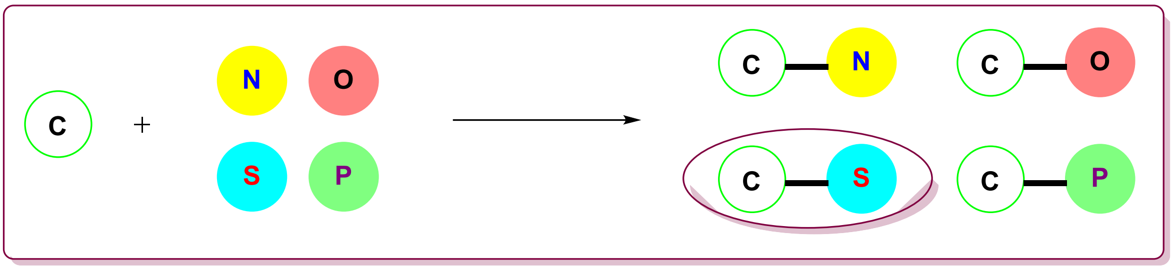
CHAPTER-1

Introduction

1.1 Introduction of Carbon-Heteroatom Bonds

The basic structure of organic molecules typically consists of carbon-carbon (C-C) bonds. Nevertheless, the presence of heteroatoms, such as N, O, P, S, etc., makes the organic molecules unique in terms of reactivity and applications. Almost all natural products, bioactive molecules, medicines, agrochemicals, materials, etc., have carbon-heteroatom bonds (C-N, C-O, C-S, and C-P). These bonds play a vital role in displaying diverse biological activities and other properties. Therefore, most attention has been given to developing methods for synthesizing new carbon-heteroatom-containing organic compounds (**Scheme 1.1**). Among the various classes of organic molecules, sulfur-containing compounds, i.e. organosulfur compounds, have received considerable interest due to their broad applications in numerous fields.



Scheme 1.1 Synthesis of carbon-heteroatom-containing organic compounds.

1.2 Organosulfur Compounds

An organic molecule with one or more carbon-sulfur bonds is known as an organosulfur compound. Organosulfur compounds are widespread and commonly found in foods, vegetables, and dietary items, providing various health benefits [1-4]. Organosulfur compounds have found wide applications in different fields, including modern organic synthesis, medicinal chemistry, drug discovery, materials science, etc. It is worth noting that more than 300 sulfur-containing FDA-approved drugs are available in the market. Organosulfur compounds can be categorized according to different sulfur-based functional groups. Some of the common functional groups in organosulfur compounds include thiol, sulfide, sulfoxide, thioacetic acid, sulfonic acid, thioamide, sulfonamide, sulfoximine, sulfinic acid, thioimidates, dithiocarbamates, sulfone, etc (**Figure 1.1**). Moreover, sulfur-containing heterocyclic compounds, such as, benzothiophene (**1**), thiophene (**2**), thiopyrone (**3**), dibenzothiophene (**4**), benzothiazole (**5**) and phenothiazine (**6**) are often found in a wide range of natural products and biologically relevant compounds[5].

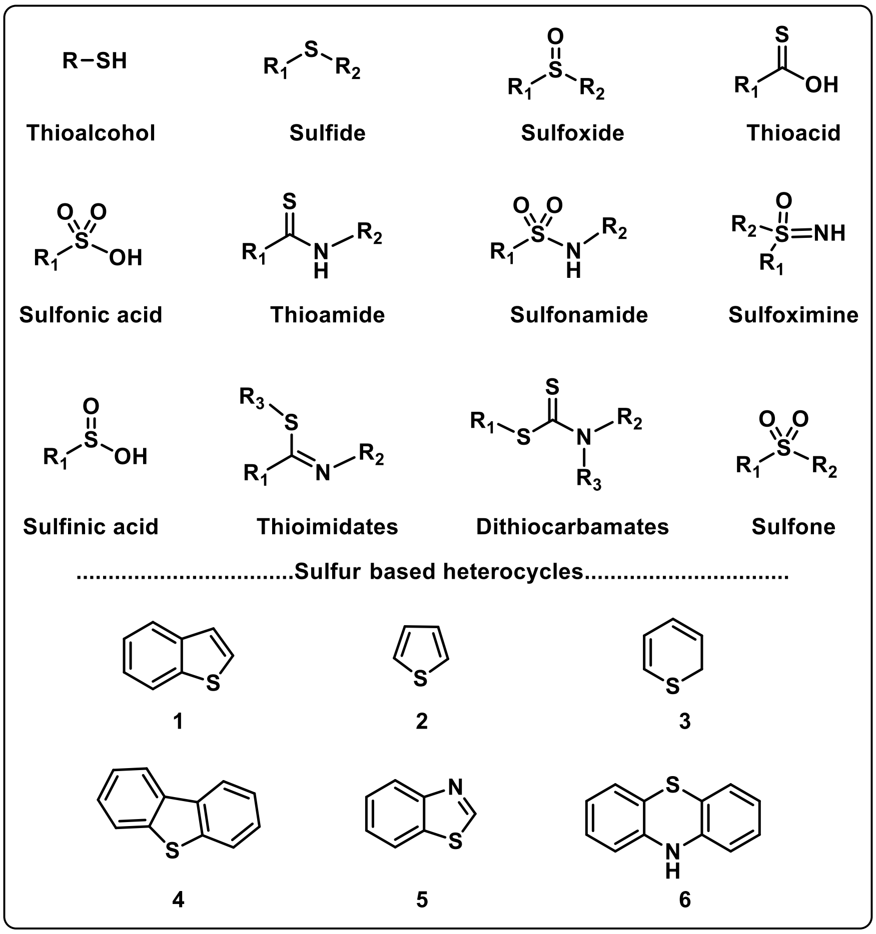


Figure 1.1 Sulfur-containing functional groups and heterocyclic compounds.

1.3 Naturally Occurring Organosulfur Compounds

A wide range of organosulfur compounds are found in nature. The amino acids methionine (**1**), cysteine (**2**), and cystine (**3**) are the natural organosulfur compounds present in most living organisms. Glutathione (**4**) is an organosulfur compound made of amino acids such as glycine, cysteine, and glutamic acid. One of the other sulfur compounds, glutathione is produced by the liver and possesses a strong antioxidant property. Besides amino acids, the vitamins biotin (**5**), thiamine (**6**), and lipoic acid (**7**) are made up of sulfur heterocycles. Gliotoxin (**8**) is a sulfur-containing natural product with disulfide linkage produced by marine-origin fungi. Allicin (**9**) is a disulfide compound mainly found in garlic with lots of health benefits.

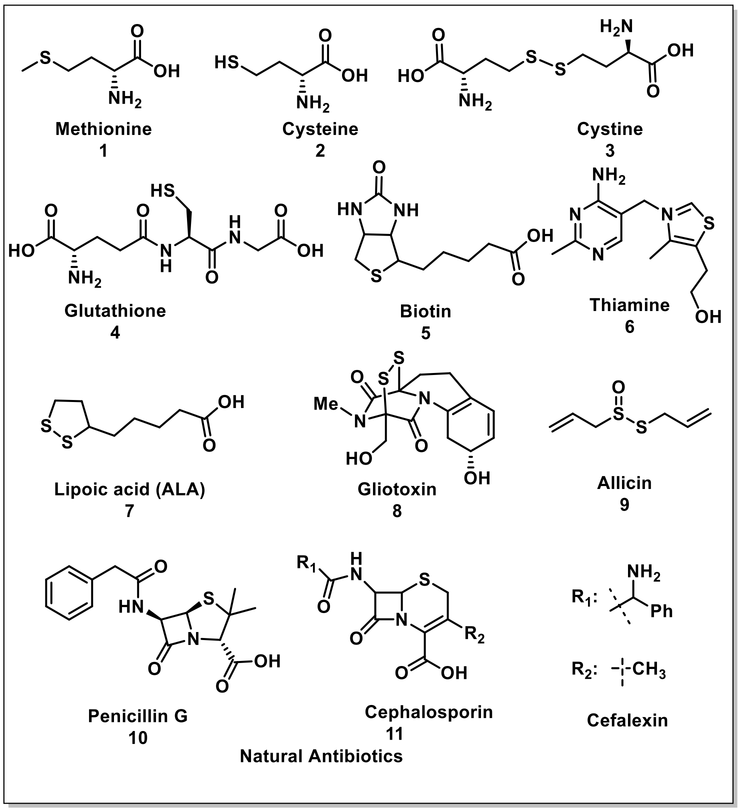


Figure 1.2 Naturally occurring organosulfur compounds and antibiotics.

On the other hand, penicillin (**10**) and cephalosporin (**11**) are important life-saving antibiotics produced by fungi. Besides, there are many sulfur-containing natural products have been isolated from plant, marine, fungi, and bacterial sources [6,7] (**Figure 1.2**).

1.4 Organosulfur Compounds as Drugs

Besides naturally occurring drugs such as penicillin and cephalosporin, there are several synthetic drugs that are being clinically used for the treatment of various diseases. For instance, zaltoprofen and alimemazine are sulfide-based synthetic drugs used as nonsteroidal anti-inflammatory (NSAID) and antihistamine agents, respectively (**Figure 1.3**). Similarly, omeprazole and sulindac are sulfoxide-based synthetic drugs used in the treatment of gastroesophageal reflux and inflammation problems (**Figure 1.3**). On the other hand, sulfone-based drugs vismodegib and amisulpride are used in the treatment of skin cancer and psychological disorders. Sulfonamides are an important class of synthetic antimicrobial drugs (e.g., Prontosil and Sulfamethoxazole) used as a broad spectrum for treating human and animal bacterial infections (**Figure 1.3**). Besides these classes of compounds, various types of organosulfur compounds like disulfides, sulfur heterocycles, thioesters, etc., have been used as drugs in various treatments[8].

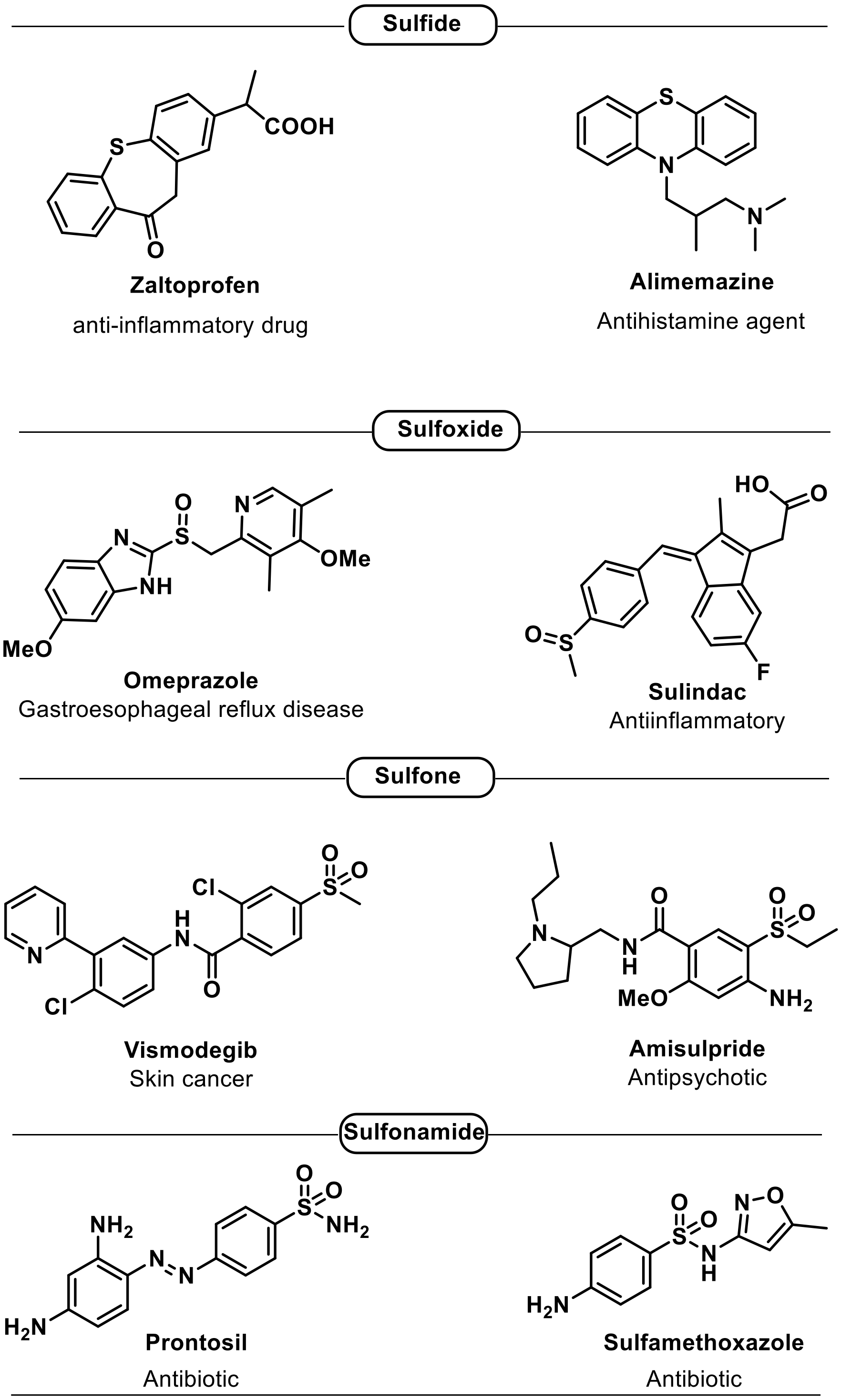


Figure 1.3 Sulfur-containing various functional groups in pharmaceuticals.

