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Sulfur Dioxide Insertion Reactions for Organic Synthesis

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Contents

Chapter 1
Introduction

Abstract In the context of increasing attention to sustainable and green chemistry, a variety of efforts have been devoted to atom economical and environmentally friendly methods to construct complex molecules. The incorporation of sulfur dioxide into small molecules is an attractive and promising strategy since it introduces the sulfonyl moiety from simple and readily available sources. Developing sulfur dioxide insertion reactions for organic synthesis has become an active research area in the last few years, particularly owing to the development of innocuous and bench-stable sulfur dioxide surrogates. In this chapter, we will highlight the importance of sulfonyl groups (—SO_2—) in diverse fields, introduce the basic properties of sulfur dioxide, and classify the reaction types derived from sulfur dioxide. We will also present the main contents and emphases of this book, and wish to give a comprehensive understanding of sulfur dioxide insertion chemistry to the readers.

Keywords Sustainable and green chemistry · Atom economical and environmentally friendly methods · Sulfonyl-containing compounds · Insertion of sulfur dioxide · Sulfur dioxide surrogates

The sulfonyl-derived functional groups represent a highly important class of moieties which are widely existed in pharmaceuticals, agrochemicals, and materials, due to their distinct electronic and structural features [1–4]. For instance, sulfonamides and sulfones are present in a broad range of marketed drugs and pesticides. Some representative examples are represented in Scheme 1.1: glimepiride is used as hypolycemic agent; torasemide is a kind of diuretics; eletriptan is used for the treatment of migraine; mesotrione is used as herbicide [5, 6]. In addition, the sulfonyl groups have diverse applications in organic synthesis as useful intermediates and are described as "chemical chameleons" due to their versatile reactivities [7, 8]. They are good leaving groups, as well as electron-withdrawing substituents in Michael acceptors. The sulfonyl groups can also increase the acidity of hydrogen in *ortho*-position and stabilize adjacent carbanions. Classical transformations of sulfones in synthetic chemistry include the Ramberg–Bäcklund reaction, Van

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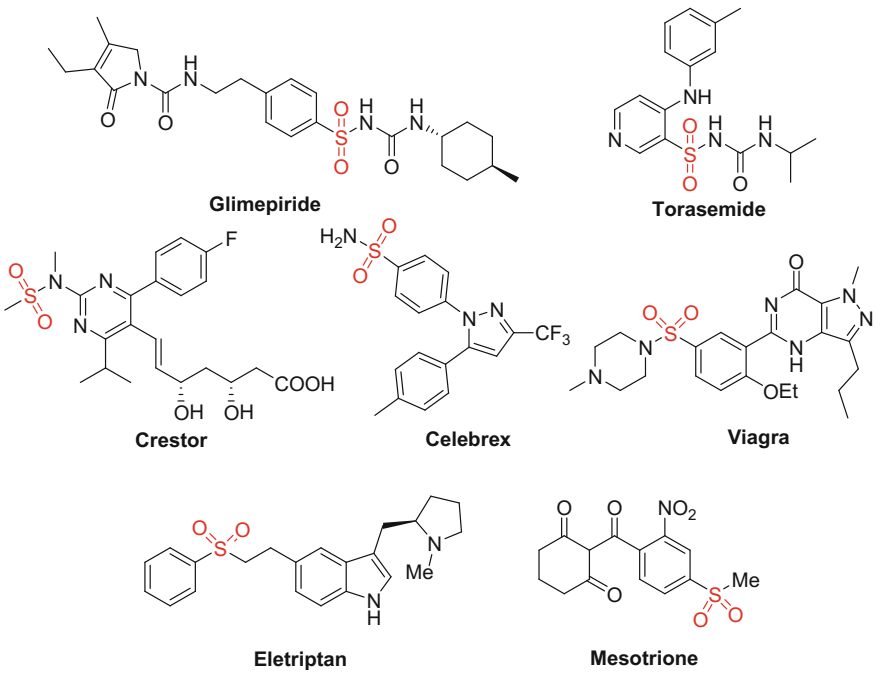
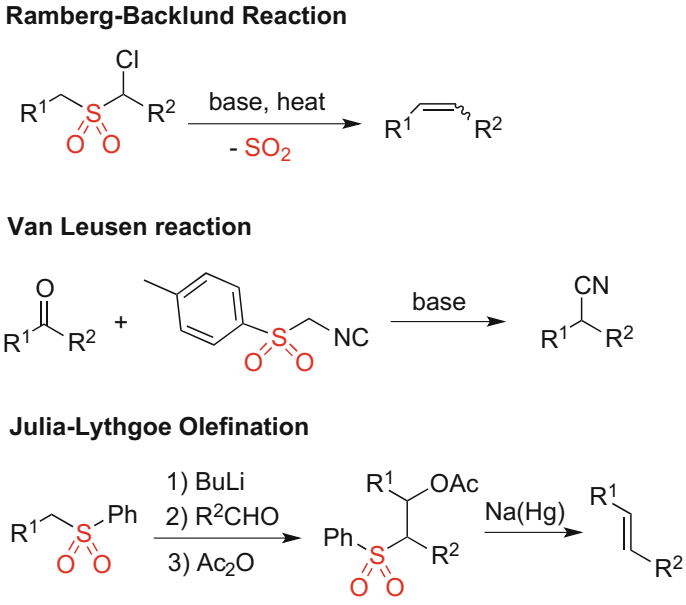


