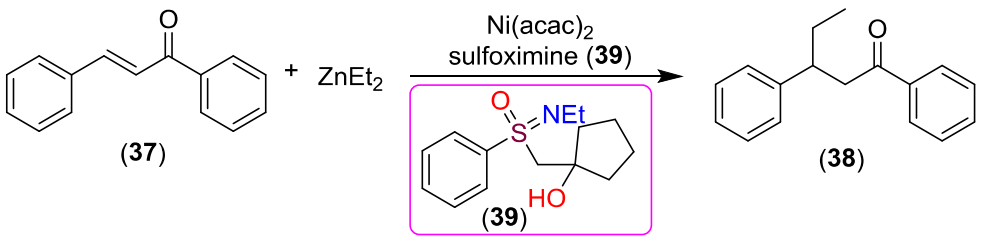
Trifluoromethylated compounds found wide applications in different fields including pharmaceuticals, agrochemicals, and functional materials. Towards this end, Shibata *et al.* have developed a novel sulfoximine based reagent **36** ([(oxido)phenyl(trifluoromethyl)-λ^4-sulfanylidene]dimethylammonium tetrafluoroborate) for the trifluoromethylation [26]. This reagent provides the desired trifluoromethylated products in good to excellent yields (Scheme **1.10**).



Scheme 1.10: Trifluoromethylation of **34** to **35** assisted by sulfoximine reagent **36.**

1.5.3 Sulfoximine as ligands:

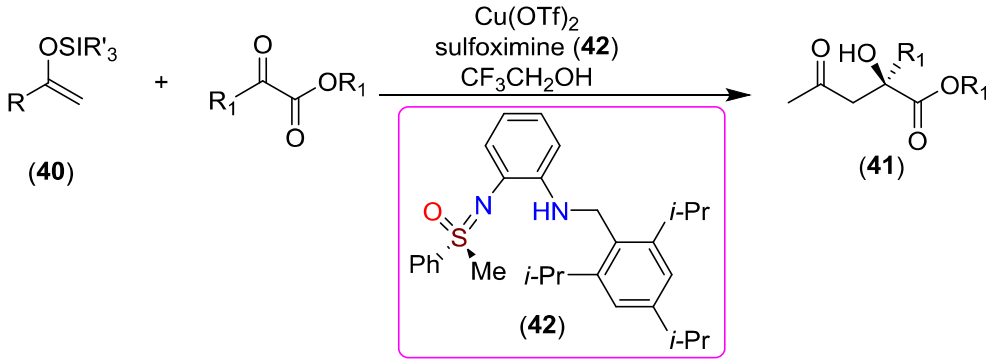
Ligands bearing oxygen and nitrogen as the donor atoms have received keen interest in organic synthesis. In this regard, the utilization of chiral sulfoximine as a metal coordinating ligand for asymmetric catalysis has come into the light in the last decade. In 1992, Bolm *et al.* reported the use of *β*-hydroxysulfoximines as ligands in nickel-catalyzed 1,4-conjugate addition of diethylzinc to chalcones for the first time [27]. In this study, *β*-hydroxysulfoximine **39** gave the best results, giving the product **38** in 71% yield with 70%ee (Scheme **1.11**).



Scheme 1.11: Conversion of chalcones to **38** assisted by sulfoximine ligand **39**.

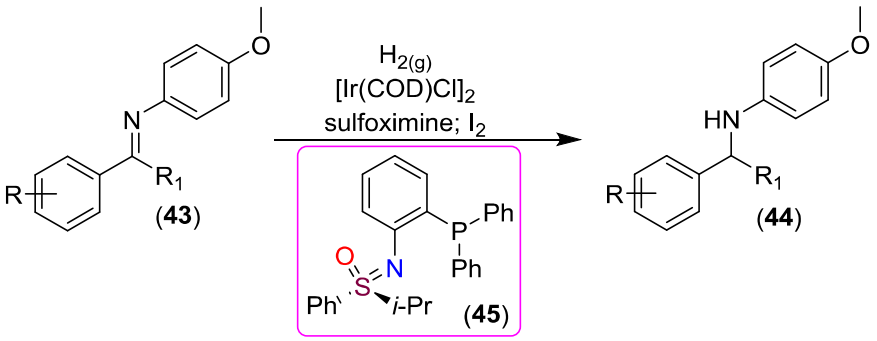
Later to the above study, several N,N-type and P,N-type sulfoximine ligands were prepared and applied in the asymmetric catalysis. Some of these N,N-ligands were used in Mukaiyama-type aldol reactions in combination with copper salts. For example, addtion of

silyl enol ethers **40** to pyruvate esters in the presence of ligand **42** and copper (II) triflate provides the product **41** in good yield with up to 99% ee (Scheme **1.12**) [28].