1.5 Organosulfur Compounds as Agrochemicals

Over the last few decades, organosulfur compounds-based agrochemicals have found important applications in modern crop protection. Organosulfur compounds are used as pesticides, insecticides, herbicides, fungicides, nematicides, synergists, etc. For instance, asulam and pyrasulfotole are sulfur-based herbicides, while thiadifluor and fluvial are sulfur-based fungicides (**Figure 1.4**). On the other hand, thiacloprid and diafenthiuron are sulfur-based insecticides. Besides these compounds, there are plenty of sulfur compounds have been used in cultivation[9] (**Figure 1.4**).

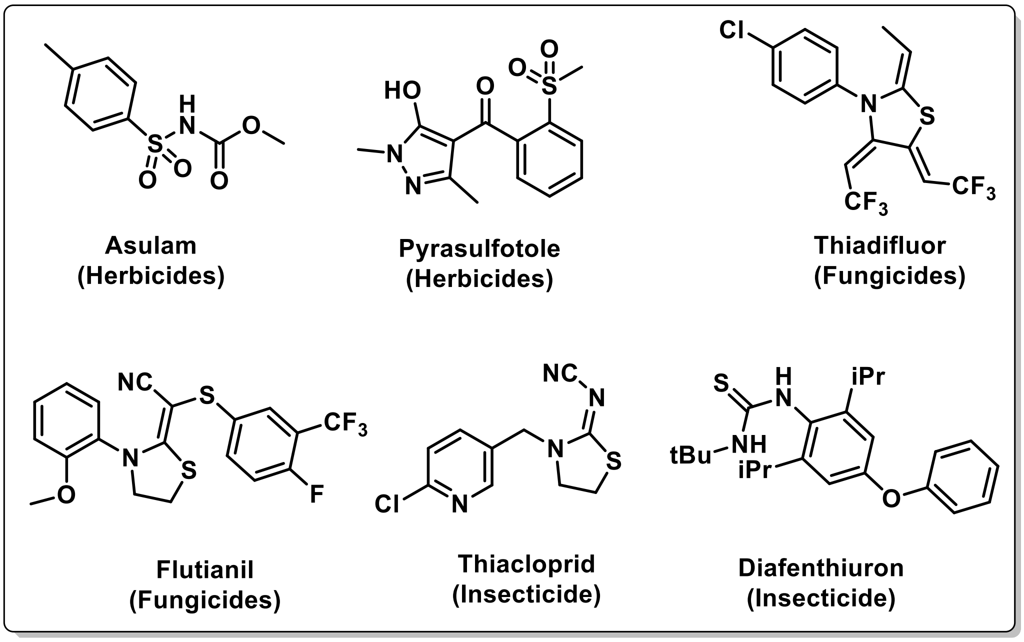


Figure 1.4 Sulfur-containing compounds in agrochemicals.

1.6 Organosulfur Compounds as Materials

Sulfur-based organic photo-conducting materials and batteries received special interest in recent years due to their unique optical and electronic properties (**Figure 1.5**). In particular, organosulfur compounds with disulfide linkages were found to be promising organic electrode materials due to their high capacities, abundance, structural diversity, and eco-friendly nature. Organosulfur compounds are being received more attention in the development of lithium-sulfur batteries. Besides that, organosulfur compounds found applications in the field of organic light-emitting diodes (LED) and organic transistor materials (OFET)[10, 11] (**Figure 1.5**).

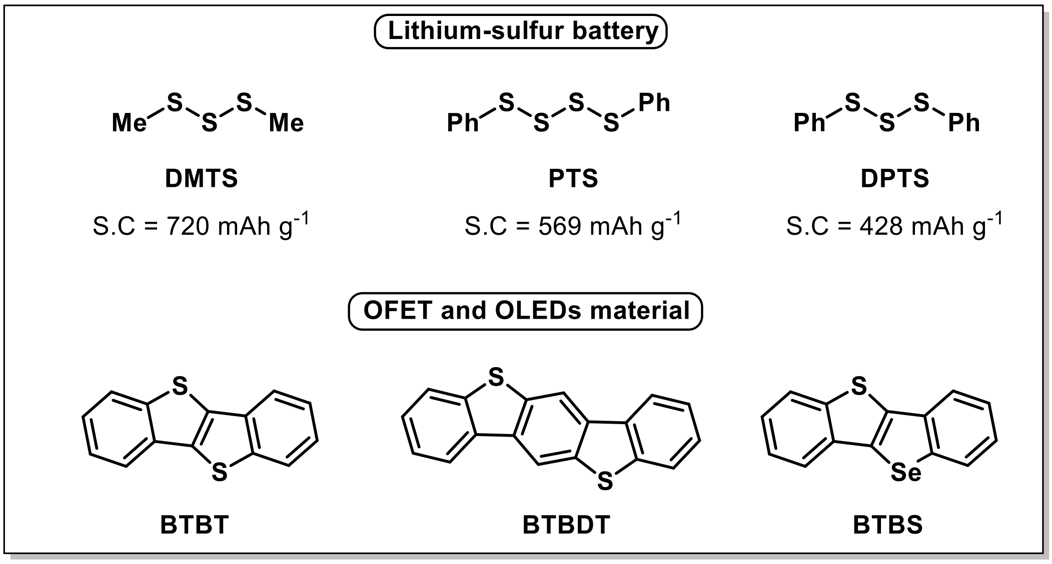


Figure 1.5 Organosulfur compounds in material science.

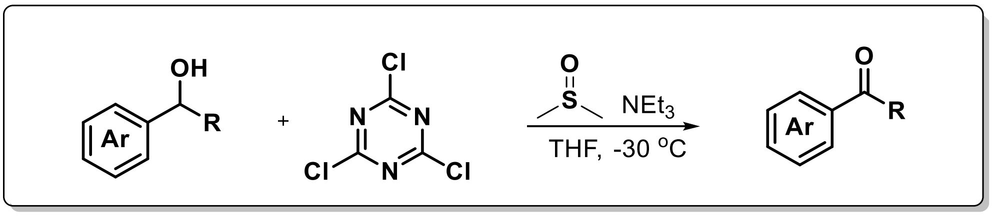
1.7 Organosulfur Compounds in Organic Synthesis

Besides their importance in medicinal chemistry and materials science, organosulfur compounds have wide applications in organic synthesis. Organosulfur compounds have been used in organic synthesis as solvents, oxidants, synthetic precursors, protecting groups, directing groups, etc.

1.7.1 Dimethyl Sulfoxide (DMSO)

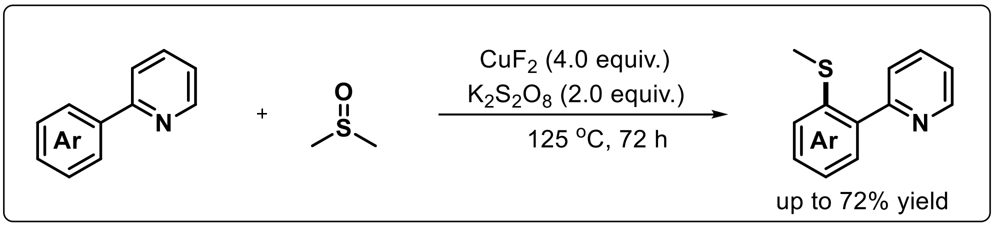
Dimethyl sulfoxide (DMSO) is one of the most versatile solvents in many organic transformations. Besides acting as a solvent, dimethyl sulfoxide was used as an oxidant, sulfur-transferring agent, methyl-transferring agent, etc[12].

Swern oxidation is the most characteristic example of dimethyl sulfoxide as an oxidant, the selective oxidation of secondary alcohol to corresponding ketone in the presence of some chloride source (oxalyl chloride, cyanuric chloride) and an organic base such as triethyl amine[13] (**Scheme 1.2**).



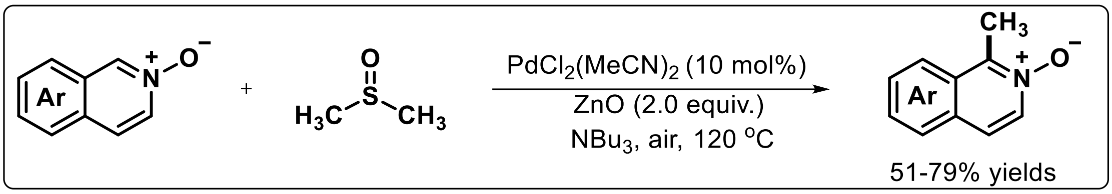
Scheme 1.2 Conversion of secondary alcohol to ketone by utilizing DMSO as an oxidant.

In 2010, Qing and co-workers described a method for methyl thiolation of aryl C-H bonds utilizing Cu(II) as a catalyst and DMSO as the source of methylthio moiety. The reaction occurs under oxidative circumstances[14] (**Scheme 1.3**).



Scheme 1.3 DMSO as a sulfur surrogate by utilizing the copper catalyst.

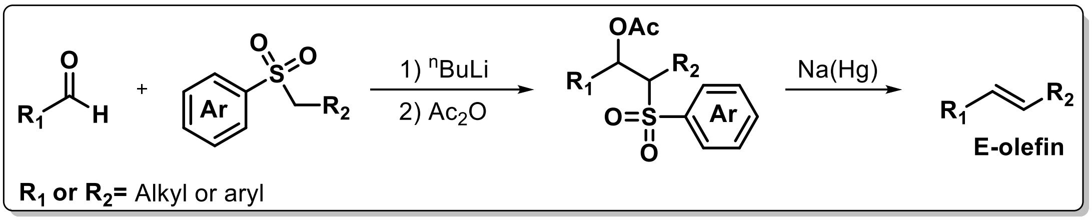
On the other hand, in 2012, Deng and coworkers published a report describing a very effective method for introducing alkyl groups onto isoquinoline N-oxides utilizing palladium as a catalyst and dimethyl sulfoxide (DMSO) as an alternative for methyl groups[15] (**Scheme 1.4**).



Scheme 1.4 Methylation of isoquinoline N-oxides with DMSO in Pd-catalyst.

