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Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry

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Abstract

The impact of the development of sulfur therapeutics is instrumental to the evolution of the pharmaceutical industry. Sulfur-derived functional groups can be found in a broad range of pharmaceuticals and natural products. For centuries, sulfur continues to maintain its status as the dominating heteroatom integrated into a set of 362 sulfur-containing FDA approved drugs (besides oxygen or nitrogen) through the present. Sulfonamides, thioethers, sulfones and Penicillin are the most common scaffolds in sulfur containing drugs, which are well studied both on synthesis and application during the past decades. In this review, these four moieties in pharmaceuticals and recent advances in the synthesis of the corresponding core scaffolds are presented.

Keywords

sulfur containing drugs; sulfonamide; thioether; sulfones; sulfur dioxide fixation; organic synthesis

INTRODUCTION

Sulfur containing compounds often show different biological activities and serve important functions in applications in the pharmaceutical industry [1]. Variety of sulfur containing scaffolds widely exists in natural products and drugs (Fig. 1). For instance, epidithiodiketopiperazine (ETP), characterized by sulfur atoms and a diketopiperazine structure, comprises a large number of metabolites, which display a range of biological activities including antiviral, antibacterial, antiallergic, antimalarial and cytotoxic properties [2]. Prevacid is a proton-pump inhibitor (PPI) which inhibits the stomach's production of gastric acids [3]. Seroquel is an atypical antipsychotic approved for the treatment of schizophrenia, bipolar disorder, and in the XR version along with a selective serotonin reuptake inhibitor (SSRI) to treat major depressive disorder [4]. In this review, several key

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

scaffolds of sulfur containing pharmaceuticals, namely sulfonamides, thioethers, sulfones and Penicillin and its derivatives, are illustrated and some recent synthetic approaches are discussed.

SULFONAMIDE CONTAINING DRUGS

From a historical perspective, sulfonamides have been a leading constituent in new drugs since the first appearance in the 1930s [5], occupying six decades over the past 100 years.

Sulfonamide drugs were the first antibiotics to be used systemically, and paved the way for the new antibiotic revolution in medicine. Nevertheless, antibiotics are not the only function of sulfonamides. Table 1 showed a list of sulfonamide containing scaffolds in pharmaceutical molecules with different indications. For example, cyclothiazide is a diuretic and antihypertensive that was originally introduced in the United States in 1963 by Eli Lilly [6].

SYNTHESIS OF SULFONAMIDES

One of the most conventional routes to sulfonamide involves the direct N-S bond formation *via* an addition-elimination process (Fig. 2). Sulfonyl chloride is a common substrate in this type of reactions, which reacts with aryl or alkyl amines to afford the corresponding sulfonamide in large scale [9].

To date, such an approach is a general method for the preparation of sulfonamide in pharmaceutical industry which still needs further improvement. In 2006, a facile sulfonamide synthesis in water under pH control was reported by Deng and co-workers [10]. The desired sulfonamide was afforded in up to 98% yield and with greater than 95% purity by simply acidifying the solution with concentrated HCl to pH=2.0 and collecting precipitated product after the reaction. Furthermore, the reaction was easily scalable to 100 grams. This method is also suitable for various amino compounds and arylsulfonyl chlorides (Fig. 3).

Flow chemistry has rapidly turned into one of the techniques that may revolutionize the synthetic sector of drug discovery in recent decades. In 2013, Gioiello and coworkers reported their work on the synthesis of sulfonamides by employing flow-based chemistry [11]. This work could therefore support medicinal chemistry program at various stages as the hit-to-lead, lead-optimization and lead candidate scale-up (Fig. 4).

Although sulfonyl chloride is often utilized in the preparation, the difficulties associated with sulfonamide synthesis stem not from the amination reaction, but rather from the preparation of sulfonyl chlorides. As an alternative, a new and convenient method for the construction of sulfonamides *via* a copper-catalyzed oxidative coupling between sodium sulfinates and amines with O_2 (1 atm) or DMSO as the oxidant was described by Jiang *et al* [12] (Fig. 5).

Very recently, another simple protocol has been developed for the synthesis of sulfonamides from sodium sulfinates and various amines through an iodine-mediated S-N bond formation

reaction at room temperature [13]. This metal-free methodology showed broad functional group tolerance, which provides a practical, cost-effective, efficient and green approach to various sulfonamides. More than 40 sulfonamides were synthesized by this method. Mild conditions and wide substrate scope make it possible to be utilized in the pharmaceutical industry (Fig. 6).

Luo *et al.* reported their $FeCl_2$-catalyzed system for the construction of sulfonamide directly from nitroarenes and sodium arylsulfinates under mild conditions [14]. It's noteworthy that they use nitroarenes instead of conventional aromatic amines as nitrogen source. In terms of substrate scope, nitroarenes either bearing electron-donating groups, such as methyl, methoxy, amido, or electron-withdrawing groups, such as chloro, cyano, trifluoromethyl, carbonyl, ester and carboxylic acid generated the desired products in good to excellent yields (Fig. 7).

Among the methods for introducing sulfonyl building blocks, fixation of sulfur dioxide into small molecules is promising and attractive. The methods have been extensively applied in the construction of some drugs [15]. In 2003, Barrett reported an one-pot procedure for the preparation of aryl- and heteroaryl substituted sulfonamides from commercially available and inexpensive aryl and heteroaryl bromides and iodides [16]. Sulfur dioxide was utilized in the reaction as an electrophilic reagent to react with Grignard reagents to introduce sulfur atom. After quenching with SO_2Cl_2, the sulfonyl chloride was formed in situ, which was then attacked by the amine to give the corresponding sulfonamides in moderate to good yields (Fig. 8).

In 2004, Vogel and co-workers found that silyl enol ethers derived from acylic and cyclic ketones underwent ene reaction with SO_2 in the presence of Lewis acid with the generation of the corresponding silyl β-oxoalkanesulfinates, which were brominated (Br_2 or NBS) or chlorinated (NCS or Cl_2) to produce the corresponding sulfonyl halides [17]. The sulfonyl halides subsequently reacted with primary and secondary amines to give the corresponding sulfonamides (Fig. 9).

The difficulties associated with the handling and use of a toxic gaseous reagent limit the application of SO_2 in organic synthesis. To deal with this problem, DABCO-bis(sulfur dioxide), DABSO, which is a bench-stable colorless solid, was utilized to instead of SO_2 gas [18]. Willis *et al.* demonstrated that DABSO, can be used as an effective replacement for gaseous sulfur dioxide in a number of established processes, leading the synthesis of sulfonamides (Fig. 10).

Furthermore, Willis and co-workers demonstrated the feasibility to prepare C-SO_2-N linkage using a palladium-catalyzed aminosulfonylation process for the first time [19]. The utilization of DABSO was the key to the success of the reaction. Efficient aminosulfonylation reactions between a range of aryl iodides and *N,N*-dialkylhydrazines, providing aryl *N*-aminosulfonamides in good to excellent yields was achieved (Fig. 11).

In the last five years, fixation of sulfur dioxide into small molecules was well investigated as an effective approach to prepare *N*-aminosulfonamides and sulfones. An efficient route to aryl *N*-aminosulfonamides *via* a palladium-catalyzed three-component coupling of

arylboronic acids, DABSO and hydrazines in the presence of oxygen (1 atm) was reported by Wu and co-workers in 2012 [20]. Various sensitive functional groups were compatible under the reaction conditions (Fig. 12).

A three-component reaction of triethoxysilanes, DABSO, and hydrazines catalyzed by copper(II) acetate was reported by Wang *et al.* [21], leading to *N*-aminosulfonamides in good yields. This is the first example of using a copper catalyzed aminosulfonylation process through the insertion of sulfur dioxide. Aryl-, alkenyl- and alkyl groups can be incorporated into the final products (Fig. 13).

A metal free coupling of aromatic and heteroaromatic amines with DABSO and hydrazines, leading to aryl *N*-aminosulfonamides in good to excellent yields, was reported by Wu *et al.* in 2014 [22]. Different functional groups including ester, hydroxyl, chloro and trifluoromethyl groups are compatible under these conditions. Subsequently, they disclosed that when 2-(allyloxy)anilines were used instead of amines, a cascade reaction was triggered to give the 1-(2,3-dihydrobenzofuran-3-yl)-methanesulfonohydrazides in good yields [23]. This cascade intramolecular 5-*exo*-cyclization and insertion of SO_2 reaction was a radical process (Fig. 14).

While these examples represent an important achievement in sulfonylation chemistry, amine nucleophiles remain incompatible with these types of couplings. To address this limitation, a new protocol was developed by Buchwald and co-workers [24]. They demonstrated that phenyl chlorosulfate represents an excellent $[SO_2Cl]^+$ synthon in the context of Pd catalyzed Suzuki Miyaura cross-coupling, which provided different kinds of sulfonamides in good to excellent yields.

THIOETHER CONTAINING DRUGS

Thioethers represents (8.8%) the third most exemplified constituent of the sulfur containing drugs [8]. The representative pharmaceuticals including cimetidine, thiethylperazine, pergolide etc are summarized in Table 2.

SYNTHESIS OF THIOETHERS

Traditional methods for the formation of C-S bond often take place in polar solvents, such as HMPA, and at elevated temperatures [25]. In 1978, Migita and co-workers first reported a Pd(0) catalyzed cross-coupling reactions of aryl iodide/bromide with thiols to give the corresponding thioethers [26]. In this pioneering work, thiophenol and thiols were both transferred to the thioether smoothly (Fig. 16).

In the next three decades, this type of transformation was well studied by organic chemists. A remarkable work was reported by Hartwig and co-workers in 2006 [27]. Using a dative ligand. they developed a general, highly efficient and functional-group-tolerant catalyst system for the coupling of aryl halides and triflates with thiols that typically occur with turnover numbers (TONs) that are 2 or 3 orders of magnitude higher than those of related couplings by previous catalysts (Fig. 17).

A Cu-catalyzed efficient procedure for the synthesis of diaryl sulfides has been described by Zhou and co-workers [28]. The aryl thiocyanate was formed in the first step, followed by hydrolysis to a thiolate ion, which reacted with aryl halide to afford the aryl thioether (Fig. 18).