Scheme 1.12: Conversion of **40** to **41** assisted by N,N-type sulfoximine ligand **42**.

Similarly, enantioselective hydrogenation of imines was achieved using iridium catalysts in the presence of chiral P,N-sulfoximine ligand **45** (Scheme **1.13**). In particular, many substrates bearing *p*-methoxy phenyl moiety (PMP) gave the products with excellent enantioselectivities (up to 98% ee) [29].

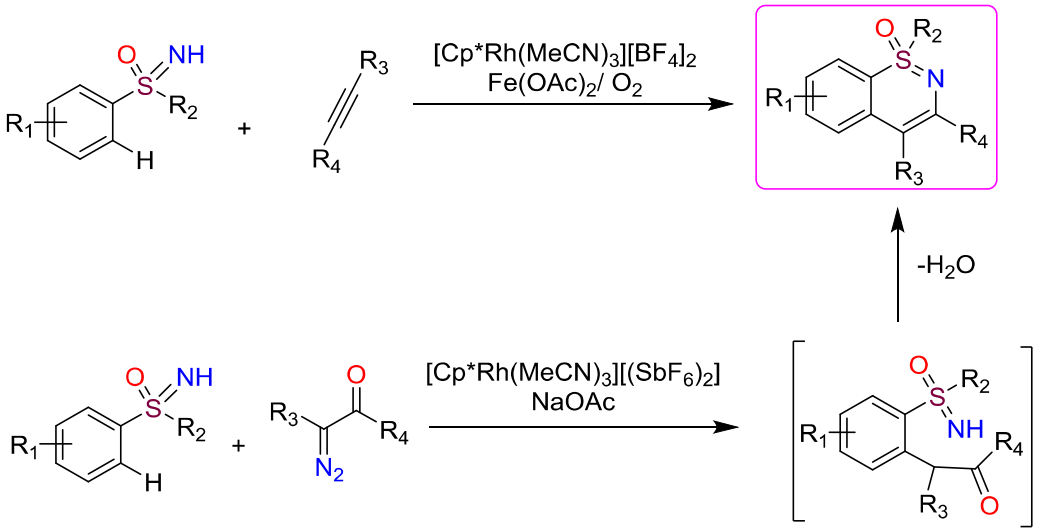


Scheme 1.13: Hydrogenations of imine **43** to **44** assisted by N,P-type sulfoximine ligand **45**.

1.5.4 Sulfoximines as directing group:

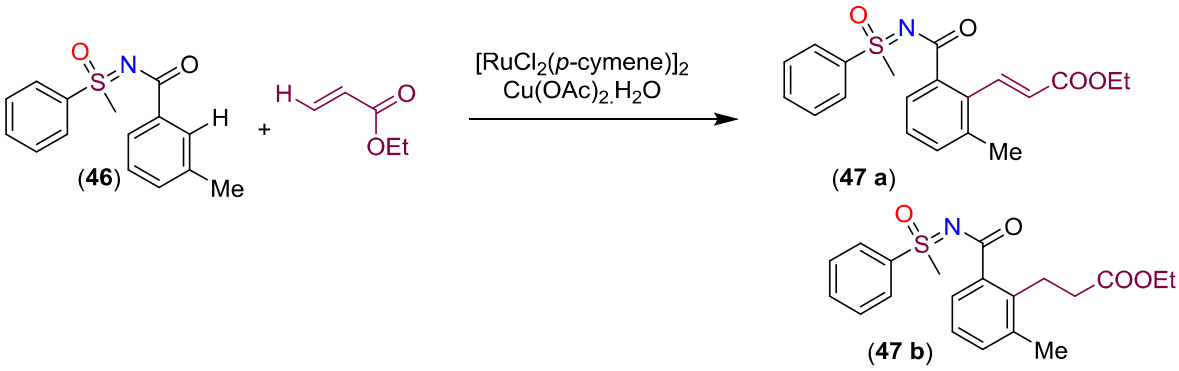
Activation of CH-bonds using transition metal catalysts with assistance of directing groups has emerged as an important tool to access various complex organic molecules. There

are several functional groups including sulfoximines were explored as a directing group [30]. Initially, in 2013, Bolm research group described the Rh-catalysed oxidative annulation of sulfoximines and internal alkynes to obtain 1,2-benzothiazines [31]. Later, in 2015 the same group explored the rhodium-catalysed sulfoximine-directed *ortho*-*C–H* alkylation with diazo compounds [32]. The reaction of *NH*-sulfoximines with different variety of alkyl- and phenyl-containing diazo esters proceeded smoothly in presence of rhodium and sodium acetate to provide 1,2-benzothiazines in excellent yields (Scheme **1.14**).