1.7.2 Julia Olefination Reactions

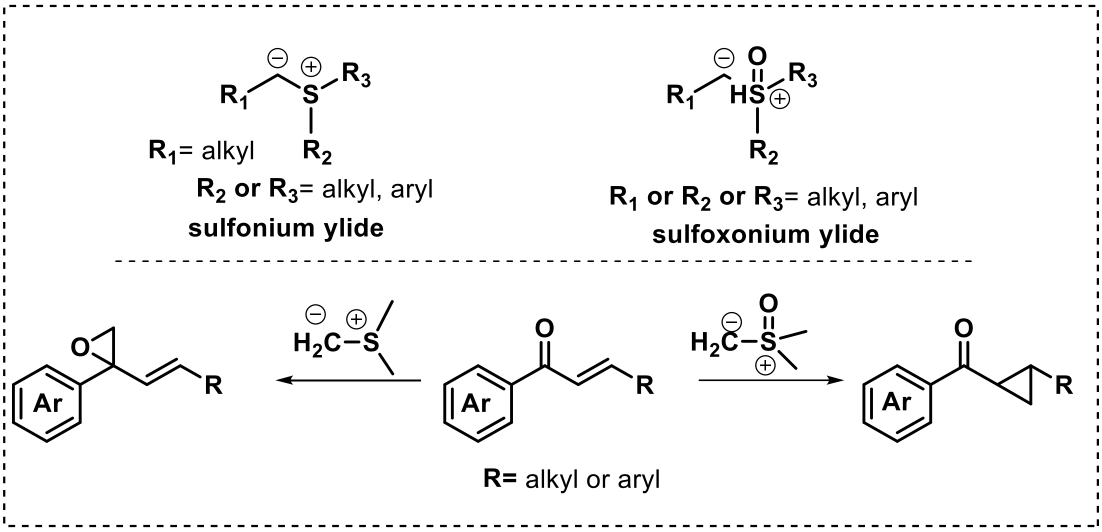
Olefination reactions received considerable attention in organic synthesis. Besides Wittig-type olefination reactions, Julia olefination reactions have wide applications in synthetic organic chemistry. The reaction of aldehydes with aryl-alkyl sulfones in the presence of a base provides stereoselectively *E*-olefins. Nevertheless, one can achieve Z-olefins by changing the reaction parameters like base, solvent, etc. [16] (**Scheme 1.5**).



Scheme 1.5 Selective synthesis of E-olefin by using sulfur dioxide as a precursor.

1.7.3 Sulfur Ylides

Sulfur ylides are 1,2-dipolar compounds in which a carbanion is attached to a positively charged sulfur atom. The application of sulfur ylides has been demonstrated in several organic transformations. There are two types of ylides, namely sulfonium ylide and sulfoxonium ylides. The reaction of sulfonium ylides with ketones or imines provides epoxides or aziridines [17]. On the other hand, the reaction of sulfoxonium methylide with α,β-unsaturated ketones provides cyclopropane rings. These reactions are called Corey-Chaykovsky reactions[18] (**Scheme 1.6**).



Scheme 1.6 Formation of epoxidation or cyclopropanation ring with sulfur ylides.

1.8 Organosulfur Compounds as Ligands

Organosulfur compounds were used as ligands in many catalytic organic transformations with different metals, including palladium, nickel, and copper. Sulfur-based ligands received good attention due to their poor σ-donor and π-acceptor nature. A few sulfur-based chiral ligands that have been used in organic reactions are listed below[19-21] (**Figure 1.6**).

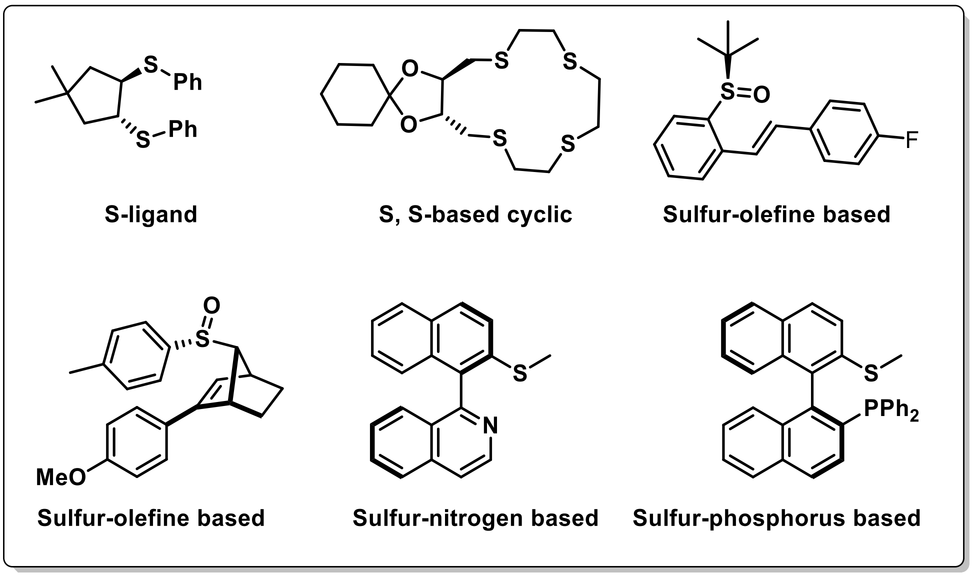
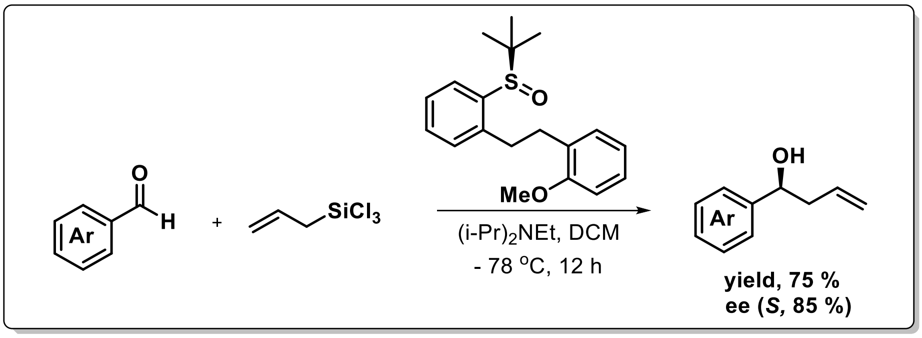


Figure 1.6 Sulfur-based chiral organic ligands.

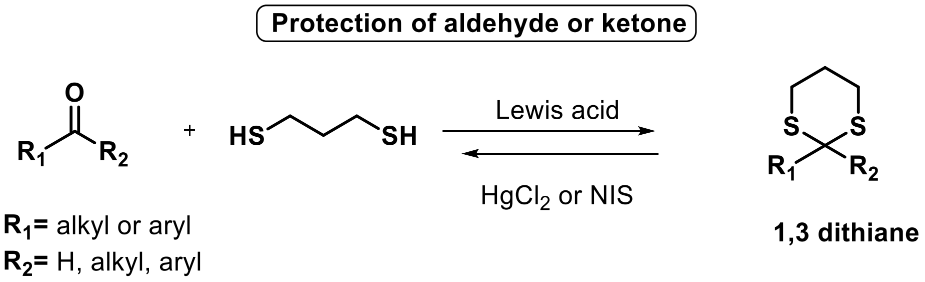
Chiral sulfoxides are stable compounds that have been utilized as ligands in asymmetric catalysis and as chiral auxiliaries in stereoselective synthesis. Like asymmetric allylation of aldehydes using allyl trichlorosilane is facilitated by chiral sulfoxides[22] (**Scheme 1.7**).



Scheme 1.7 Chiral sulfoxide facilitates allylation of aldehydes using trichlorosilane.

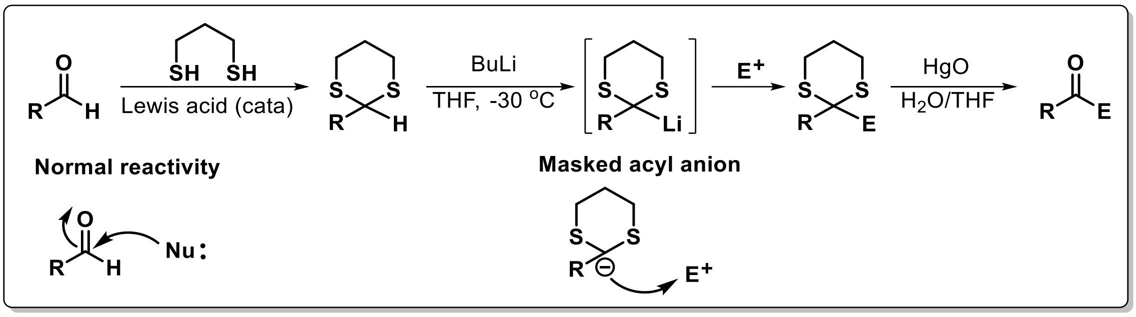
1.9 Organosulfur Compounds as a Protecting Group

Synthetic organic chemistry relies on reagents and catalysts to build new molecules efficiently. In this context, protecting groups plays an important role in avoiding undesired reactions due to the presence of other sensitive functional groups. Among various types of protecting groups, sulfur-based protecting groups play an important role in organic synthesis. Protection of aldehyde and ketones with 1,3-propanedithiol or 1,2-ethanedithiol provides 1,3-dithianes and 1,3-dithiolanes in good yields. These compounds are stable under various conditions and can be deprotected using mercury or halogen-based reagents (**Scheme 1.8**).



Scheme 1.8 Protection of ketone or aldehyde with dithiol.

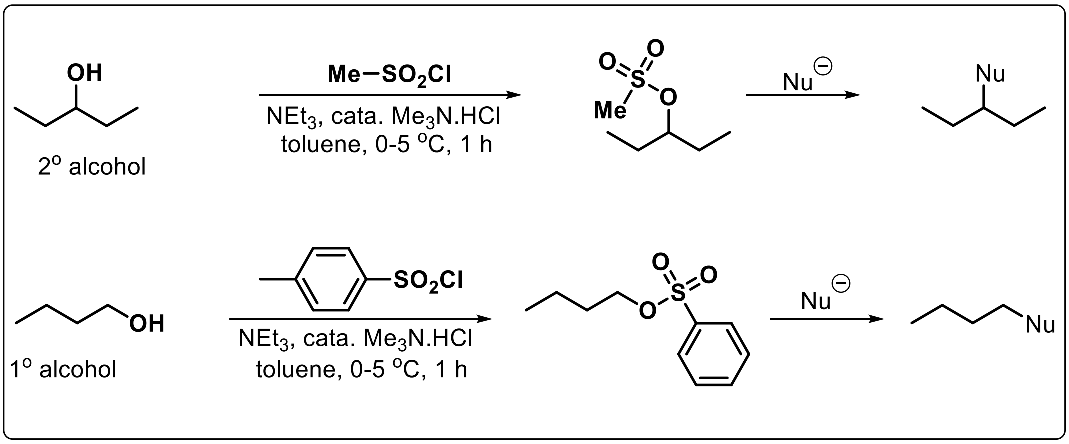
1,3-Dithianes have been used to generate acyl anion equivalents (i.e., Umpolung- a reversal of the normal reactivity of acyl carbon atoms), and that allows the formation of new carbon-carbon bonds[23-25] (**Scheme 1.9**).



Scheme 1.9 Umpolung type reaction of acyl carbon.