In 2013, Jiang and co-workers developed a Pd-catalyzed double carbon-sulfur bond formation using sodium thiosulfate as sulfurating reagent [29] (Fig. 19a). This method provides an efficient way for the synthesis of substituted 1,4-benzothiazine derivates which are structural elements to a variety of pharmaceutically active compounds and natural products. In their subsequent work, the intermolecular sulfur atom transfer between aryl halide and alkyl thiosulfate was achieved to give a variety of thiosulfate [30] (Fig. 19b).

A highly efficient Cu-catalyzed dual C S bonds formation reaction, proceeding in alcohol and water under air, was reported by Jiang *et al* [31], in which inodorous stable $Na_2S_2O_3$ is used as a sulfurating reagent (Fig. 20a). As a novel sulfur source, $Na_2S_2O_3$ shows its irreplaceability in this system. In contrast with organic thiols and thiophenols, its intrinsic properties helped us to accomplish this S atom transfer reaction in a highly efficient manner. Further study indicated that this transformation could take place between 1-aryltriazenes, $Na_2S_2O_3$ and alkyl halides at room temperature, in which water functioned as a green solvent [32] (Fig. 20b).

Another novel and highly efficient Cu catalyzed protocol for S-arylation reaction of thiols is through oxidative coupling with aryl and heteroaryl boronic acids at room temperature [33]. A wide variety of thiols and arylboronic acids had been screened, and most of the substrates afforded the desired S-arylation products in good to excellent yields under mild conditions (Fig. 21).

Recently, a well-defined (POCOP)Rh system for the catalytic coupling of aryl bromides and chlorides with aryl and alkyl thiols was reported by Ozerov *et al* [34]. (POCOP)Rh(H)(Cl) was demonstrated to be an active precatalyst for the coupling of aryl chlorides and bromides with aryl and alkyl thiols under reasonable conditions (Fig. 22).

SULFONE CONTAINING DRUGS

Sulfones are found in numerous medicines and drug candidates under development for the treatment of a host of diseases impacting human health worldwide (Table 3). For example, Diazoxide is a potassium channel activator, which causes local relaxation in smooth muscle by increasing membrane permeability to potassium ions. This switches off voltage-gated calcium ion channels, preventing calcium flux across the sarcolemma and activation of the contractile apparatus.

Diazoxide is often used as a vasodilator in the treatment of acute hypertension or malignant hypertension [35].

SYNTHESIS OF SULFONES

Sulfone is most commonly prepared by the oxidation of a precursor sulfide [36], which is usually obtained from a conventional nucleophile electrophile combination. However, the use of an oxidative route precludes the presence of oxidation-sensitive functional groups, and the corresponding sulfide precursors often require the use of foul-smelling thiols for their preparation (Fig. 23).

Since a breakthrough was made by Willis for the generation of aryl *N*-aminosulfonamides using bench-stable reliable DABSO as the S source, the rapid development for the insertion of sulfur dioxide into small molecules has been reported [37]. Willis and co-workers developed a simple and efficient process for the palladium-catalyzed conversion of aryl and heteroaryl halides into the corresponding ammonium sulfinates, which can be converted into sulfones smoothly (Fig. 24).

Rocke and co-workers reported that organozinc reagents reacted with DABSO and the resulting zinc sulfinate salts were alkylated in situ to afford sulfones [38]. This transformation has a broad scope and is compatible with a wide range of functional groups including nitrile, secondary carbamates, and nitrogen-containing heterocycles (Fig. 25).

Wu *et al.* described a useful method for synthesis sulfones *via* a reaction of aryldiazonium tetrafluoroborates, DABSO and aryliodonium tetrafluoroborates under metal-free conditions [39]. *N*-aminosulfonamide was the intermediate in this transformation. It's noteworthy that the reaction was carried out under mild conditions which enabled the protocol to be attractive for further construction of sulfones containing drugs (Fig. 26).

PENICILLINS AND CORRESPONDING DRUGS

Penicillins, the well-known antibiotics containing sulfur atom, play a significant role in fighting against syphilis, or infections caused by staphylococci and streptococci. Though certain kinds of bacteria are resistant to Penicillins, they are still the popular antibiotics in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms [40].

SYNTHESIS OF PENICILLINS

Penicillin is a secondary metabolite of certain species of *Penicillium* and is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. The mass production of penicillins is mainly based on biosynthesis and semisynthesis. The first chemical synthesis of penicillin was accomplished by John C. Sheehan in 1957 [41]. Although the initial synthesis developed by Sheehan was not appropriate for mass production of penicillins, one of the intermediate compounds in their synthesis 6-aminopenicillanic acid (6-APA), was the nucleus of penicillin. It can be obtained from the fermentation brew of the *Penicillium* mold and used as the main building block for the preparation of numerous semisynthetic penicillins.

In addition, chemists have still taken efforts to develop new chemical methods to achieve the core structure of penicillins. In the 1970s, Maki *et al.* reported intramolecular radical cyclization to give penicillin derivatives [42]. Upon irradiation in acetonitrile, β-lactam led to 3-methylenecepham methyl ester and 3-methyl-2-cephem methyl ester. The dilution proved to have a dramatic effect on the course of this cyclization process, as β- and α-(benzothiazoylthiomethyl)penam derivatives were formed preferentially at higher concentration (Fig. 27).

Cabri and co-workers have extensively studied the transition metal-mediated version of this kind of radical process [43]. Initially, they found that both Fe(III) and Mn(III) could promote this reaction and later developed catalytic versions, using the same metals (Fig. 28a). They have also developed catalytic Fe(III) Cu(II) and Mn(III) Cu(II) variants, which furnished α-methyl-substituted penicillin in a highly stereoselective manner (Fig. 28b).

A concise and flexible route to bicyclic sulfur-based β-lactam was reported by Hales and co-workers in 1997 [44]. azomethine ylide strategy for assembling bicyclic β-lactams constitutes a simple, versatile, and above all, direct synthesis of penams and penems. This chemistry permits access to a range of penicillins, some of which are difficult to prepare by conventional methods (Fig. 29).

A rigid framework with stereochemistry different than that of penicillin, is designed to be a suitable scaffold for the development of compounds inhibiting pilus formation in uropathogenic *Escherichia coli* was synthesized by Almqvist and co-workers [45]. The obtained compounds will be evaluated as chaperone inhibitors in the near future. The excellent and reproducible yields in the synthesis of the β-lactam and the convenience with which Meldrum's acid derivatives are prepared constitute a platform for future development of statistically diverse libraries of optically active β-lactams.

CONCLUSION

In summary, the most common sulfur containing drugs and recent advances in the synthesis of the core scaffolds, including sulfonamides, thioethers, sulfones and penicillins are presented. Other sulfur containing moieties such as thiophenes and thiazoles can be found in pharmaceutical molecules as well. Although many novel protocols have been developed, some challenges still remain. More general methods and process to synthesize sulfur containing pharmaceutical molecules are still urgent to be developed.

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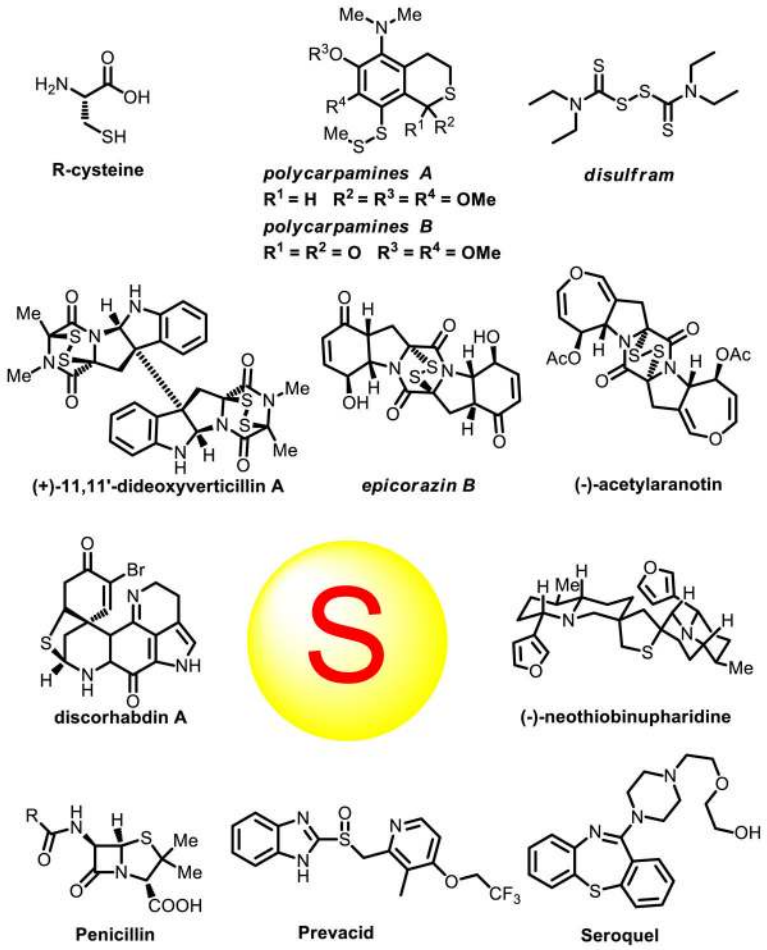


Fig. 1.

Representative sulfur containing scaffolds in natural products and pharmaceuticals

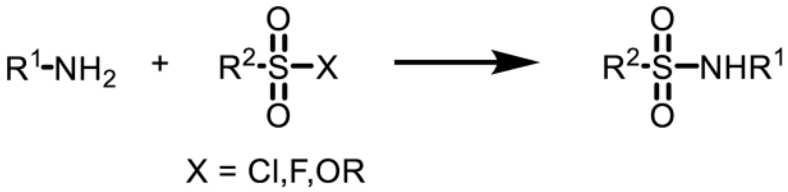


Fig. 2.
Conventional routes to sulfonamide

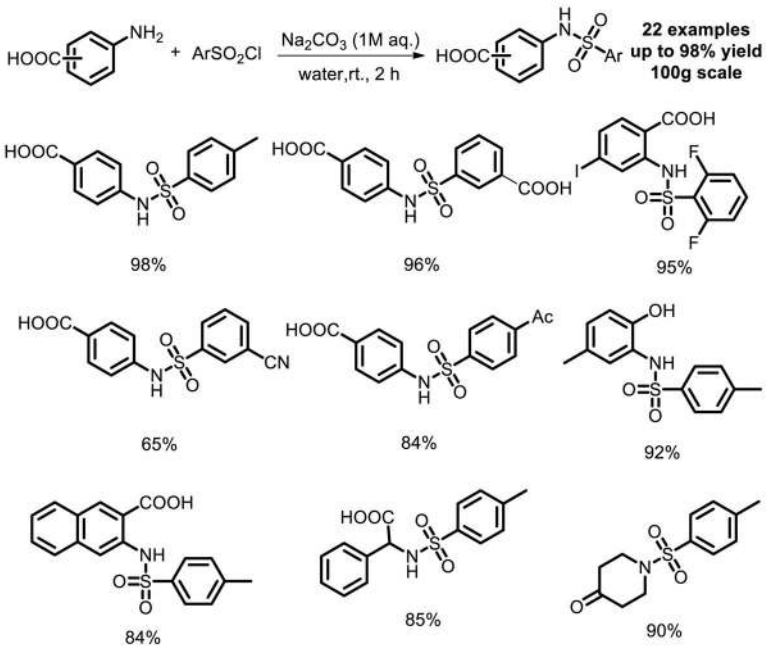


Fig. 3.
Environmentally benign sulfonamide synthesis in water.