Scheme 1.14: Rh-catalysed oxidative annulations of 1,2-benzothiazine.

A further important contribution in sulfoximine-directed C–H activation reactions was developed by Sahoo et al. by using *S*-methyl-*S*-phenylsulfoximine (MPS) as a directing group [33]. This motif is easy to install and remove on carboxylic acids, and demonstrated excellent reactivity under Ru- and Pd-catalysis on *o*-CH hydroxylation. In 2014, Ru(*p*-cymene) catalyzed sulfoximine directed *ortho*- and chemoselective C–H alkenylations was explored (Scheme **1.15**) [34]. Later several other groups reported sulfoximine-directed C–H activation reactions.



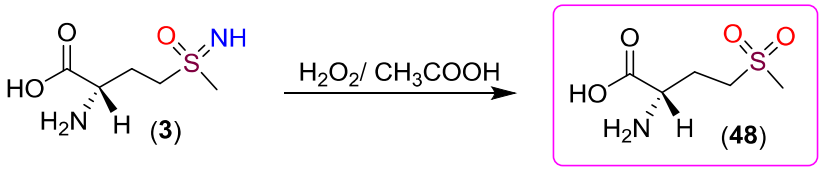
Scheme 1.15: Ru-catalysed oxidative C–H alkenylations of **46**.

1.6 Reactions of sulfoximine

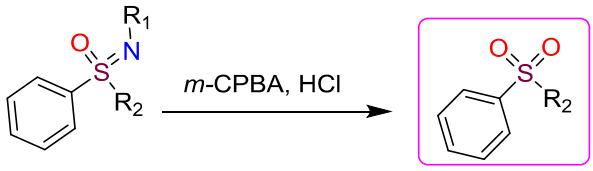
Sulfoximines undergo variety of reactions including oxidation, reduction, α-functionalization, *N*-functionalization reactions, etc. These reactions provide structurally diverse sulfoximines in organic synthesis. Some of these reactions are listed below.

1.6.1 Oxidation of Sulfoximines

Sulfoximines undergo oxidation reactions in the presence of peroxides to provide corresponding sulfones. For instance, oxidation of methionine sulfoximine with hydrogen peroxide in acetic acid at 40 ^{o}C provides methionine sulfone (Scheme **1.16**) [35]. On the other hand, the peroxide *m*-CPBA was also used for the transformation of sulfoximines to sulfones (Scheme **1.17**) [36].



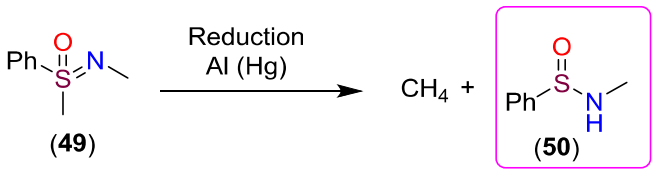
Scheme 1.16: Oxidation of **3** to **48**.



Scheme 1.17: Oxidation of *N*-protected sulfoximine to sulfone**.**

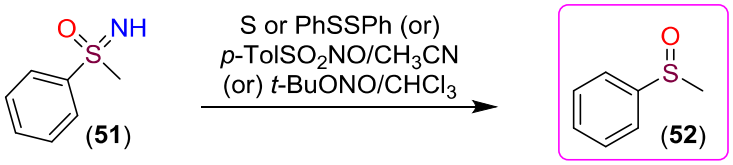
1.6.2 Reductions of sulfoximine

N-Functionalized sulfoximines undergo reduction with different reducing agents to provide sulfinamides as the major product. For instance, the reaction of *N*-methyl-*S,S*-methylphenyl sulfoximines with aluminium amalgam in aqueous THF provides phenylsulfinamides (Scheme **1.18**) [37].



Scheme 1.18: Reduction of sulfoximine.

The reductive deimination of sulfoximine takes place with different reagents including *p*-toluenesulfonyl nitrite, sulfur, diaryl disulfide, and *tert*.-butyl nitrite, etc. (Scheme **1.19**). These reactions provided sulfoxide as the product [38].