1.10 Organosulfur Compounds as Leaving Groups

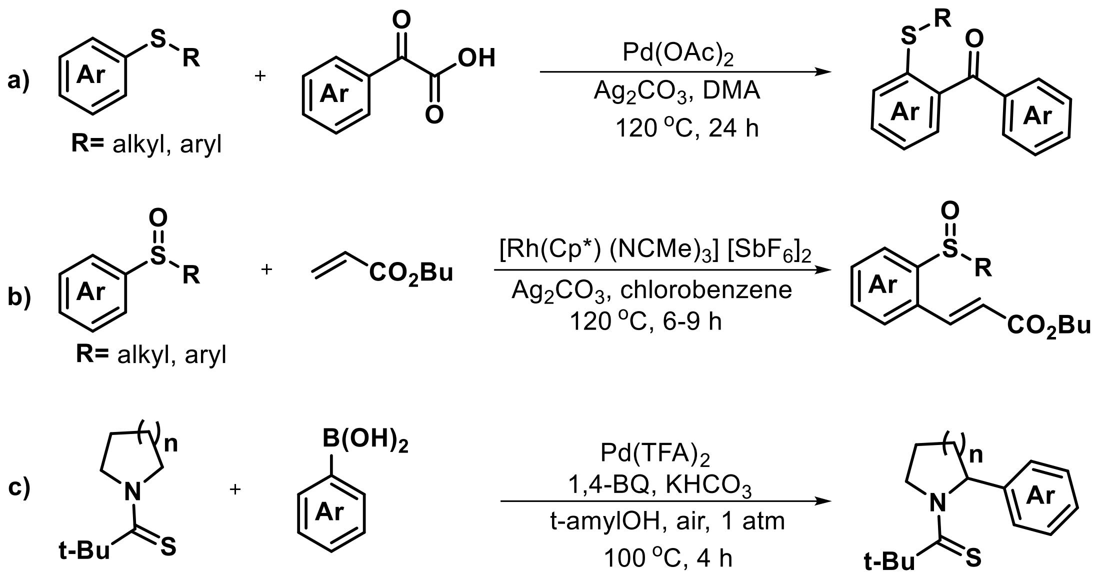
Sulfur-based leaving groups played an important role in organic synthesis. The reaction of alcohols with sulfonyl chlorides provides O-tosyl, O-triflate, and O-mesylate types of sulfonyl esters [26]. These compounds undergo nucleophilic substitution reactions with different nucleophiles under mild conditions (**Scheme 1.10**).



Scheme 1.10 Sulfur-based protecting groups for alcohol and their good leaving group tendency.

1.11 Organosulfur Compounds as a Directing Group

Directing groups assisted C-H functionalization reactions have gathered enormous interest in organic synthesis. Various directing groups, including amides, amines, oximes, etc, have been used in C-H functionalization reactions. Among the various directing groups, sulfur-containing directing groups, e.g., thioethers [27] **(a),** sulfoxide [28] **(b),** and thioamide [29] **(c),** etc., were used efficiently in palladium and rhodium-catalyzed reactions[30, 31] (**Scheme 1.11**).

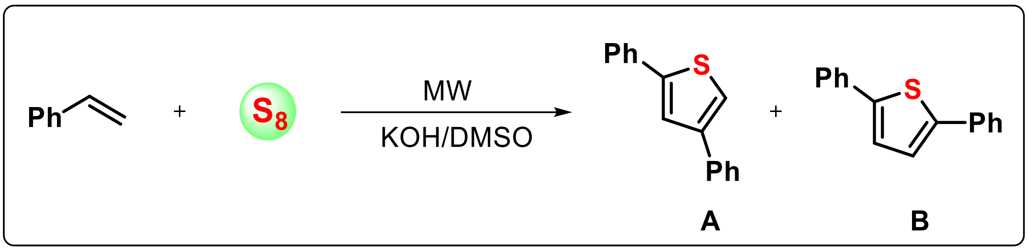


Scheme 1.11 Palladium and rhodium-catalyzed acylation, olefination and arylation using sulfur-based directing groups.

The above sections clearly indicate the importance of organosulfur compounds in different fields. In this context, the synthesis of organosulfur compounds has received significant attention in the past few decades due to their biological and synthetic applications. The section below outlines a brief introduction to organosulfur compound synthesis.

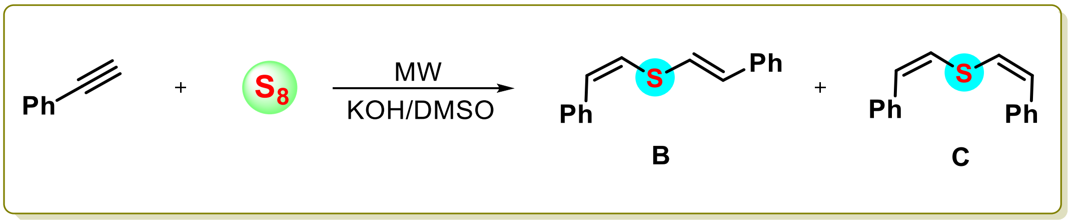
1.12 Synthesis of Organosulfur Compounds

Different strategies have been employed for the synthesis of organosulfur compounds. Elemental sulfur (S_8) and Lawesson's reagent play an important role in introducing a sulfur group in organic molecules. Sulfur heterocyclic compounds have been achieved by reacting aryl olefins with elemental sulfur[32] (**Scheme 1.12**).



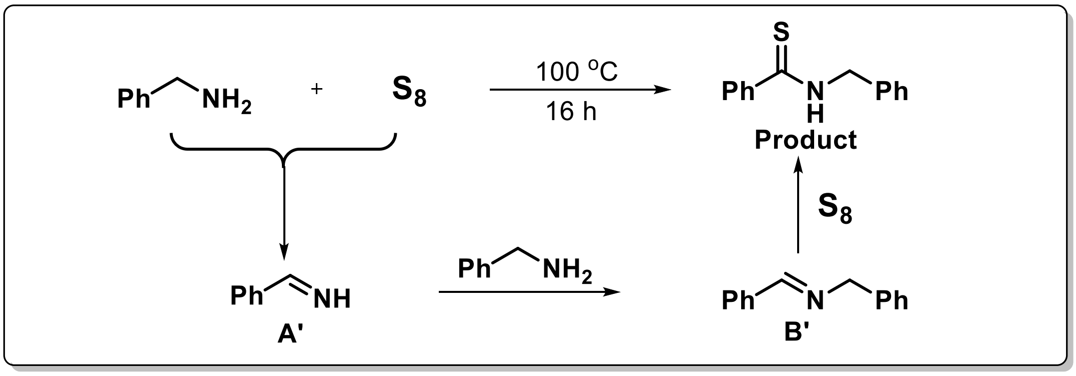
Scheme 1.12 Synthesis of 2,4- and 2,5- diphenylthiophenes by using octasulfur.

In 2004, the Tromifov group explored the reaction of phenylacetylene with the S_8 with KOH/DMSO at 50°C to obtain two isomers of distyryl sulfide, specifically the Z, E **(B)** and Z, Z **(C)** isomers, in a ratio of 2:1 [33] (**Scheme 1.13**).



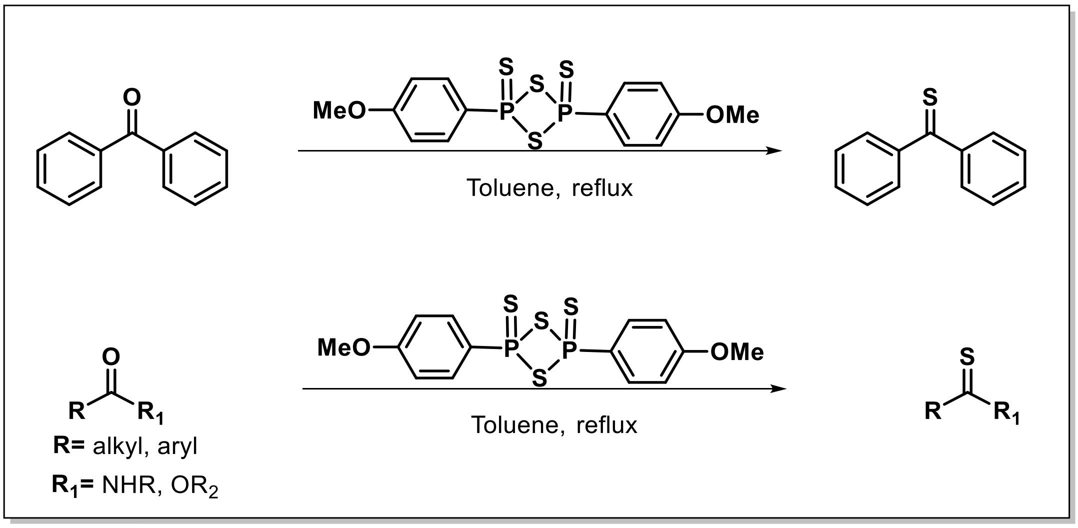
Scheme 1.13 Synthesis of distyryl sulfide by using octasulfur and microwave irradiation.

In 1948 Mcmillan group examined the interaction between elemental sulfur and an aliphatic amine. When benzylamine is heated with elemental sulfur at 100°C, it forms N-benzyl thiobenzamide by a cascade reaction[34]. Followed by the oxidation of benzylamine is converted into an imine **(A')** by the process of transimination at NH to imine **(B'),** which again undergoes sulfuration, resulting in its conversion into thioamides (**Scheme 1.14**).



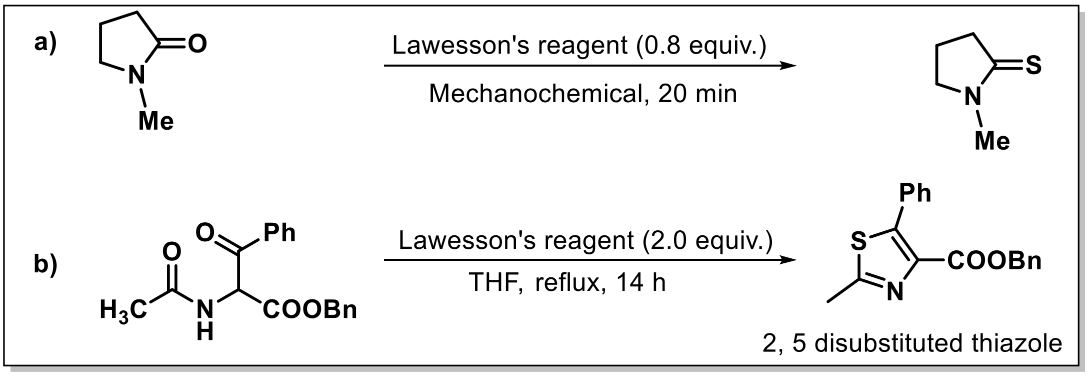
Scheme 1.14 Synthesis of thioamide by using sulfur in the presence of heating.

Like elemental sulfur (S_8), Lawesson's reagent is also well used in synthesizing organosulfur compounds. In particular, ketones, amides and esters can be converted into thioketones, thioamides and thioesters, respectively[35-38] (**Scheme 1.15**).



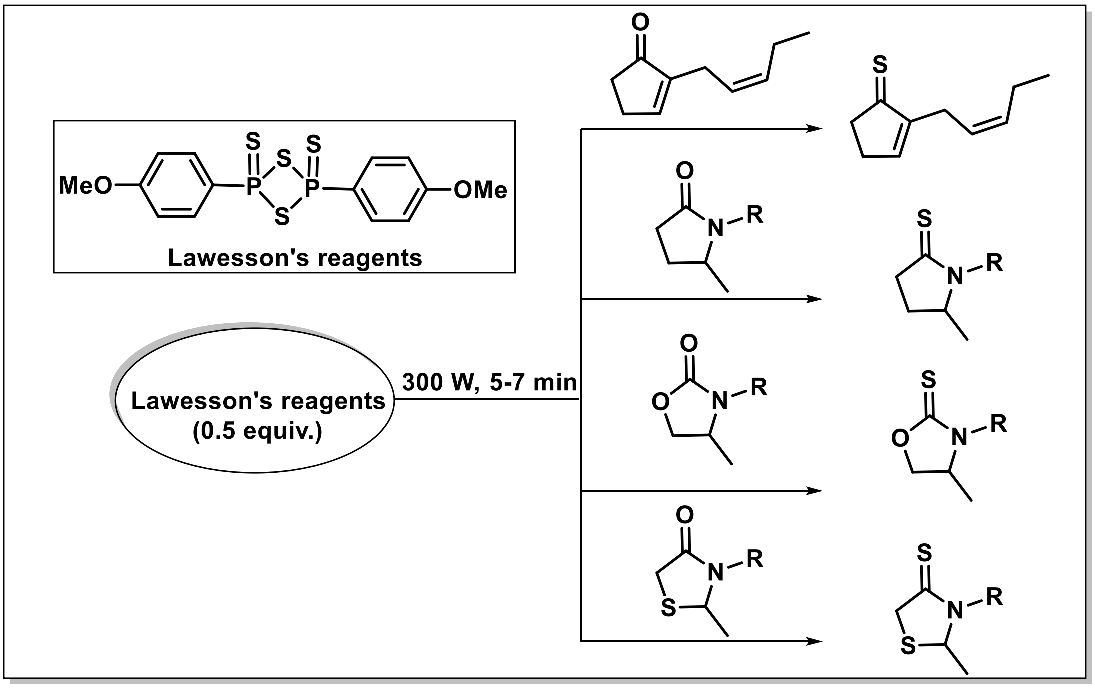
Scheme1.15 Conversion of keto analogs into thio analogs by using sulfur source.