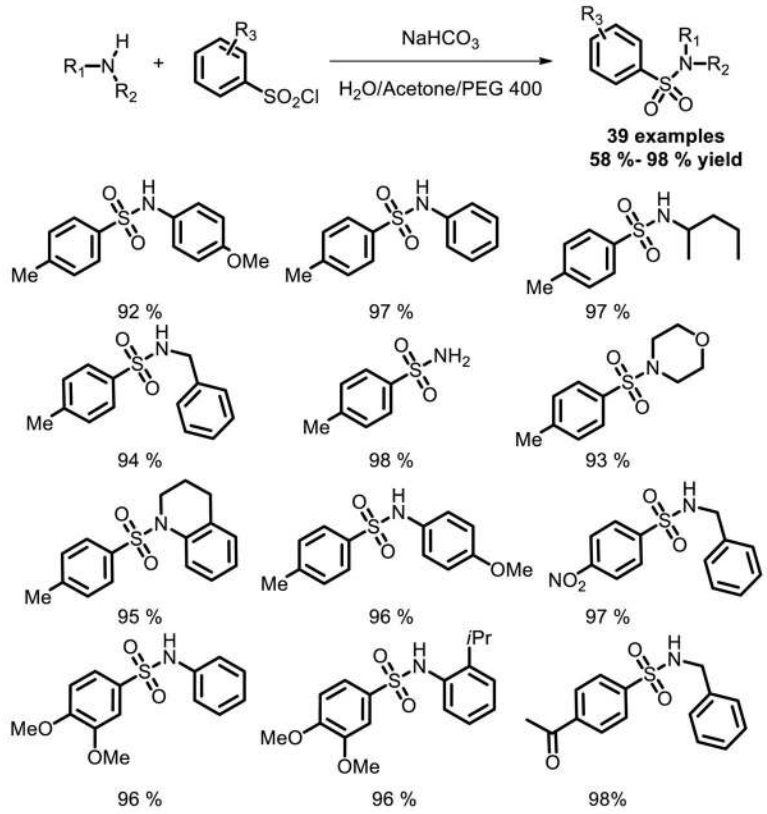


Fig. 4.
Sulfonamide synthesis involving flow chemistry.

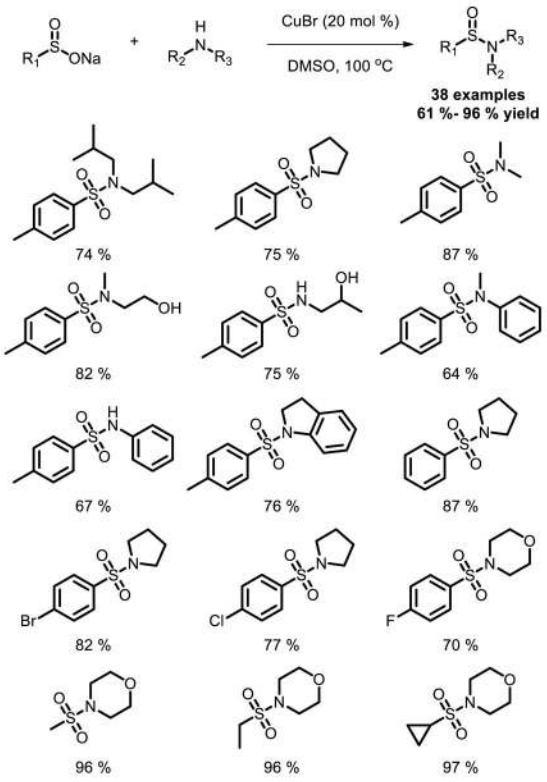


Fig. 5.
Cu catalyzed sulfonamide synthesis between sodium sulfinates and amines

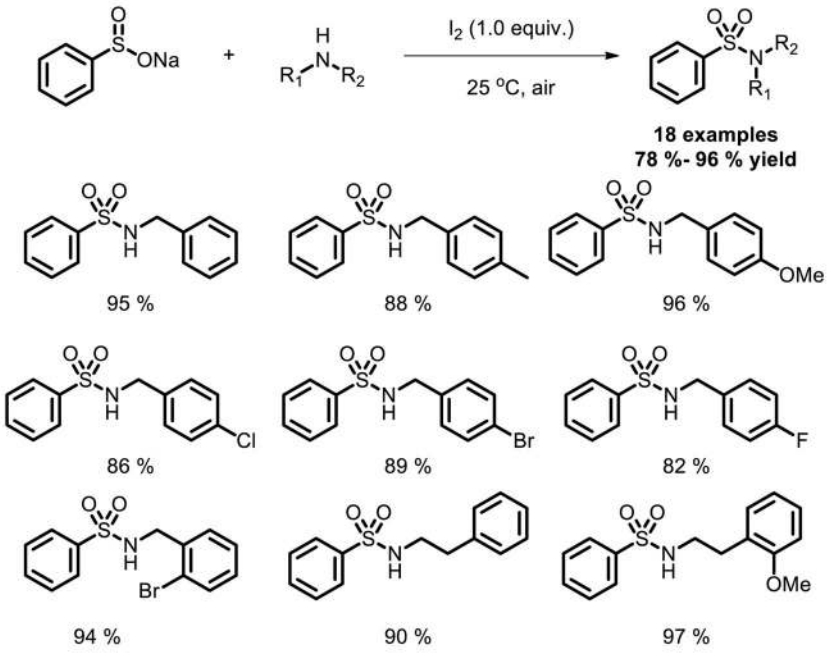


Fig. 6.
Sulfonamide synthesis *via* a metal free oxidative coupling.

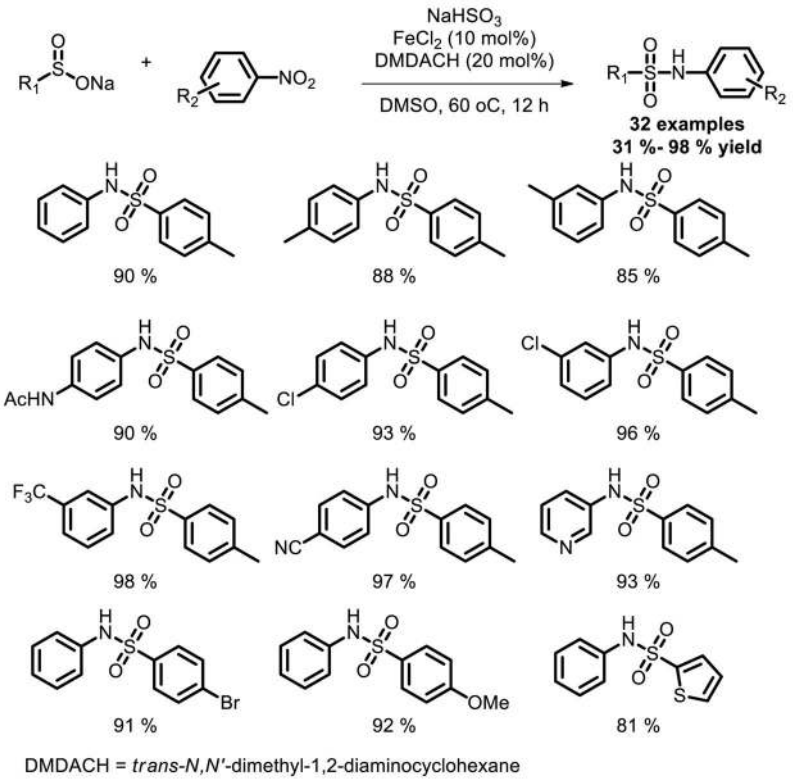


Fig. 7.
Fe catalyzed sulfonamide synthesis using nitroarenes as the nitrogen sources.

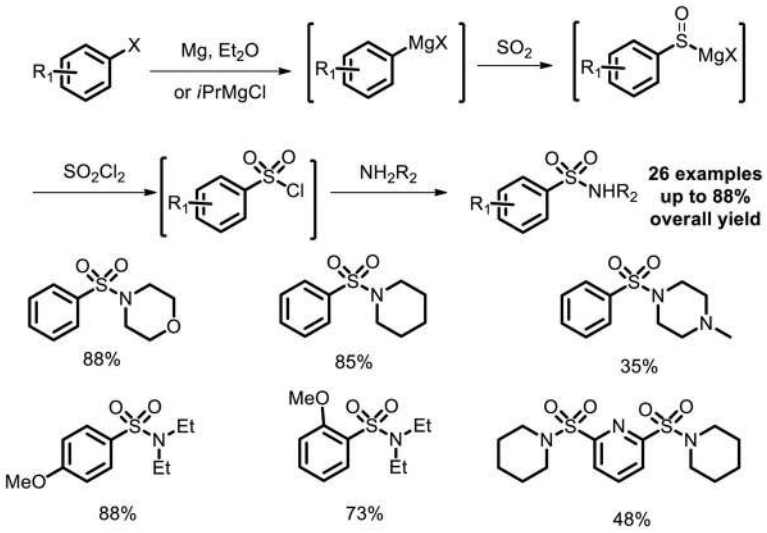


Fig. 8.

Sulfonamide synthesis using SO_2 fixation protocol.