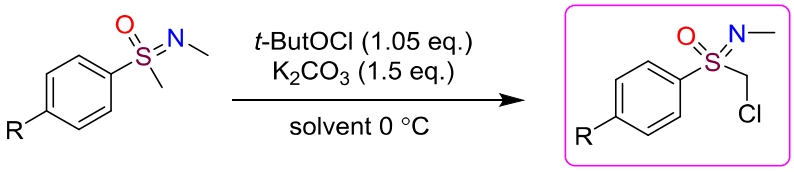


Scheme 1.19: Reductive deimination of sulfoximines by different methods.

1.6.3 α-Functionalization of sulfoximines

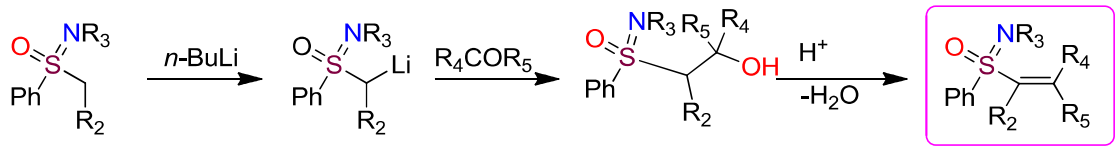
N-Functionalized sulfoximines can undergo different α-substitution reactions under different reaction conditions. In 1978, Johnson and co-workers demonstrated the synthesis of α-

chlorosulfoximines from *N*-methyl-*S,S*-methyl phenyl sulfoximines using *tert.*butyl hypochlorite at 0 °C in the presence of K_2CO_3 (Scheme **1.20**) [39].



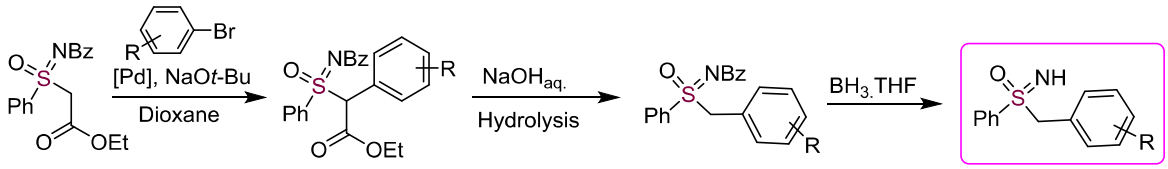
Scheme 1.20: α-Chlorination of methyl protected sulfoximines.

On the other hand, *N*-methyl-*S,S*-methyl phenyl sulfoximines undergo facile α-lithiation in the presence of *n*-BuLi which can be added to aldehydes or ketones to get *S*-vinyl sulfoximines as the products (Scheme **1.21**) [40].



Scheme 1.21: *α*-Lithiation of sulfoximine.

In another approach, palladium-catalyzed intermolecular α-arylations of *N*-benzoyl sulfoximine ethyl ester with variety of aryl bromides was demonstrated under mild reaction conditions. These reactions afford α-arylated products which can be converted into *NH*-phenyl benzyl sulfoximines with additional steps (Scheme **1.22**) [41].



Scheme 1.22: *α*-Arylation of *N*-benzyl sulfoximine.

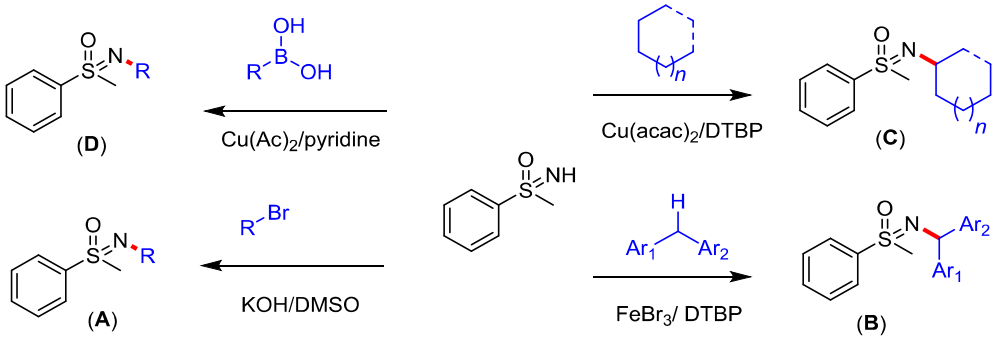
1.6.4 *N*-Functionalization of sulfoximines

Among the different reactions of sulfoimnes, *N*- functionalization reactions received considerable interest in chemistry and biology. For instance, *N*-arylation, alkylation,

aroylation, vinylation, alkynylation, cyanation, thiocyanation, sulfonylation, phosphorylation, trifluoromethylation, thiotrifluoromethylation, etc. have been successfully demonstrated under different reactions conditions [30, 42]. Some of these reactions are discussed below.