In addition, Lawesson's reagents also play an essential role in the conversion of cyclic amides into cyclic thioamides [39] and the synthesis of 1,3 thiazole from α-amido-β-ketoesters[40] (**In scheme 1.16**, **a and b**).



Scheme 1.16 Synthesis of heterocyclic thioamide and thiazole by using lawesson's reagents.

Besides using the conventional methods, which require prolonged reaction time, elevated temperatures, dry solvents etc., Pawełczyk et al. reported a microwave assistant transformation of ketone to thioketone in Z-jasmone, pyrrolidinone, oxazolidinone and thiazolidinone derivatives [41] (**Scheme 1.17**). This approach offers advantages such as high yield, environmental friendliness, and cost-effectiveness, etc. [42, 43].



Scheme 1.17 Synthesis of fragrant thioketones by using microwave techniques.

On the other hand, there are numerous organic and inorganic sulfur compounds, including sodium sulfide (**1**), sodium dithionate (**2**), potassium metabisulfite (**3**), potassium thiocyanate (**4**), DABSO (**5**), rangolite reagent (**6**), carbon disulfide (**7**), thiourea (**8**), etc., were used as the sulfur source in the C-S bond forming reactions (**Figure 1.7**). The conventional methods used for the formation of C-S bonds consist of two main approaches: (**a**) transition metals promoted cross-coupling reactions with thiols or other sulfur source and (**b**) transition metal-free formation C-S bonds (**Scheme 1.18, a** and **b**).

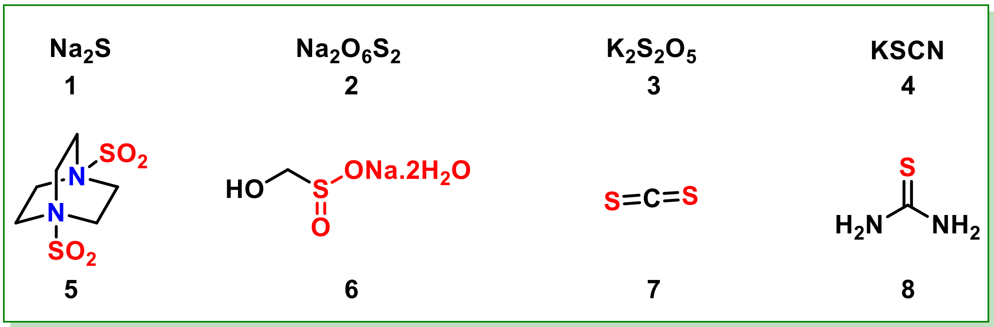
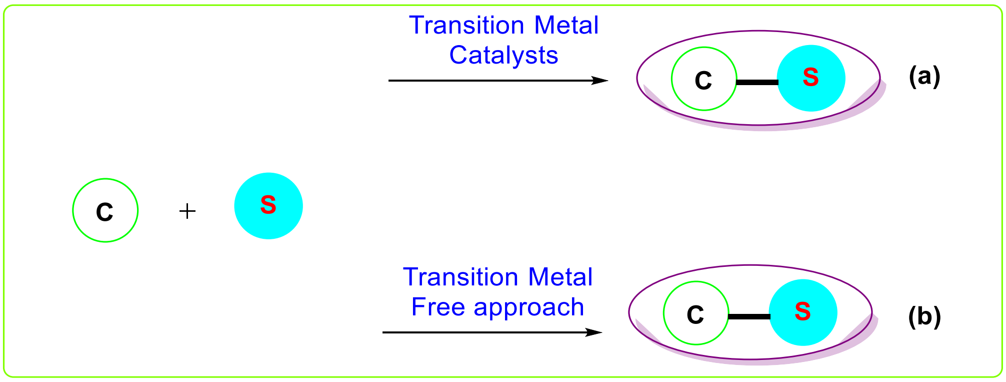


Figure 1.7 Sulfur sources

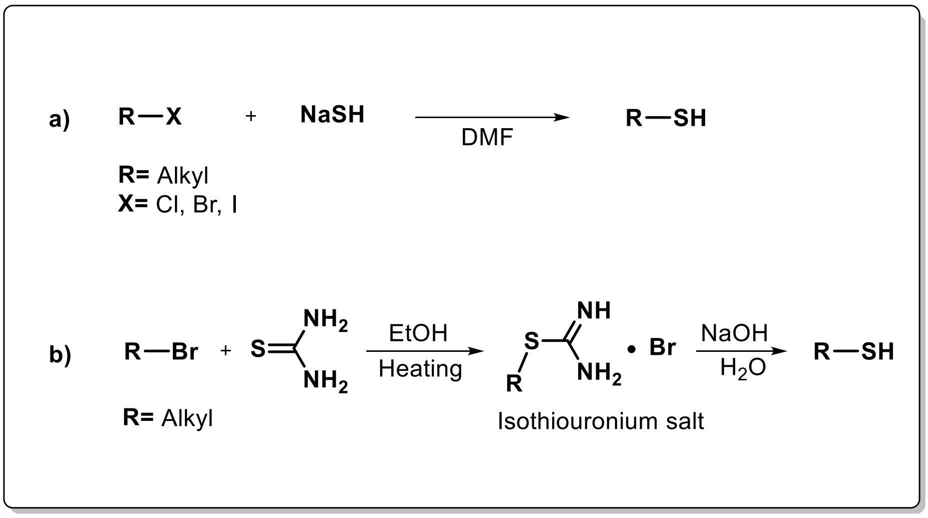


Scheme 1.18 Conventional methods for the synthesis of C-S bonds.

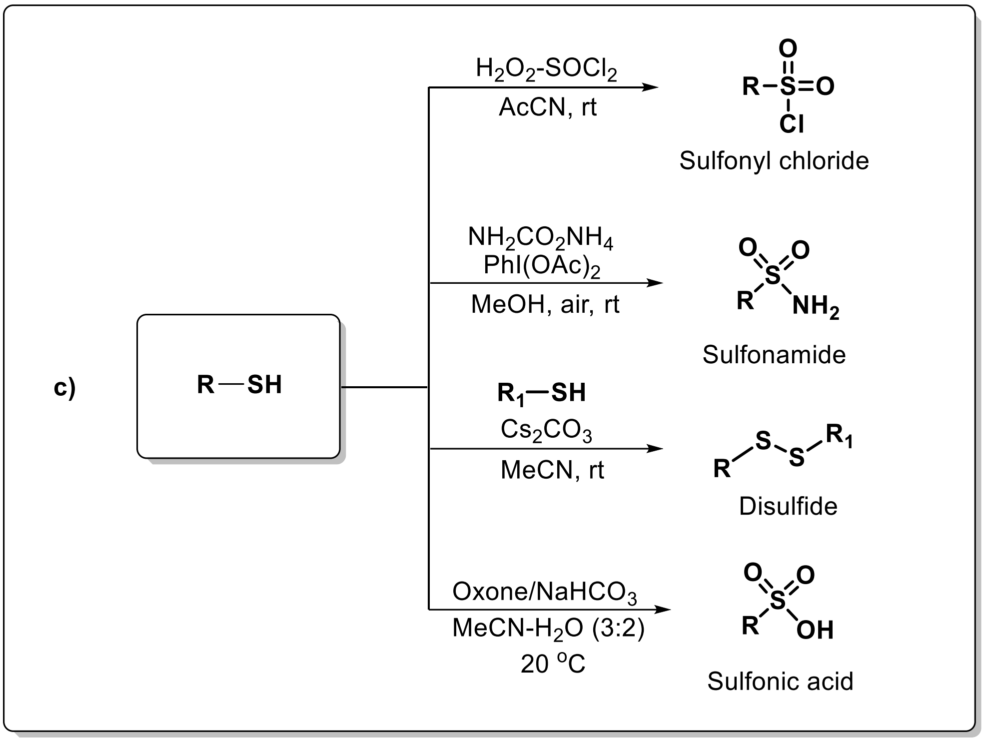
Carbon-sulfur bond formation has been achieved on ***Sp*^{3}** carbon, ***Sp*^{2}** carbon, and ***Sp*** carbons under different conditions. Some of the methods discussed here.

1.13 Formation of C-S Bonds with *Sp*^{3} Carbons

The classical methods for the construction of C–S bonds with ***Sp*^{3}** carbons traditionally involve the nucleophilic substitution reaction between alkyl halides and thiol surrogate. For instance, the synthesis of alkyl thiols can be achieved from simple alkyl halides with sodium sulfide or sodium hydrosulfide (Na_2S or NaSH) via SN_2 type reactions (**Scheme 1.19, a**), On the other hand, the reaction of alkyl halides with thiourea provides isothiouronium salt as an intermediate, which is hydrolyzed to thiols [44] (**Scheme 1.19, b**). The resulting thiols can be converted to various other sulfur functional groups like sulfonyl chloride, sulfonamide, disulfides and sulfonic acid, etc[45-48] (**Scheme 1.20, c**).

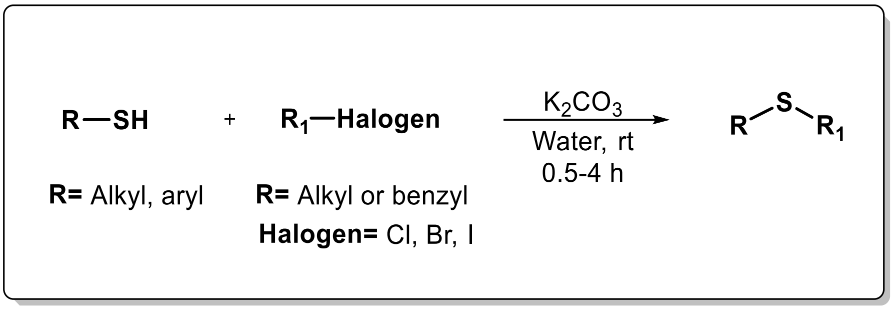


Scheme 1.19 Conventional methods for the synthesis of ***Sp*^{3}**-C-S bonds.

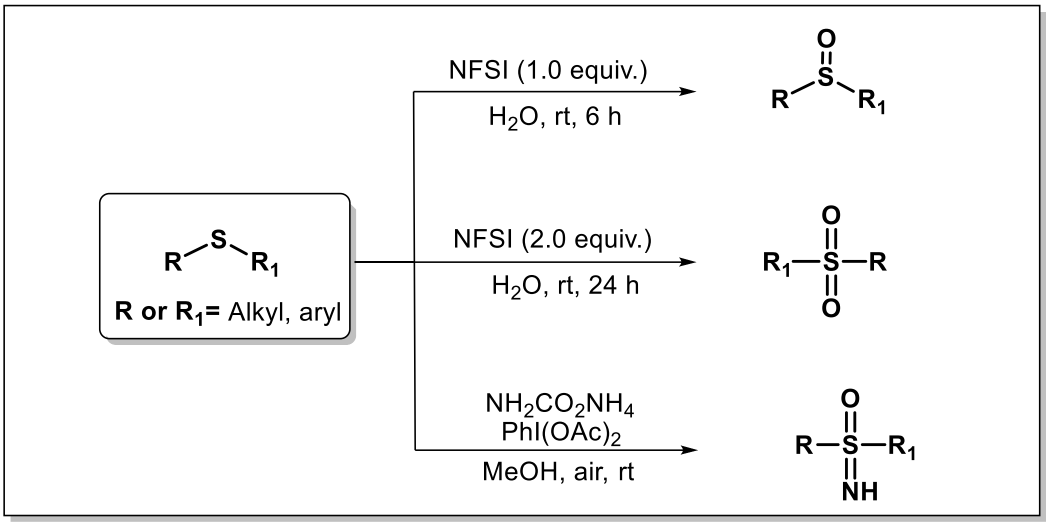


Scheme 1.20 Synthesis of various functional groups by using thiol as starting material.