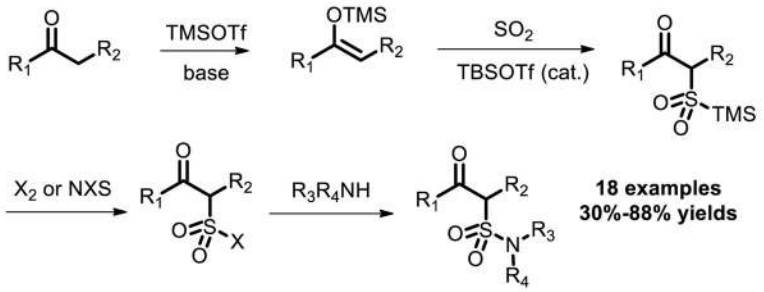


Fig. 9.

Sulfur dioxide mediated one-pot, three- and four-component syntheses of polyfunctional sulfonamides.

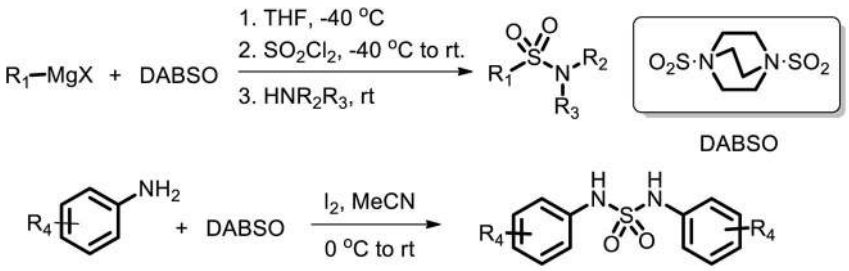


Fig. 10.

DABSO used instead of SO_2 in sulfonamide synthesis.

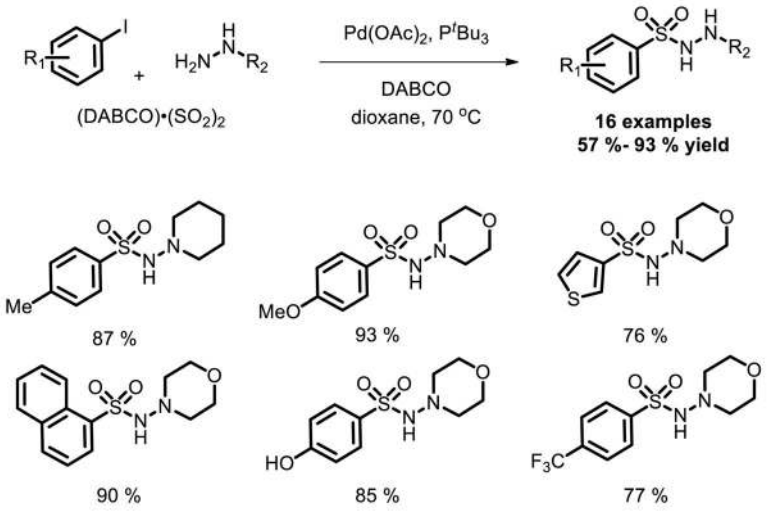


Fig. 11.

Pd catalyzed aminosulfonylation of aryl halides using DABSO as sulfur source.

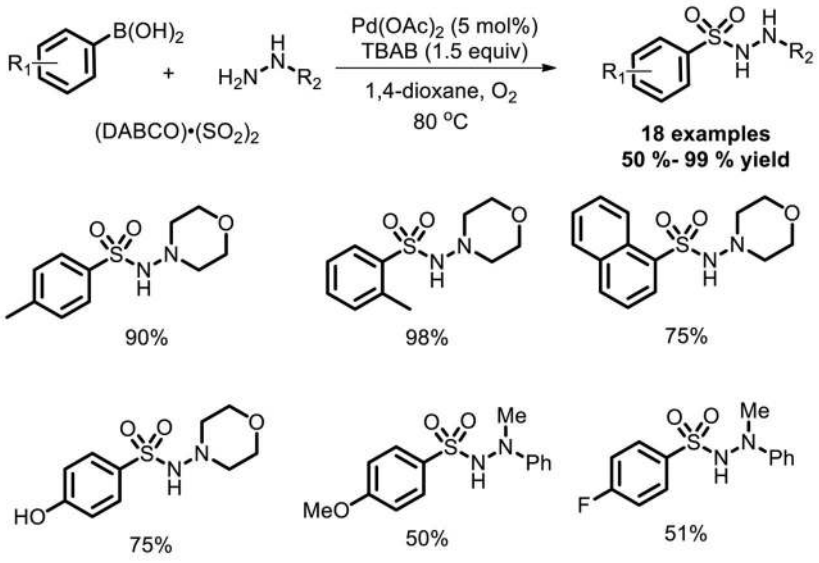


Fig. 12.

Pd catalyzed three-component coupling of arylboronic acids, DABSO and hydrazines.

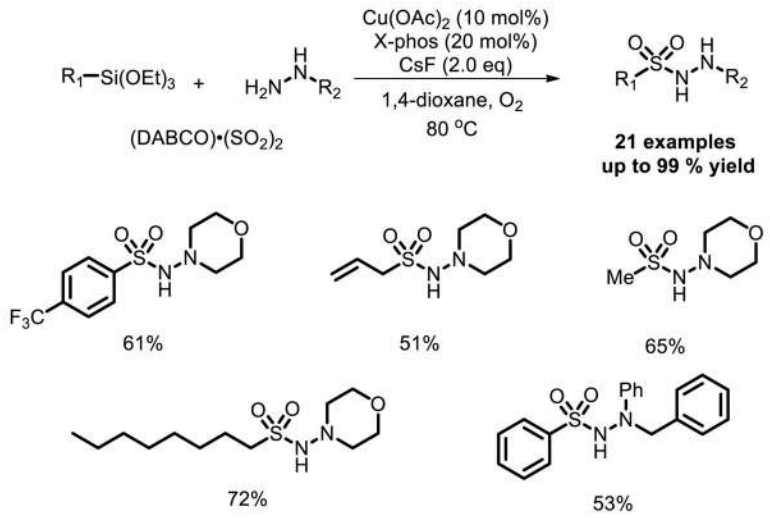


Fig. 13.

Cu-catalyzed three-component reaction of triethoxysilanes, sulfur dioxide, and hydrazines.

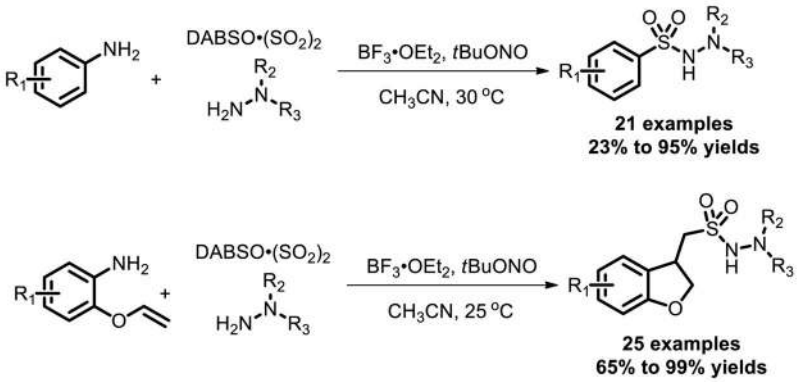


Fig. 14.

Functionalized *N*-aminosulfonamides synthesis via free radical reactions.

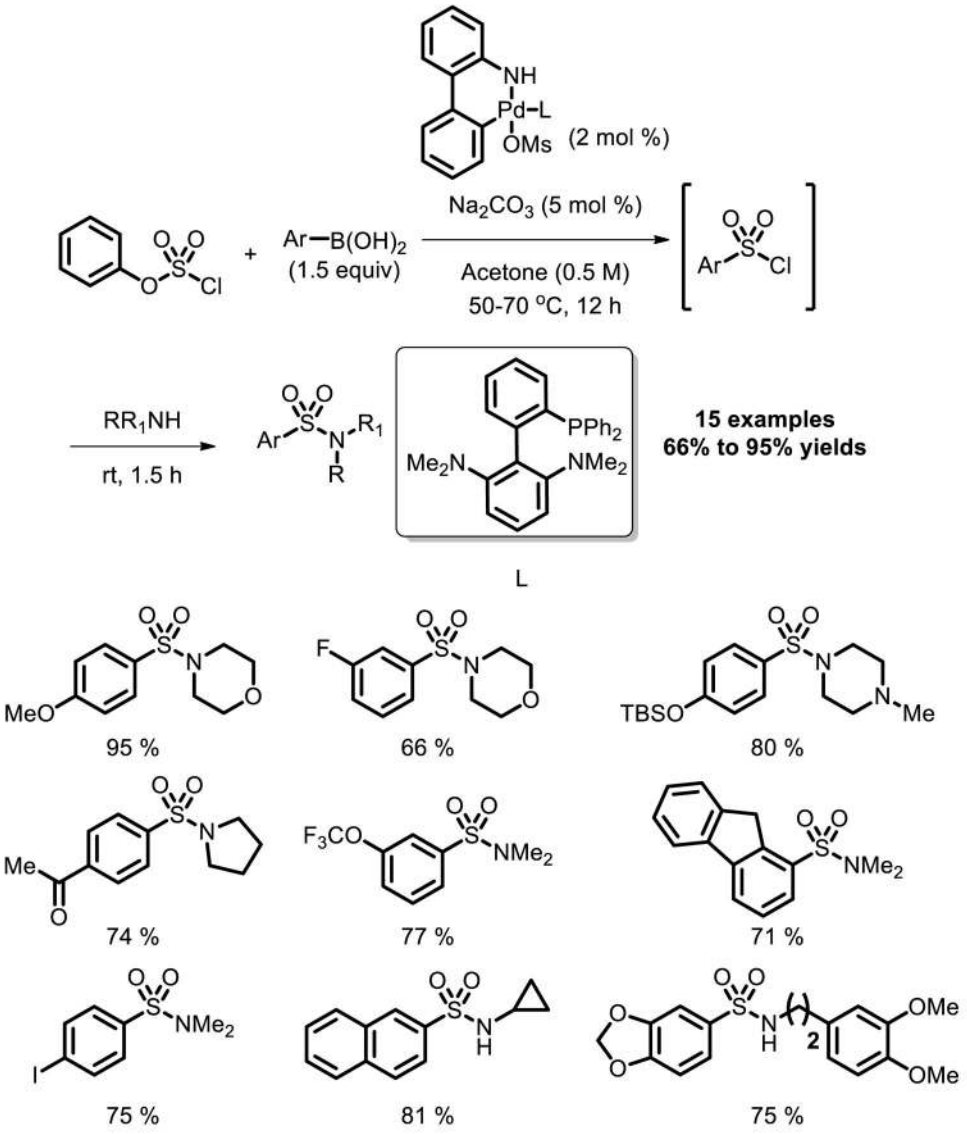


Fig. 15.