_N_-Alkylation of _NH_-sulfoximines

_N_-Alkylation of _NH_-sulfoximines was traditionally achieved by using alkyl halides in the presence of KOH in DMSO [43]. Further, _N_-alkylation of sulfoximines with diaryl methanes was demonstrated under iron catalyzed cross-dehydrogenative coupling route (Scheme **1.23**) [44]. Alternatively, _N_-alkylation of sulfoximines with unactivated alkanes was achieved using copper catalyst in the presence of di-_tert_.-butyl peroxide (DTBP) as an oxidant [45]. On the other hand, a simple method was developed by our group for the _N_-alkylation of _NH_-sulfoximines using alkyl boronic acid with copper catalyst [46].

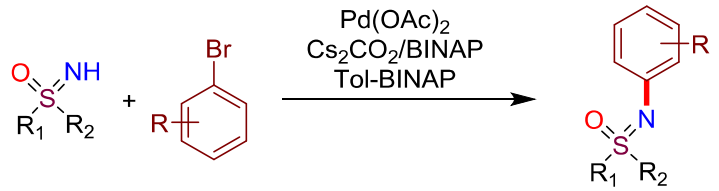


Scheme 1.23: _N_-Alkylation of _NH_- sulfoximine.

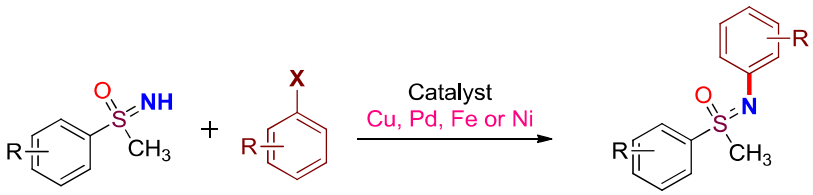
_N_-Arylation of _NH_-sulfoximines

_N_-Arylation of sulfoximine was first demonstrated by Bolm et al. using aryl bromides as an aryl donor in the presence of palladium catalysts [47]. These reactions were carried out under reflux conditions using BINAP ligands (Scheme **1.24**). Later to this investigation, a handful number of methods for _N_-arylation of sulfoximine have been developed under milder conditions by different research groups [42]. In particular, use of arylboronic acids,

diaryliodonium salts, aryl sulfonates, aryl siloxanes, etc., have been explored as aryl donors in the presence of diffferent metal catalysts (Scheme **1.25**). Details of these works and there merits and demerits are discussed in the **chapter 2.**



Scheme 1.24: Pd catalyzed first report of *N*-arylation of sulfoximine.

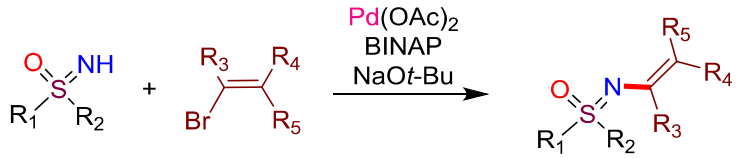


X= $B(OH)_2$, Halogens, NH_2-NH_2, etc

Scheme 1.25: Metal catalyzed *N*-arylation of sulfoximine.

N-Alkenylation of *NH*-sulfoximines

The first pioneering example of *N*-alkenylation (vinylation) of sulfoximine was reported from Bolm group in 2004 using vinyl bromides in presence of $Pd(OAc)_2$ [48]. These reactions were carried out under reflux condition using BINAP ligands (Scheme **1.26**). Later, some other methods for the preparation of α or β substituted *N*-vinylsulfoximines were also demonstrated [42].

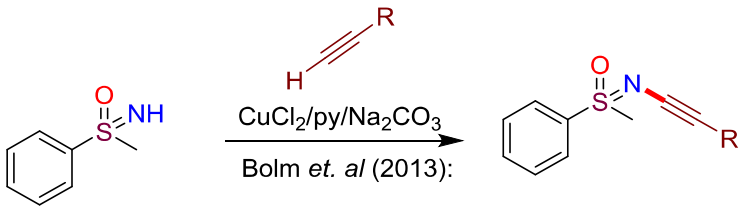


Scheme 1.26: Pd catalyzed *N*-alkenylation of sulfoximine.