On the other hand, the synthesis of sulfides has been achieved from alkyl or aryl thiols vial S-alkylation reactions using alkyl halides [49] (**Scheme 1.21**). This sulfide has been further converted into sulfoxide, sulfone, sulfoximine, etc., via oxidation reactions[50-52] (**Scheme 1.22**).

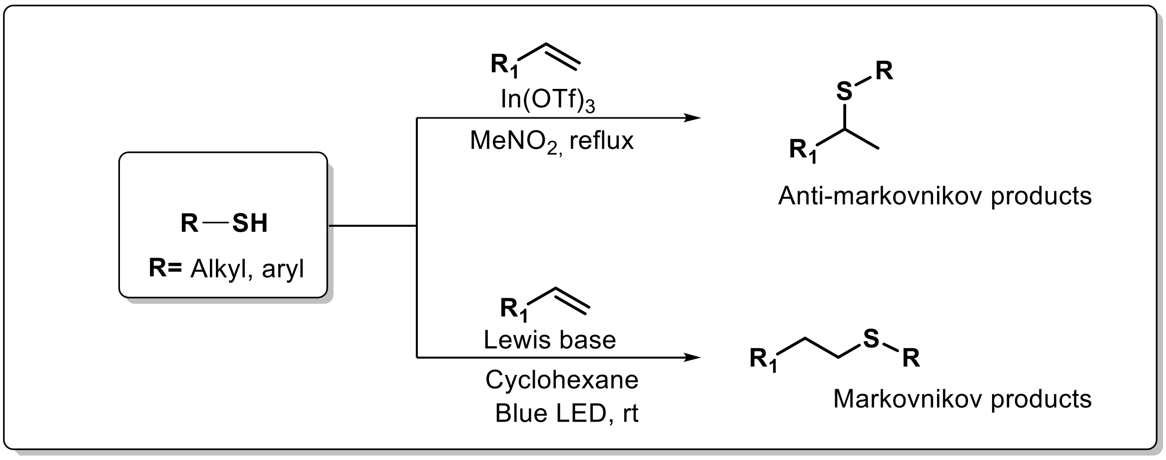


Scheme 1.21 Synthesis of sulfides from thiols and alkyl halides.



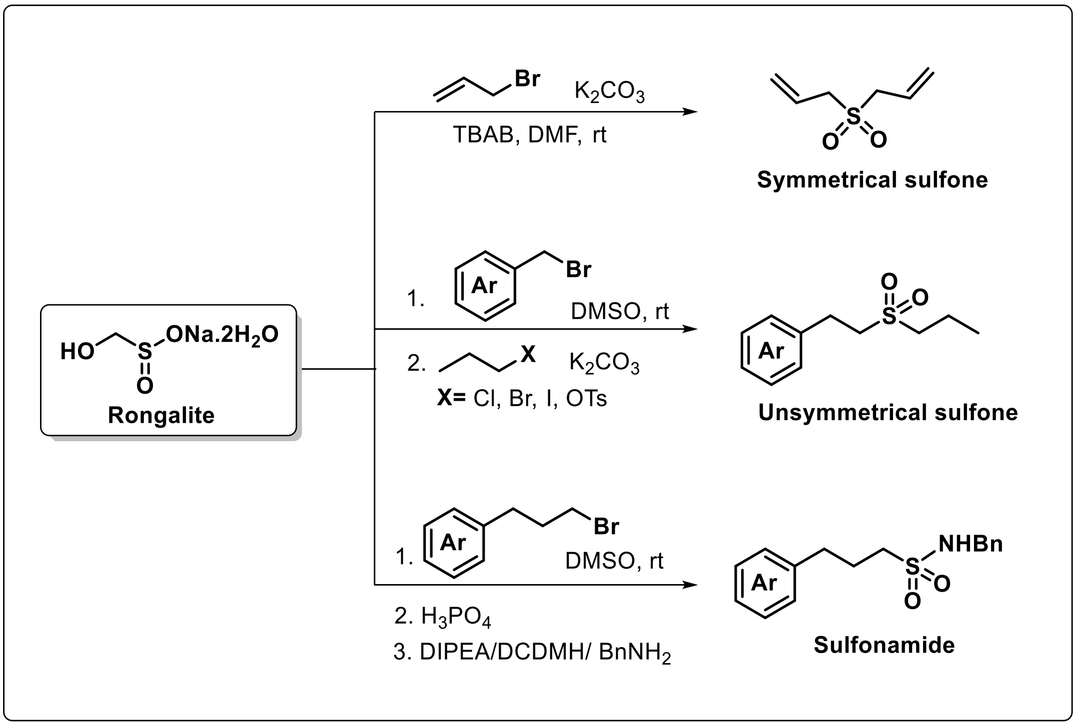
Scheme 1.22 Synthesis of various functional groups by using sulfides as a precursor.

Besides this approach, adding thiols to alkenes provides different sulfides under mild conditions. The reaction is known as Thiol-Ene Addition Click Reaction (TEC) and can be performed in the presence of light, heat, or catalysts[53, 54] (**Scheme 1.23**).



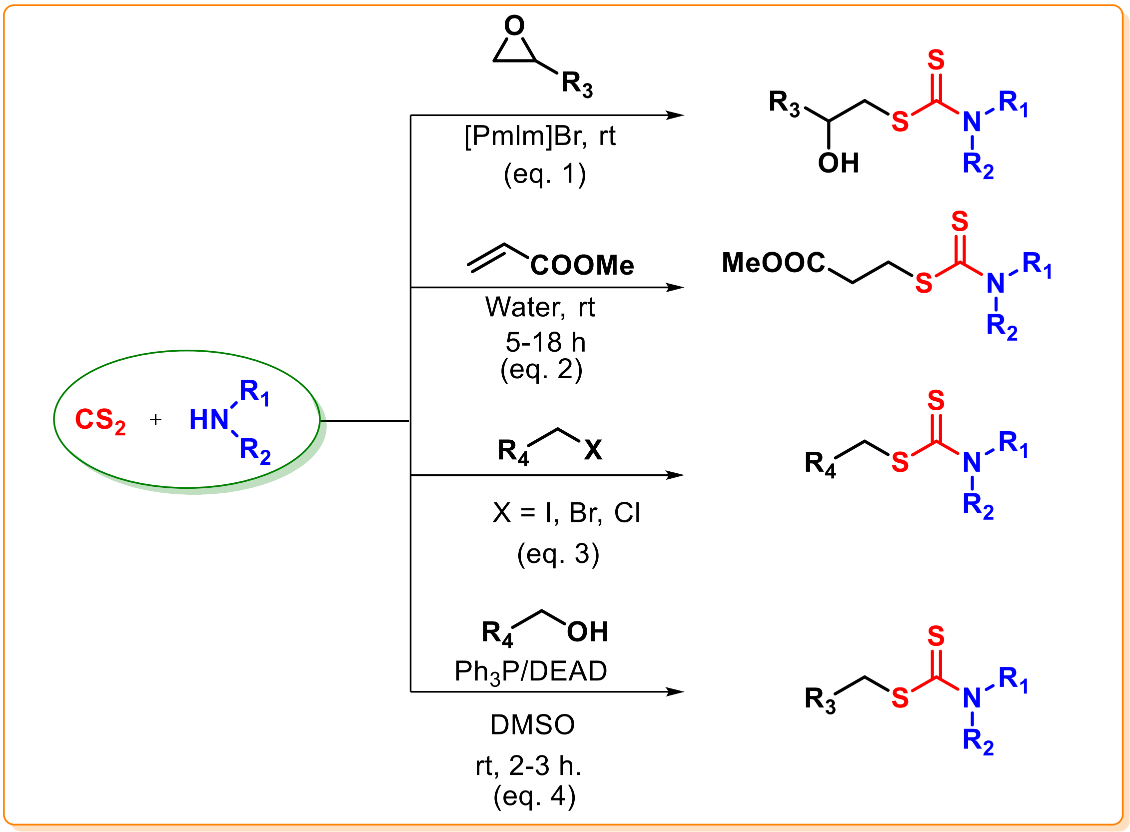
Scheme 1.23 Synthesis of sulfides from thiol and olefines under different conditions.

Rongalite (sodium hydroxymethanesulfinate) is used as sulfur-dioxide surrogate in organic synthesis. Several applications of rongalite are well-investigated in organic chemistry. The reaction of alkyl halides with rongalite provides sulfone and sulfonamide products with good yields[55, 56] (**Scheme 1.24**).



Scheme 1.24 Synthesis of sulfones and sulfonamides by using rongalite reagents.

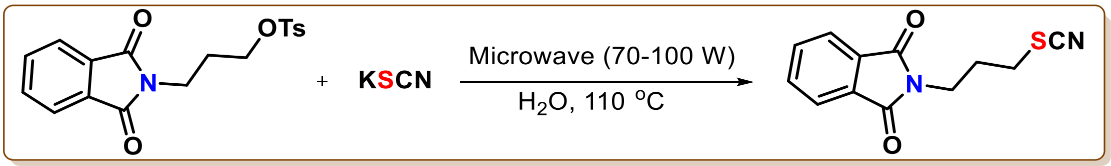
Carbon disulfide is well-used as sulfur surrogates in organic synthesis. Dithiocarbomates are found in wide applications in different fields, including medicinal chemistry. The reaction of amine with epoxides, Michael acceptors, alkyl halides and alcohols in the presence of carbon disulfide provides dithiocarbomates with good yields[57-60] (**Scheme 1.25,** eq-1, 2, 3 and 4).



Scheme 1.25 Synthesis of S-alkyl dithiocarbamates.

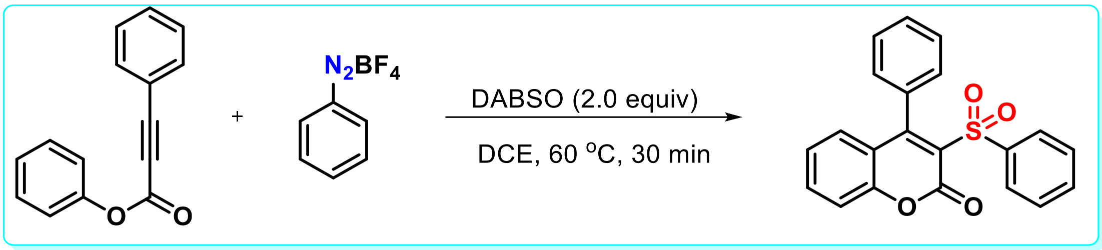
Similarly, potassium thiocyanate, DABSO, sodium dithionites and thiourea dioxides are used in the formation of C-S bonds with ***Sp***^{3} carbons.

In 2006, Verma and his co-workers developed a practical and effective approach utilizing microwave irradiations for the synthesizing of thiocyanates in the presence of an aqueous medium[61] (**Scheme 1.26**).



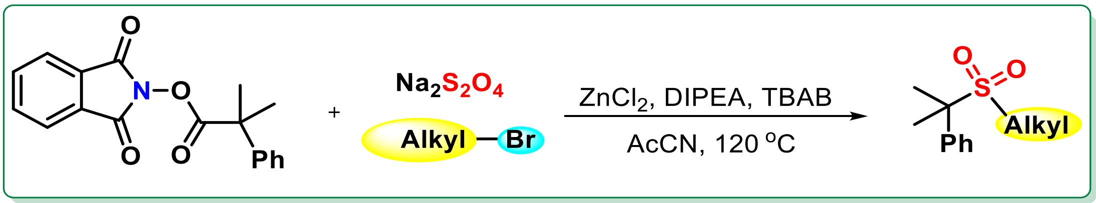
Scheme 1.26 Synthesis of thiocyanates under microwave irradiations.