Synthesis of aryl sulfonamides *via* Pd catalyzed chlorosulfonylation of arylboronic acids.

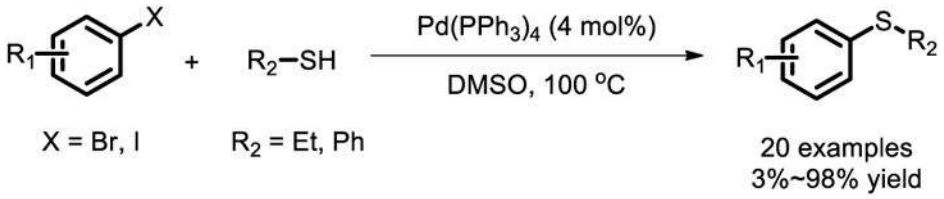


Fig. 16.
Synthesis of aryl thioethers *via* Pd catalyzed Ullman coupling.

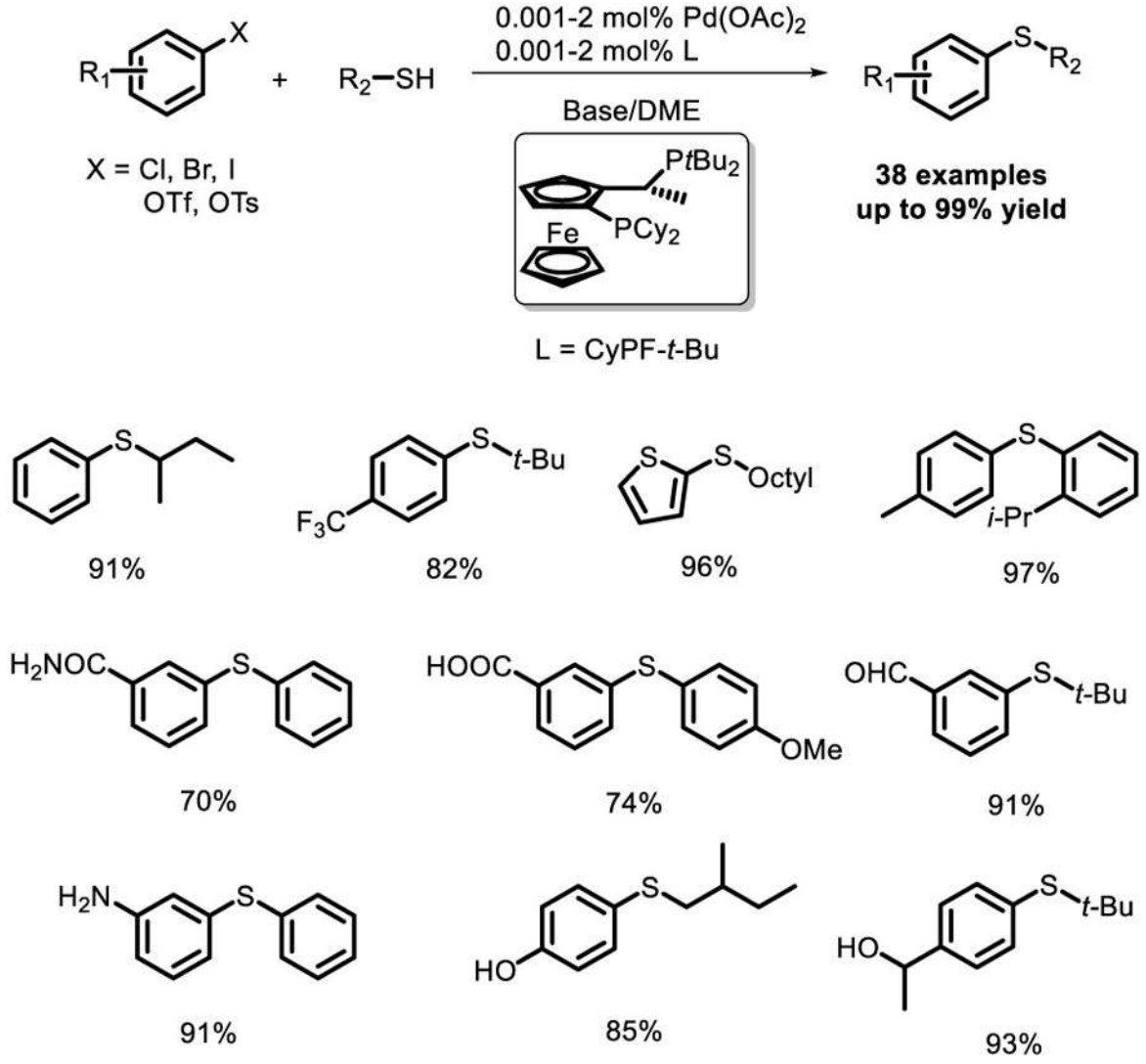


Fig. 17.
Long-lived catalyst for the Pd-catalyzed coupling of aryl halides with thiols.

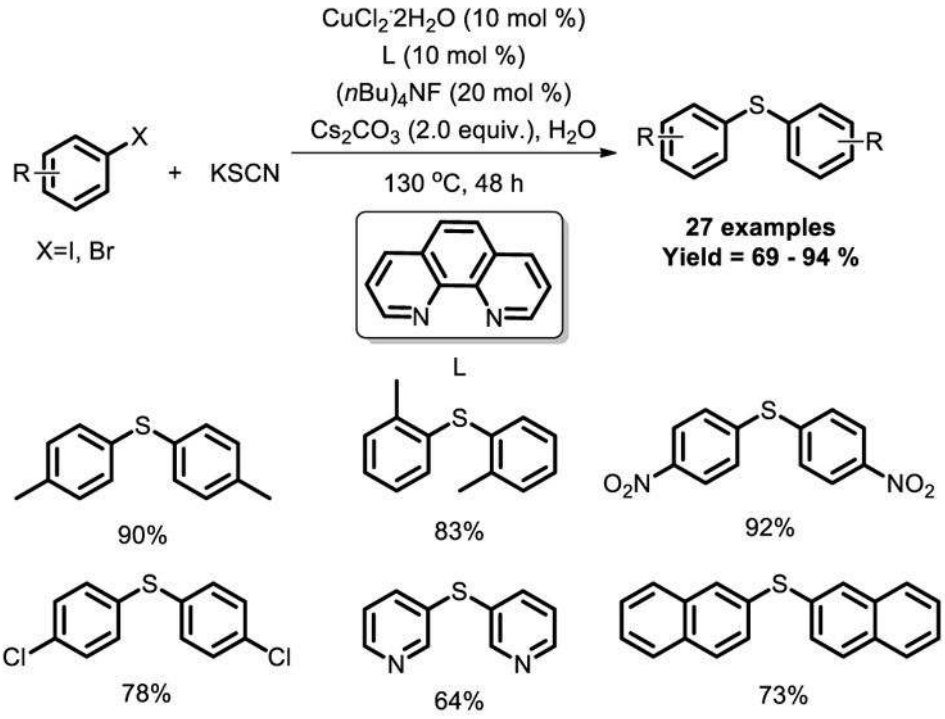


Fig. 18.

Copper-catalyzed carbon-sulfur bond formation protocol in water.

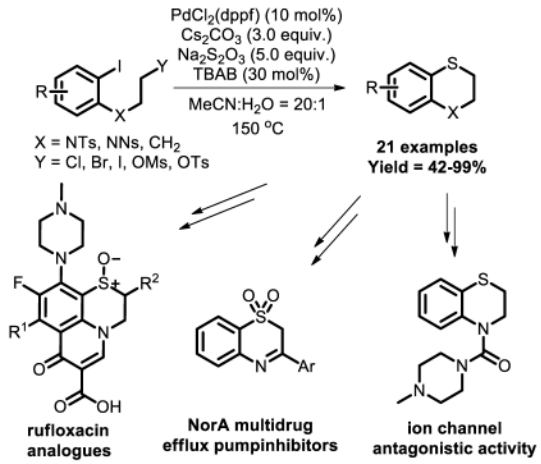


Fig. (19a)

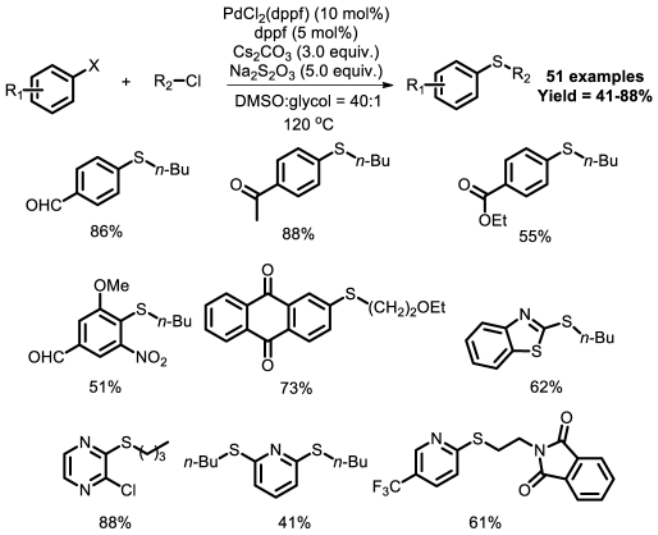


Fig. (19b)

Fig. 19.

Fig. 19a. Intramolecular direct cross-coupling using $Na_2S_2O_3$ as a sulfurating reagent.

Fig. 19b. Intermolecular direct cross-coupling access to diverse aromatic sulfides using $Na_2S_2O_3$ as a sulfurating reagent.