N-Alkynylation of *NH*- sulfoximine

In 2013, *N*-alkynylation of *NH*- sulfoximine with terminal alkynes was first demonstrated by Bolm at al. *via* copper catalyzed C-H/N-H cross dehydrogenative coupling reactions (Scheme

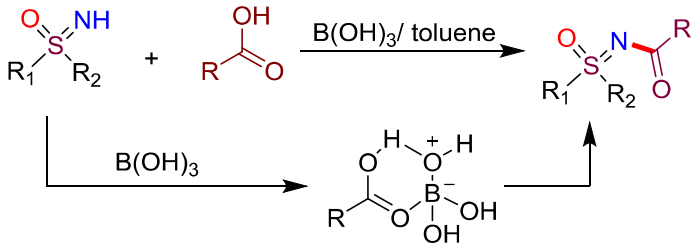
1.27) [49]. Later, the same group reported the *N*-alkynylation of sulfoximine with aryl propiolic acid and bromo acetylenes using copper catalysts [42].



Scheme 1.27: Cu catalyzed *N*- alkynylation of *NH*- sulfoximine.

N-Acylation of *NH*- sulfoximines

In 2011, *N*-acylation of sulfoximines was successfully demonstrated using carboxylic acid as an acyl source in the presence of boric acid by Harmata *et al*. This reaction provided the desired products in good yields (Scheme **1.28**) [50].



Scheme 1.28: *N*-Alkynylation of *NH*- sulfoximine.

Later, *N*-acylation of reactions of sulfoximines was demonstrated by using aldehydes and methyl arenes in the presence of metal or metal free conditions *via* oxidative coupling reactions [30]. On the other hand, in 2016, Sekar and co-workers demonstrated a palladium catalyzed carbonylation of *NH*-sulfoximines with aryl halides (X=I, Br) in the presence of carbon monoxide gas [51]. The merits and demerits on *N*-acylation of sulfoximines are discussed in more detail in the **chapter 3.**

Other *N*-functionalization reactions

Besides all above transformations, *N*-thioetherification, *N*-cyanation, *N*-Sulfonylation, *N*-trifluromethylthiolation, *N*-trifluoromethylation, *N*-Silylation, etc., were also demonstrated under different reaction conditions. These works are recently reviewed independently by Ghosh *et al.* and Nikpassand *et al.* [30, 42].

1.7 Summary and Objectives of the thesis

The above discussion provides a short overview on the significance of sulfoximine compounds in various fields. Although sulfoximine compounds were known from 1950s, its applications in synthetic organic chemistry as well as in medicinal chemistry are being developed very recently. As a result of these advancements, some sulfoximine compounds are in different phase of clinical trials for cancer and diabetes. On the other hand, sulfoximines are also being used as organocatalysts, ligands, chiral auxiliaries and directing groups, etc. in modern organic synthesis.

As discussed earlier, sulfoximines undergo different types of reactions and transformations. Among them, *N*-functionalization of sulfoximines allows quick access to diverse sulfoximines compounds for biological applications. Hence, various methodologies have been developed for *N*-arylation, alkylation, vinylation, alkynylation, cyanation, thiocyanation, phosphoramidation, etc. These methodologies have emerged as promising approach for the fabrication of sulfoximine scaffolds.

However, many challenges with respect to selectivity, yields, reaction conditions, etc., demand the developments of new synthetic methods for the *N*-functionalization of sulfoximines. **Towards this end, the main objectives of the thesis work entitled**

"Development of new synthetic routes for the preparation of *N*-aryl, acyl and phosphoryl sulfoximines," are.....

1. To synthesize *N*-aryl sulfoximines using aryldiazonium salts as a source of aryl group under mild conditions.
2. To synthesize *N*-acyl sulfoximines from *NH*-sulfoximines and aryl iodides in the presence of $Mo(CO)_6$ as a solid CO source.
3. To synthesize α-keto *N*-acyl sulfoximines from *NH*-sulfoximines and acetophenones in the presence of selenium oxide (SeO_2) under mild reaction conditions.
4. To synthesize sulfoximine *N*-phosphoramidate from *NH*-sulfoximines and dialkyl phosphonate under mild reaction conditions.

1.8 References

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