In 2016, Wu and co-workers developed a three-component tandem process to synthesize derivatives of 3-sulfonated coumarins with a catalyst-free approach, this method involves the combination of aryldiazonium salt, DABSO, and aryl propiolates in a DCE. Based on kinetics and experimental investigations, the reaction was conducted by treating aryldiazonium tetrafluoroborates with DABSO, forming charge-transfer complexes[62] (**Scheme 1.27**).



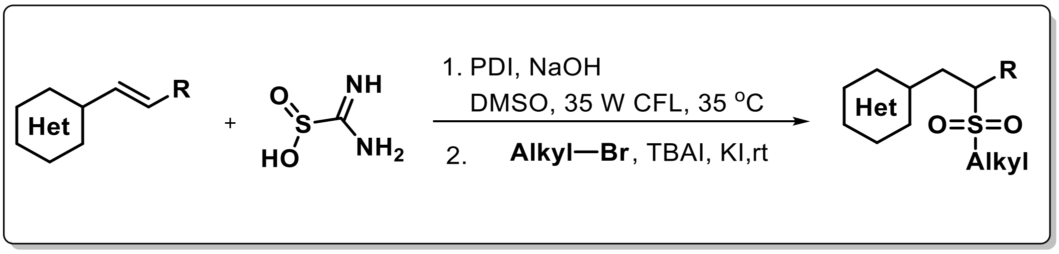
Scheme 1.27 Synthesis of 3-sulfonated coumarins with catalyst-free approach.

In 2020, Wang and Jiang introduced a direct and efficient method for synthesizing sterically bulky sulfones. This method involves a multicomponent decarboxylative cross-coupling reaction of N-hydroxy phthalimide ester, sodium dithionite, and alkyl halides. Sodium dithionite accomplishes two roles in this perspective: firstly, as a source of sulfur dioxide, and secondly, as a radical initiator for the decarboxylation process.[63] (**Scheme 1.28**).



Scheme 1.28 Synthesis of alkyl sulfone by using sodium dithionite.

In 2021, Jie Wu and his colleagues established an alternate and complementary method for synthesizing a broad spectrum of sulfone compounds. Thiourea dioxide has been utilized as a surrogate of the sulfonyl group in the preparation of sulfones and various other organosulfur compounds[64] (**Scheme 1.29**).



Scheme 1.29 Synthesis of sulfone compounds by utilizing thiourea dioxide.

1.14 Formation of C-S Bonds with *Sp*^{2} Carbons

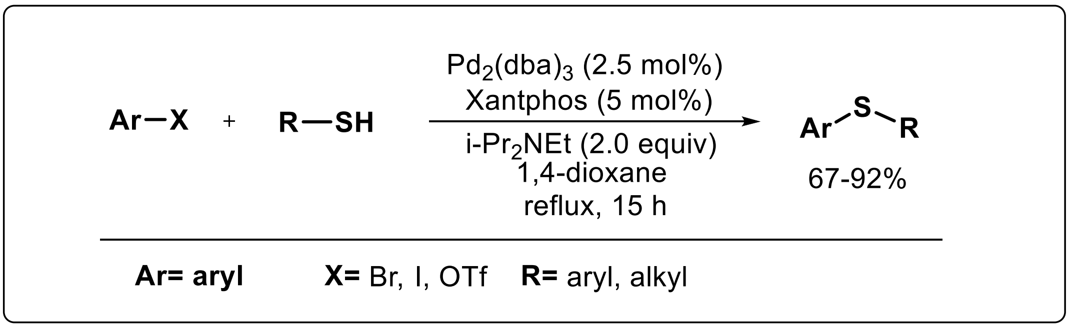
Unlike ***Sp***^{3} carbons, forming C-S bonds with ***Sp***^{2}carbons is difficult. The conventional methods to form C-S bonds in ***Sp***^{2} carbons rely on transition metals-promoted cross-coupling reactions. Many metals were used for cross-coupling aryl or alkyl thiols with various aryl sources, including aryl boronic acid, aryl diazonium salts, aryl halides, indoles, etc. Some of the metal-catalyzed methods are outlined below.

1.15 Synthesis of S-Aryl Sulfides via Cross-Coupling Reactions

Synthesis of sulfides (thioethers) via C-S bond-forming reactions received considerable attention in organic synthesis due to their biological importance and synthetic applications. The coupling reaction between aryl halides and thiols (or disulfides) in the presence of transition metals/ligands leads to the formation of diaryl sulfides or aryl-alkyl sulfides. Some of the *S*-arylation reactions are described below.

1.16 Palladium-Catalyzed *S*-Arylation Reactions

The formation of a C–S bond using transition metal catalysts has received growing interest over the past few years. In this context, palladium-catalyzed C–S bond formation, among the different metals, allows the synthesis of structurally diverse unsymmetrical functionalized aryl sulfides and sulfones under mild conditions. For instance, in 2004, Itoh and Mase established a method for the formation of chemical bonds between aryl halides/triflates and thiols utilizing palladium as a catalyst and Xantphos as a ligand in the presence of diisopropyl ethylamine base[65] (**Scheme 1.30**).

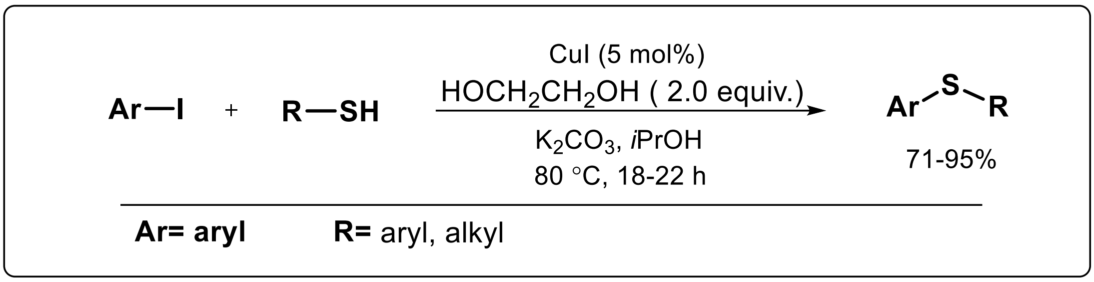


Scheme 1.30 Palladium-catalyzed C-S cross-coupling of aryl halides and thiols.

1.17 Copper-Catalyzed *S*-Arylation Reactions

Besides palladium, copper is also a widely used metal in C-S bond-forming reactions owing to their availability, cost-effectiveness, and low toxicity. In 2002, Buchwald and

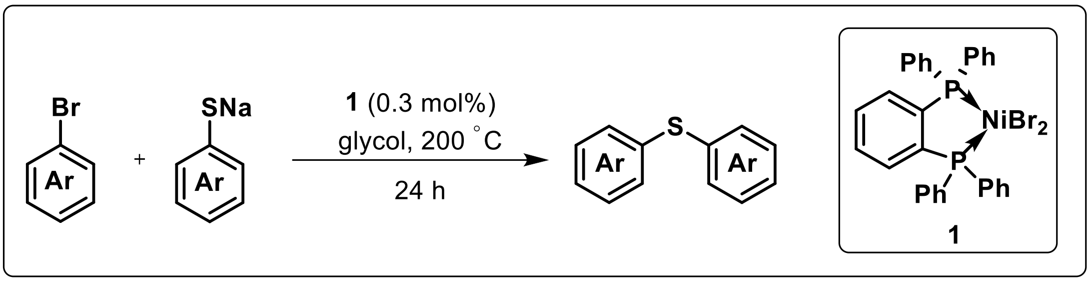
Kwong explored copper-catalyzed C-S bond construction reactions from thiols and aryl iodides using copper iodide[66] (**Scheme 1.31**).



Scheme 1.31 Copper-catalyzed *S*-arylation of aryl halides.

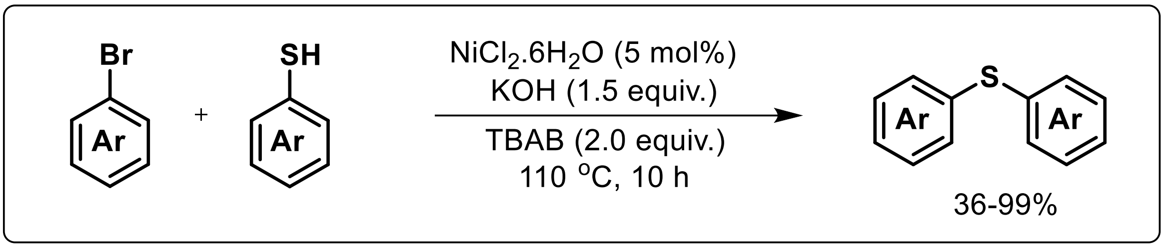
1.18 Nickel-Catalyzed *S*-Arylation Reactions

Nickel-catalyzed C-S bond-forming reactions received significant interest in organic synthesis besides palladium and copper catalysts. In 1981, the research group of Cristau reported the first-ever example of C−S cross-coupling bond formation by Ni-phosphorous complex **1** as a catalyst between aryl bromide and sodium thiolates[67] (**Scheme 1.32**).



Scheme 1.32 Nickel-catalyzed C-S bond cross-coupling reaction.

In 2008, Punniyamurthy and co-workers published a report on the synthesis of sulfide via cross-coupling of aromatic thiols and aryl halides by utilizing a nickel-catalyzed ligand-free approach; the investigation found that aryl iodides resulted in high yields of the desired products[68] (**Scheme 1.33**).



Scheme 1.33 Nickel-catalyzed ligand-free synthesis of sulfides.

1.19 Other Metals

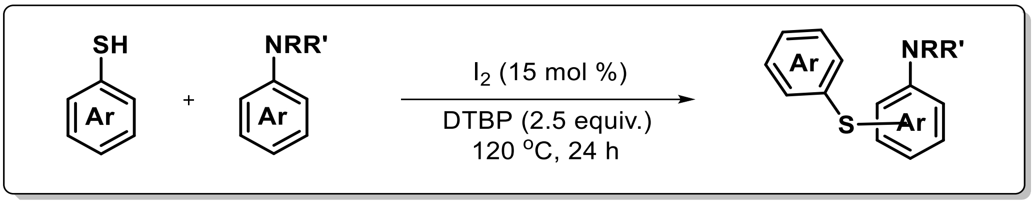
Iron, Manganese, Cobalt, Indium, Gold, Rhodium, Silver, Bismuth and Lanthanum were also used as a catalyst for the C-S bond formation reactions.

1.20 Metal Free-Approach for the Formation of C-S Bonds with *Sp*^{2} Carbons

Metal-free organic reactions have received enormous interest in the research community. There are several methods have been developed for the formation of C-S bonds under metal-free conditions. The commonly employed reagents for the sulfenylation reactions include molecular iodine (I_2), $I_2/K_2S_2O_8$, inorganic salts (such as $K_2S_2O_8$, RSO_3Na), N-iodosuccinamide (NIS) and many more.

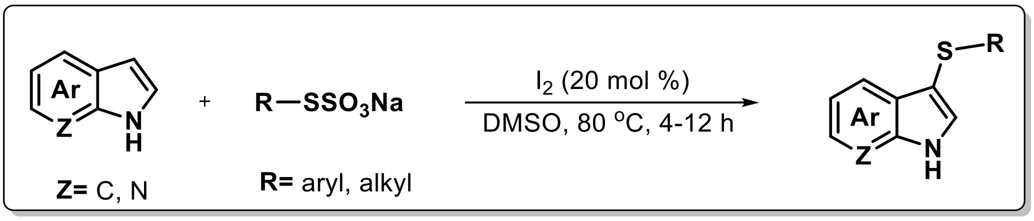
1.21 Synthesis of *Sp*^{2}-C-S Bonds by Utilizing Molecular Iodine

Molecular iodine and other iodine-based salts have shown to be effective catalysts or mediators for several useful transformations in the field of transition metal-free C−S bond synthesis. For instance, I_2/DMSO and $I_2/K_2S_2O_8$ combination has been demonstrated to be a straightforward and effective catalytic system[69a-b]. In 2015, Wang and co-workers utilized a metal-free iodine-catalyzed method to introduce arylthio groups into substituted anilines. A wide range of diaryl sulfides were prepared under solvent-free conditions[69c] (**scheme 1.34**).