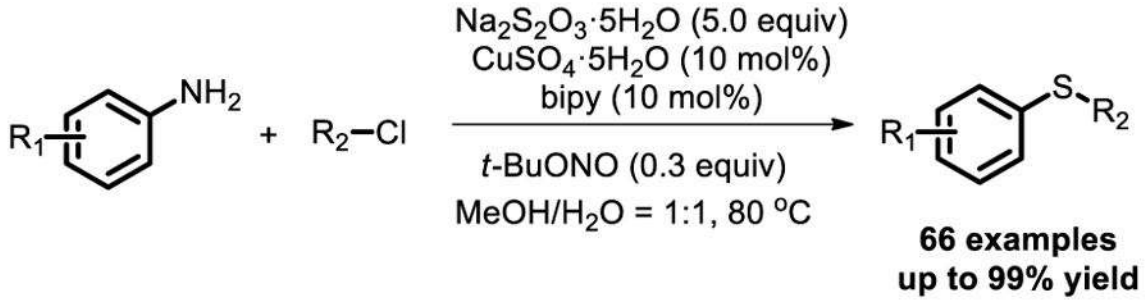


Fig. (20a)

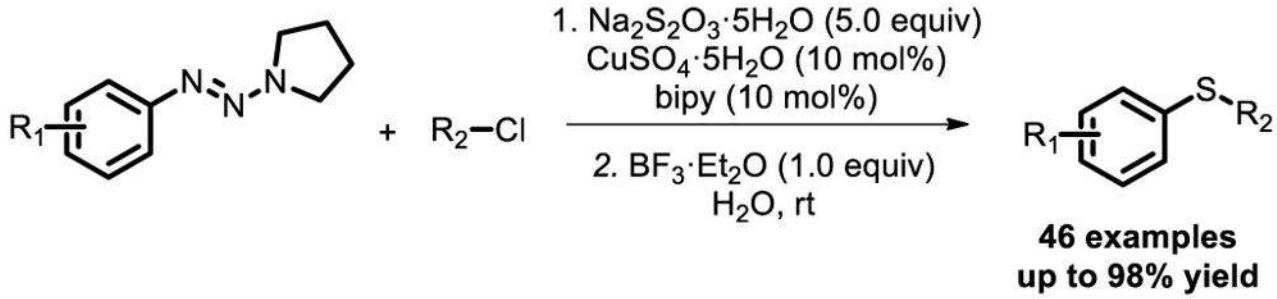


Fig. (20a)

Fig. 20.

Fig. 20a. Cu-Catalyzed S-transfer reaction: from amines to sulfides.

Fig. 20b. Cu-Catalyzed S-transfer reaction: from 1-aryltriazenes to sulfides.

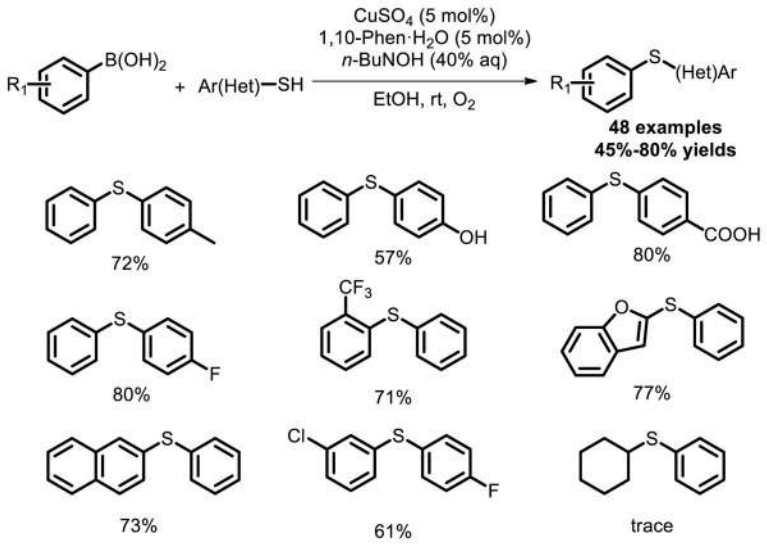


Fig. 21.
Chan Lam-type S-arylation of thiols with boronic acids.

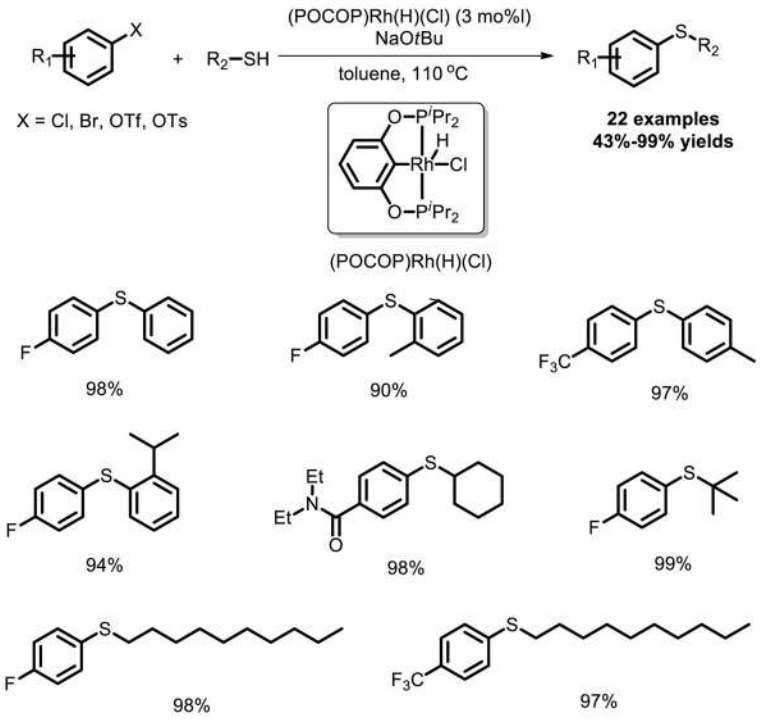


Fig. 22.
(POCOP)Rh catalyst for the coupling of aryl halides with thiols.

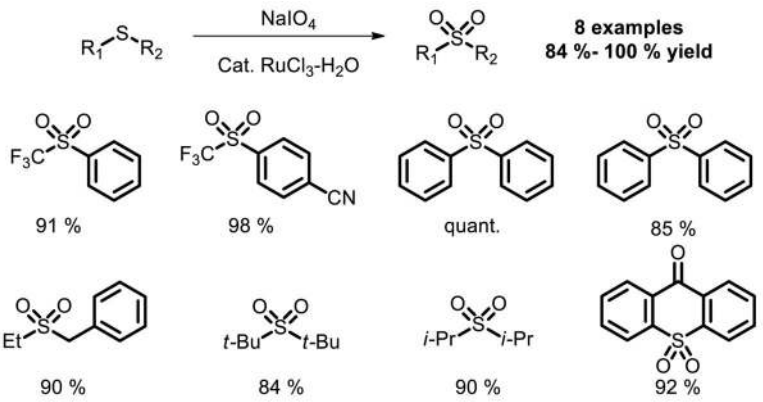


Fig. 23.
Ru catalyzed oxidation of thioethers to sulfones.

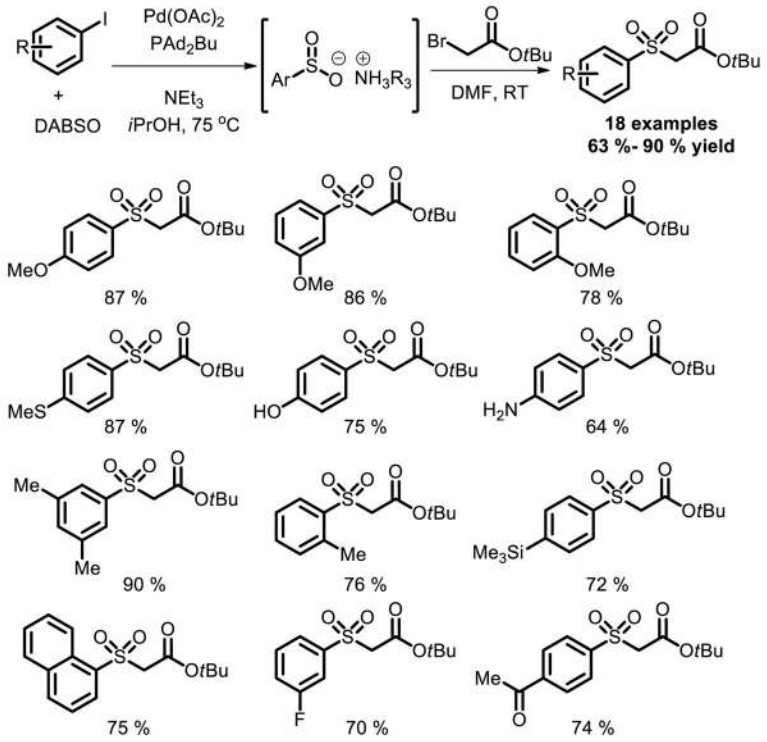


Fig. 24.

Pd catalyzed synthesis of ammonium sulfinates from aryl halides and DABSO.

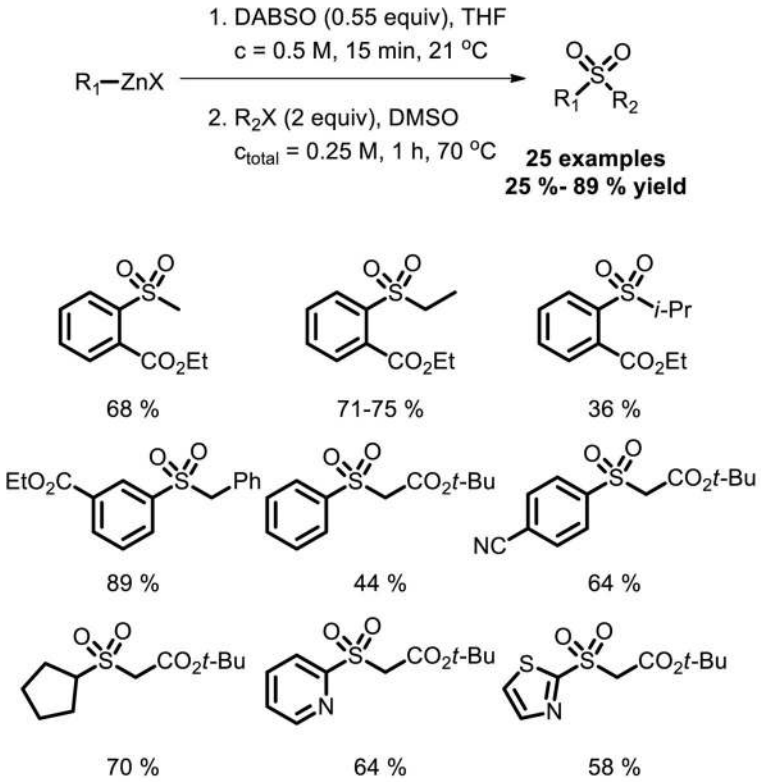


Fig. 25.

Synthesis of sulfones from organozinc reagents, DABSO, and alkyl halides.

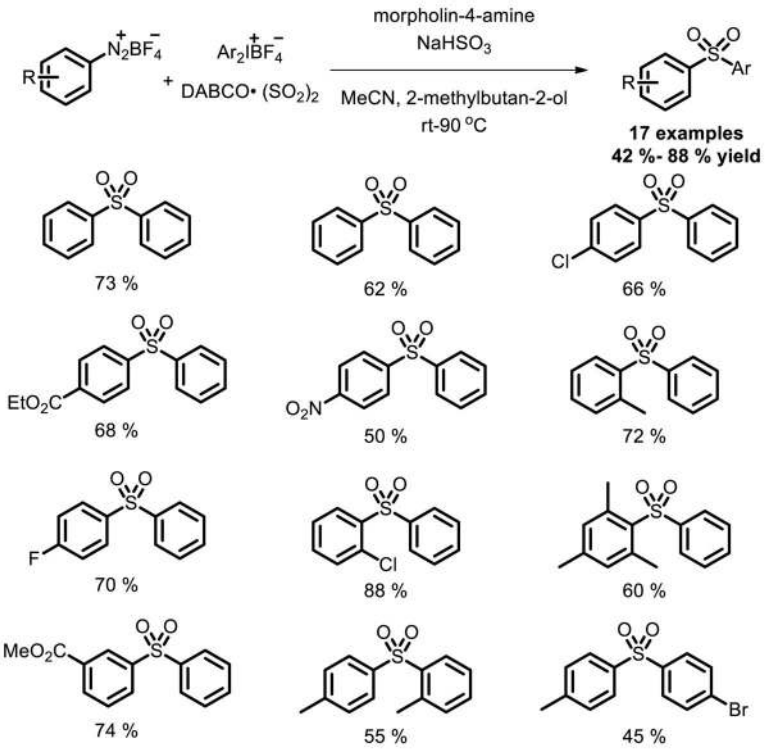


Fig. 26.

Synthesis of sulfones from aryldiazonium tetrafluoroborates, DABSO, and aryliodonium tetrafluoro-borates.

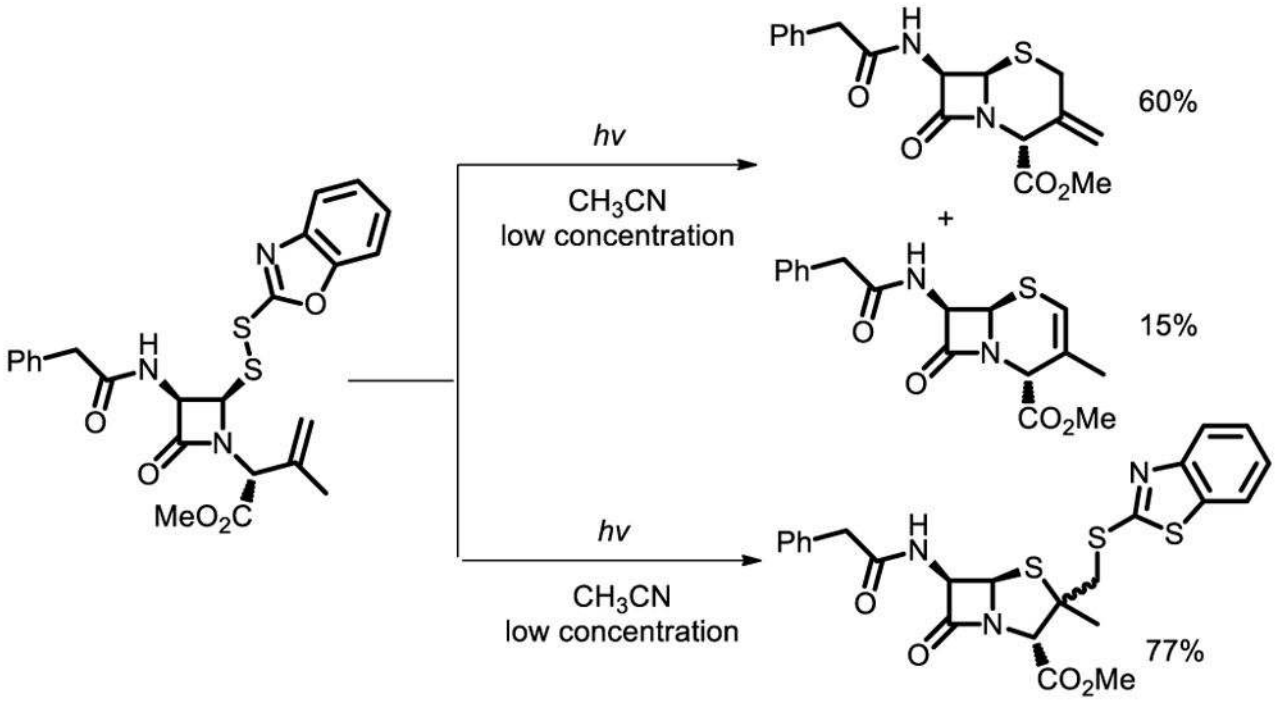


Fig. 27.
Synthesis of penicillin derivatives via light promoted radical cyclization.

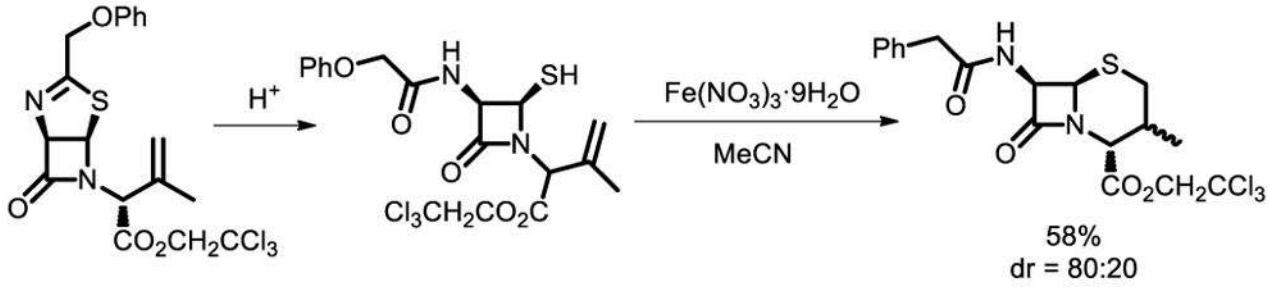


Fig. (28a)

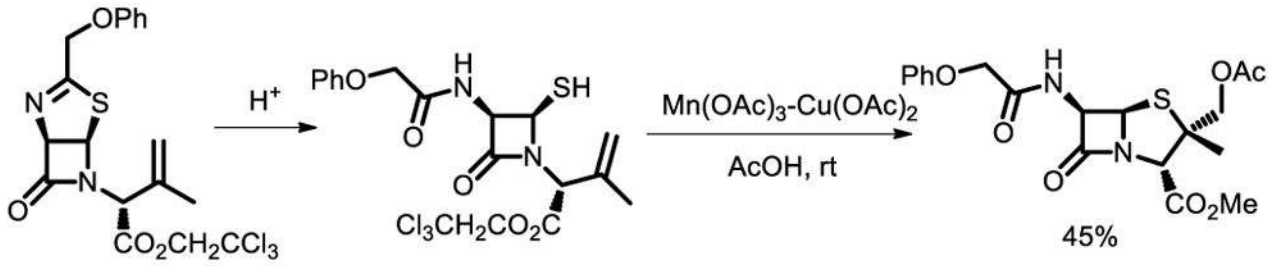


Fig. (28b)

Fig. 28.

Fig. 28a. Synthesis of penicillin derivatives via Fe(III) promoted radical cyclization.

Fig. 28b. Synthesis of penicillin derivatives via Mn(III) Cu(II) promoted radical cyclization.

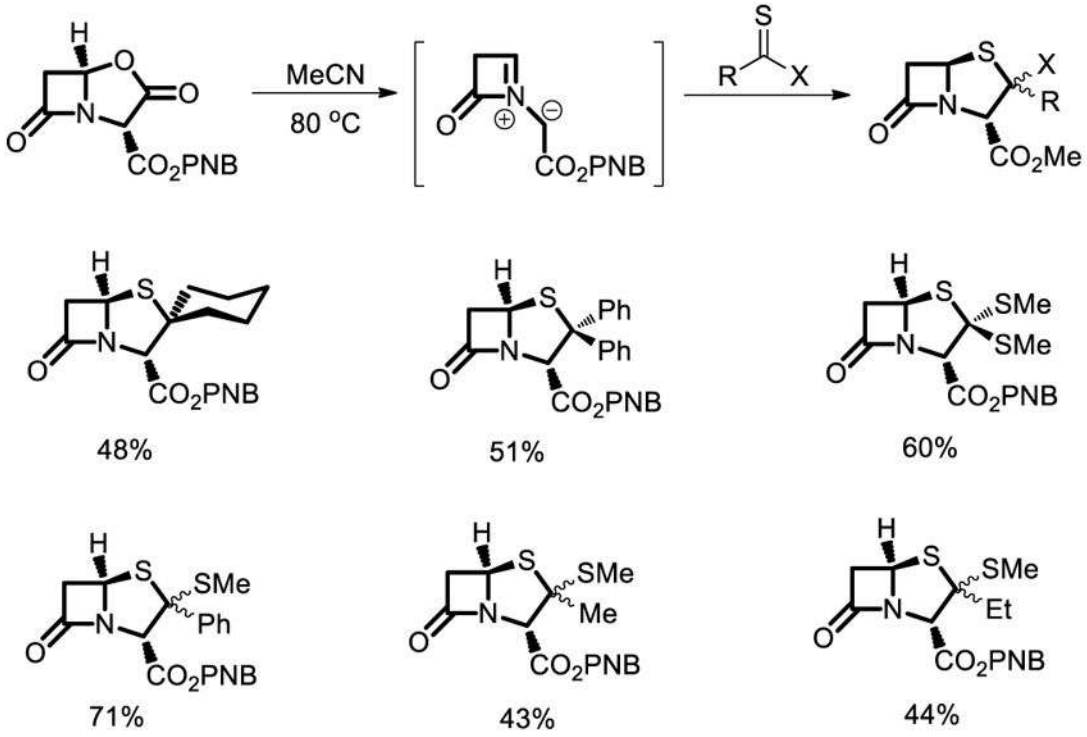


Fig. 29.
A direct approach to penams via azomethine ylide.