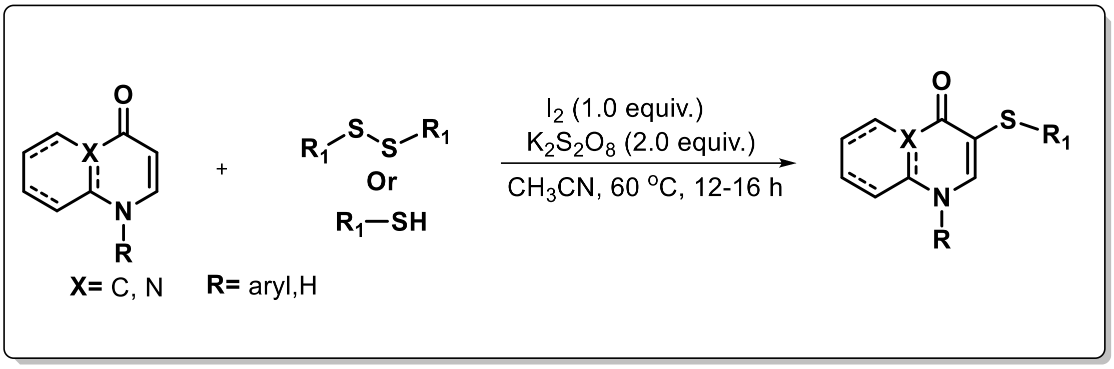
Scheme 1.34 I_2-catalyzed direct arylthiation of substituted anilines with thiols.

In 2016, Luo and co-workers accomplished a molecular iodine-catalyzed C3-sulfenylation of indoles using an odourless Bunte salts as a sulfenylating agent. In this reaction, DMSO was used as an oxidant and solvent[70] (**Scheme 1.35**).



Scheme 1.35 the C_3-sulfenylation of indoles using Bunte salts catalyzed by I_2.

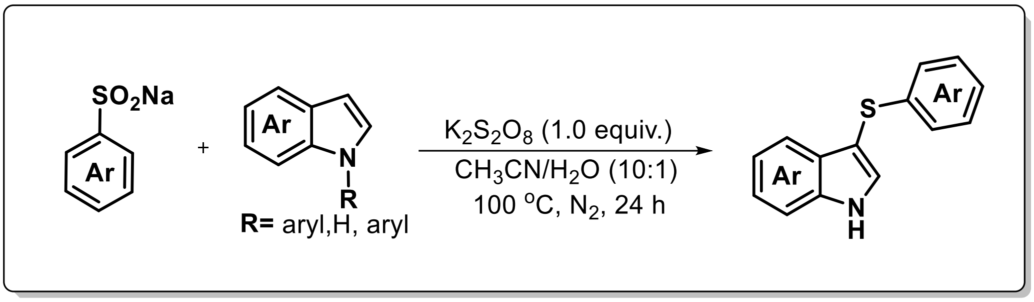
In 2019, Beukeaw and colleagues expanded the potential use of molecular iodine by combining it with $K_2S_2O_8$ to achieve a metal-free regioselective sulfenylation at the C-3 and C-5 positions of 4-quinolones and uracils, respectively[71] (**Scheme 1.36**).



Scheme 1.36 Sulfenylation of 4-quinolones and uracils using disulfides/thiols is facilitated by I_2.

1.22 Using Inorganic Salts

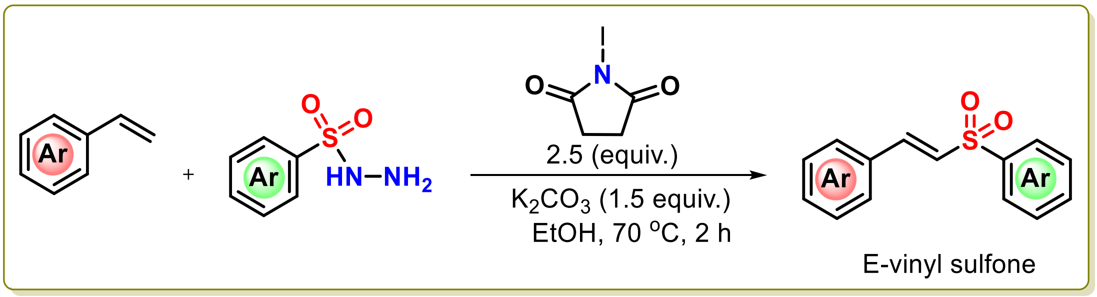
In 2014, Rao and co-workers demonstrated the S-arylation of indoles using sodium arene sulfinates in the presence of $K_2S_2O_8$ under reflux conditions. This reaction provides 3-arylthioindoles in good yields[72] (**Scheme 1.37**).



Scheme 1.37 $K_2S_2O_8$-mediated thiolation of indole with arenesulfinate salts.

1.23 *N*-Iodosuccinamide (NIS) Mediated Synthesis of Vinyl Sulfone

In 2019, Mal and co-workers developed a regio- and stereoselective C(***Sp***^{2})-H sulfonylation of styrenes with sulfonyl hydrazide. The coupling reaction was promoted by the NIS while the reaction proceeded through a radical mechanism [73] (**Scheme 1.38**).



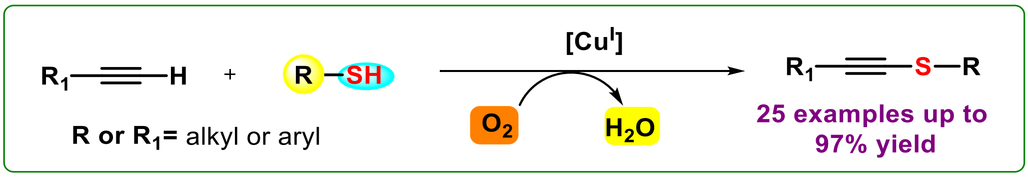
Scheme 1.38 NIS mediated stereoselective C(***Sp***^{2})-H sulfonylation of styrenes.

Besides these methods, many photocatalytic and electrochemical methods have recently been developed for forming C-S bonds with ***Sp***^{2} carbons[73b-c].

1.24 Formation of C-S Bonds with *Sp* Carbons

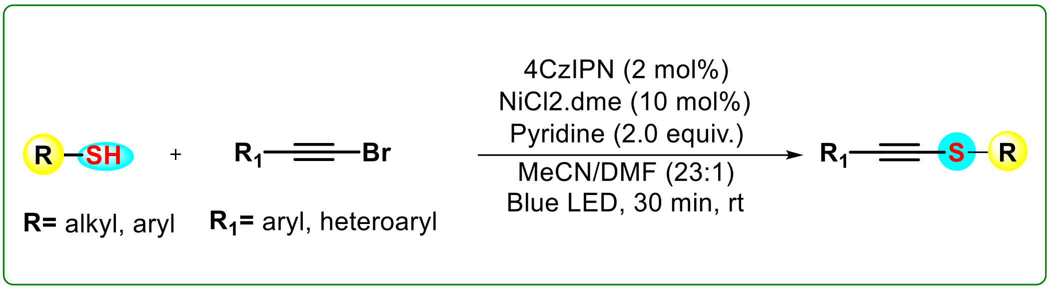
The formation of the C-S bond with **Sp** carbon received considerable attention in organic synthesis. However, similar to ***Sp***^{2} carbon, the formation of a C-S bond with ***Sp*** carbon is also difficult and typically achieved by copper and nickel-catalyzed cross-coupling reactions.

In 2013, Yang and M. Rioux published a report on the Cu(I) catalysed synthesis of alkynyl sulfides via cross-dehydrogenative coupling of terminal alkynes with thiols. The molecular oxygen was used as the oxidant while the desired S-alkenyl sulfides were obtained in excellent yields[74] (**Scheme 1.39**).



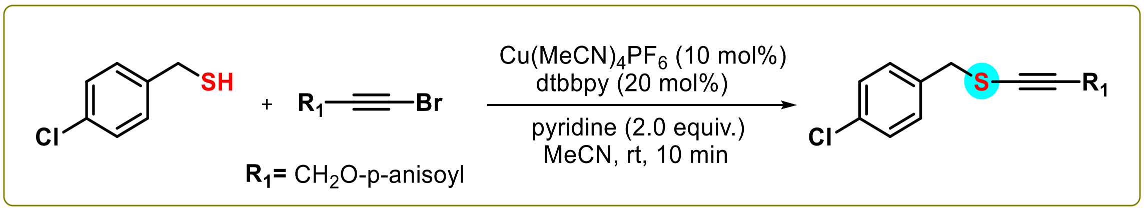
Scheme 1.39 Copper-catalyzed thiolation of alkynes.

On the other hand, in 2017, Shawn K. Collins and co-workers developed a photocatalytic route for the synthesis of S-alkenyl sulfides from thiols and bromoalkynes. An organic carbazole-based sensitizer, 4CzIPN, and nickel chloride were used to promote coupling reaction in the presence of blue LED[75] (**Scheme 1.40**).



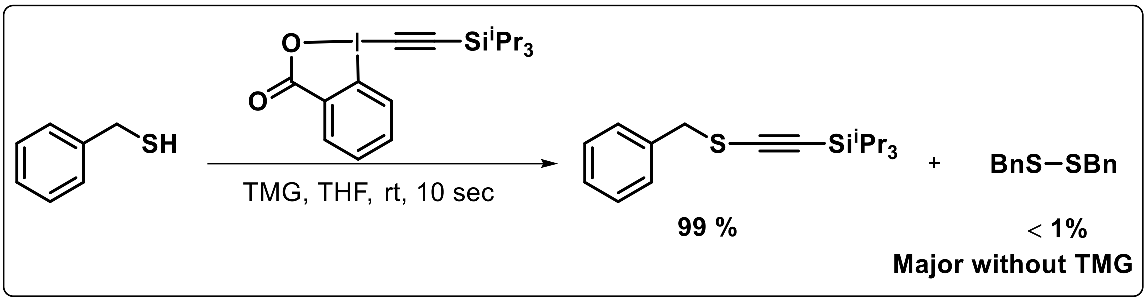
Scheme 1.40 Synthesis of alkynyl sulfides using a photochemical dual-catalytic method.

In 2020, the same group developed a general Cu-catalysed synthesis of alkynyl sulfides from thiols and alkynyl bromides using $Cu(MeCN)_4PF_6$, 4,4′-di-tert-butyl-2,2′-dipyridyl (dtbbpy), pyridine in acetonitrile under mild conditions[76] (**Scheme 1.41**).



Scheme 1.41 Copper-catalysed cross-coupling reaction of thiols and bromoalkynes.

In 2014, Waser and co-workers also demonstrated a transition-metal-free protocol using ethynyl benziodoxolone (EBX) reagents to promote the C−S bond formation reaction. This method provides the desired products with excellent yields[77] (**Scheme 1.42**).



Scheme 1.42 Hypervalent iodine-mediated alkynylation of thiols.

1.25 The Scope of the Present Thesis Work

Organosulfur compounds are very important building blocks in synthetic organic chemistry, medicinal chemistry, agrochemicals, and materials. The importance of organosulfur compounds is increasing continuously, and designing new molecules and developing new synthetic methods is also growing. In this aspect, **the present thesis aims to develop new synthetic routes to achieve some organosulfur compounds via the formation of C-S bonds with *Sp*^{3} and *Sp*^{2}carbons.** Four objectives were designed and executed in the present thesis. The objectives include,

1) Synthesis of (3)-S-arylthioindoles from indole and thiophenols in water.

2) Synthesis of functionalized thioimidates from thioamides and boronic acids.

3) Synthesis of functionalized S-benzyl dithiocarbamates from diazo-compound via multi-component reactions.

4) Synthesis of α-arylsulfone propanamide from α-halohydroxamates.

1.26 References

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