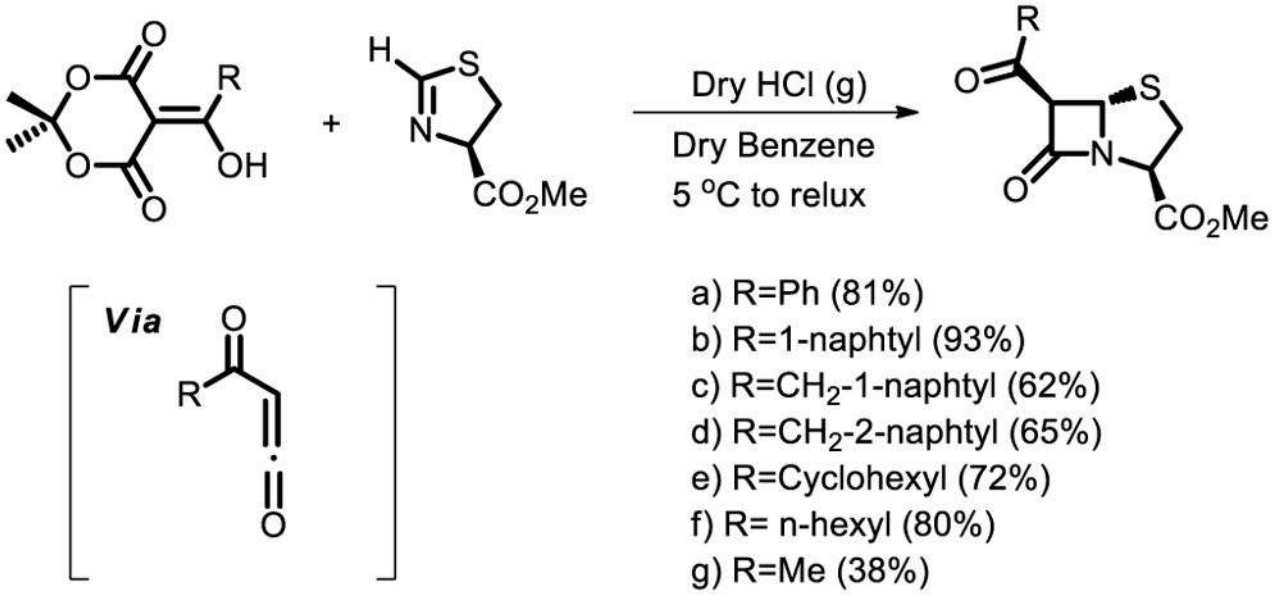
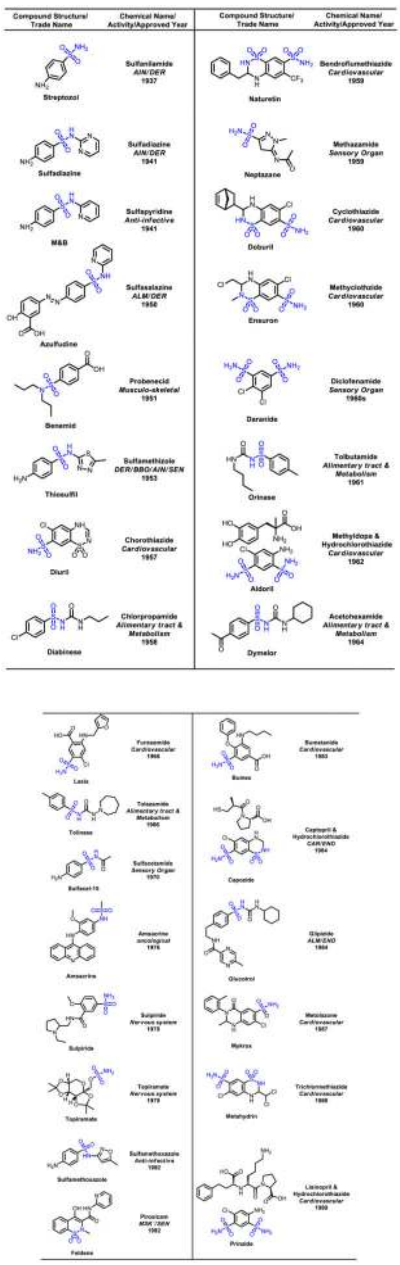
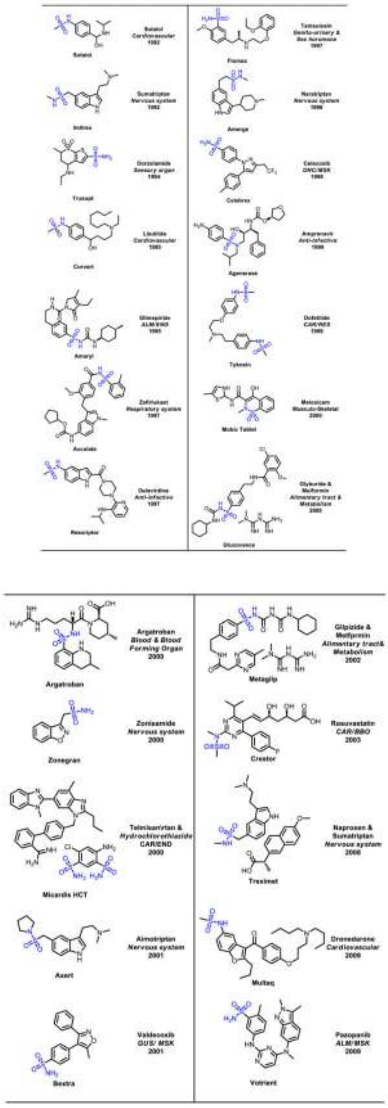


Fig. 30.
A stereoselective synthesis of optically active β-lactams from Meldrum's acid derivatives.

Table 1

Sulfonamide containing scaffolds in pharmaceutical molecules [7, 8].





ALM = alimentary tract & metabolism; AIN = anti-infective; BBO = blood & blood forming organs; CAR = cardiovascular system; DER = dermatological; END = endocrine system; GUS = genito-urinary & sex hormones; MSK = musculo-skeletal system; ONC = oncological; RES = respiratory system; SEN = sensory organs.

Table 2

Thioether containing scaffolds in pharmaceutical molecules [7, 8].

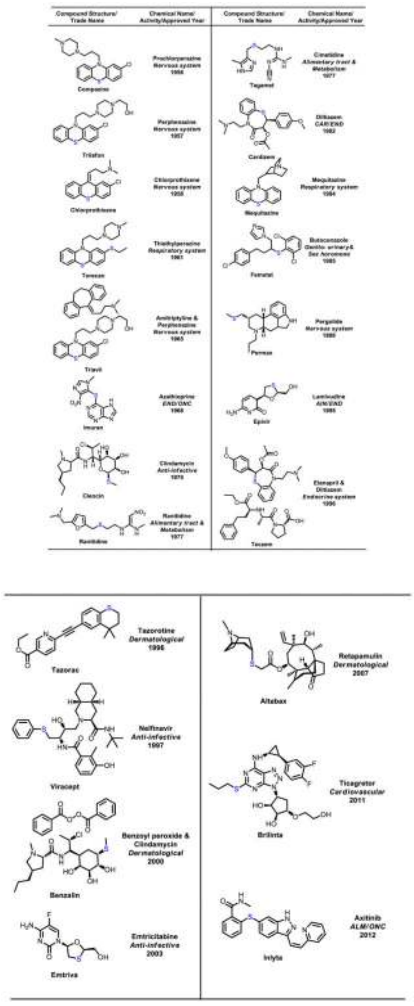


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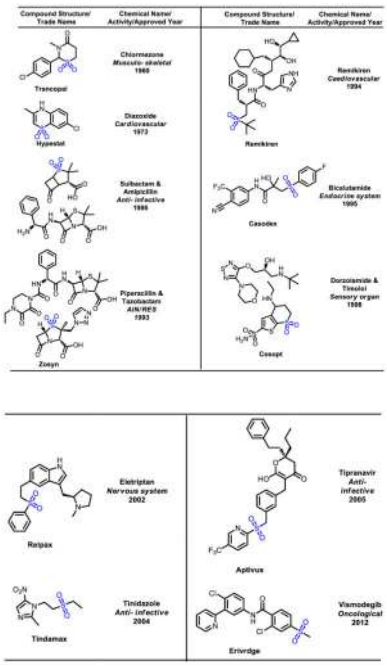
Table 3

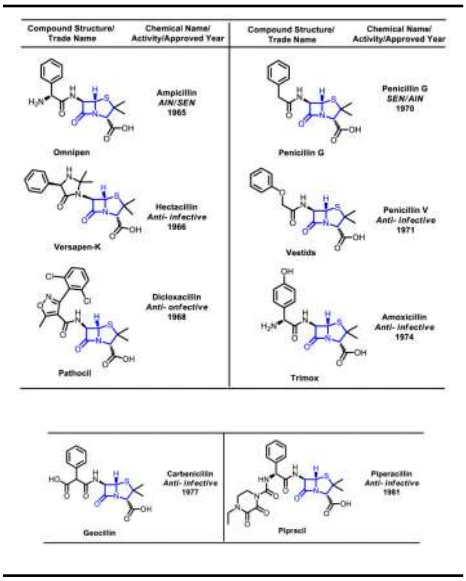
Sulfone containing scaffolds in pharmaceutical molecules [7, 8].



ALM = alimentary tract & metabolism; AIN = anti-infective; BBO = blood & blood forming organs; CAR = cardiovascular system; DER = dermatological; END = endocrine system; GUS = genito-urinary & sex hormones; MSK = musculo-skeletal system; ONC = oncological; RES = respiratory system; SEN = sensory organs.

Table 4

Penicillins and related drugs [7, 8].



ALM = alimentary tract & metabolism; AIN = anti-infective; BBO = blood & blood forming organs; CAR = cardiovascular system; DER = dermatological; END = endocrine system; GUS = genito-urinary & sex hormones; MSK = musculo-skeletal system; ONC = oncological; RES = respiratory system; SEN = sensory organs.