Scheme 1.1 Selected examples of marketed drugs featuring a sulfonyl group

Leusen reaction, and Julia–Lythgoe olefination (Scheme 1.2). The most traditional method for the preparation of sulfonamides is the direct amination of sulfonyl chlorides with the corresponding amines [9], and sulfones are usually generated by alkylation of sulfinate salts (which are also usually synthesized from the corresponding sulfonyl chlorides) or oxidation of the corresponding sulfides or sulfoxides [10]. However, the preparation of sulfonyl chlorides (including oxidative chlorination of organosulfurs and electrophilic aromatic substitution with chlorosulfonic acid) usually suffers from significant limitations [11]. These methods commonly experience harsh conditions, scope limitations, and require toxic and pollution-carrying chlorinating agents or oxidants. Additionally, organosulfurs are usually foul-smelling and oxidation-sensitive functional groups may not be tolerated under the oxidative conditions.

Green and sustainable chemistry is in great demand since increasing attentions have been paid to chemical pollution and resource depletion [12]. Thus, a variety of efforts have been devoted to developing efficient and practical synthetic methods upon readily available reagents to construct complex molecules. Among them, the incorporation of sulfur dioxide into small molecules has been recognized as an attractive and promising strategy since it introduces the sulfonyl moiety from simple and readily available sources, especially considering the importance of

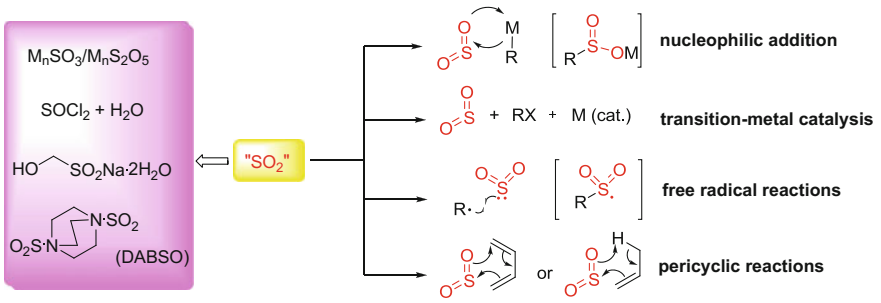


Scheme 1.2 Selected name reactions containing the conversion of sulfonyl group

sulfonyl-containing compounds and the significant drawbacks of their traditional preparative methods [13–15].

Sulfur dioxide is a toxic gas with a pungent smell and exists in the Earth's atmosphere in a very small concentration at about 1 ppm. It is produced naturally from volcanic activity and artificially from industrial processes such as fossil fuel combustion. It is harmful for the environment since it is a potently global warming gas and it is a cause of acidic rain. Sulfur dioxide has long been used as a preservative especially in winemaking ever since the ancient Romans. In chemistry, it is produced on an enormous scale of millions of tons annually and its main industrial use is as a feedstock for producing sulfuric acid. The unique structure of sulfur dioxide conduces to its versatile reactivity. The nucleophilic ability resulted from a lone pair in a high-lying σ-based HOMO and the electrophilic property by reason of its low-lying symmetry LUMO have largest coefficient on sulfur, leading to the amphoteric characteristic of sulfur dioxide [16]. However, compared with the well-established carbon monoxide insertion chemistry, the transformations of sulfur dioxide are still limited and SO_2-based reactions are not frequently used in organic synthesis. The most significant factor is certainly the handling problem caused by its property of a toxic gas.

Recently, the rapid development of sulfur dioxide insertion chemistry has been witnessed, particularly thanks to the utilization of innocuous and bench-stable sulfur dioxide surrogates. This book summarizes the commonly used sulfur dioxide surrogates (Scheme 1.3, left part) in sulfur dioxide insertion reactions and also



Scheme 1.3 Common sulfur dioxide surrogates and four types of sulfur dioxide insertion reactions

shows the diverse reactivities to highlight the progress on the development of efficient synthetic methods through sulfur dioxide insertion. According to the types of transformation, these reactions are classified into four parts: (i) nucleophilic addition with organometallic reagents; (ii) transition metal catalysis; (iii) free radical reactions; and (iv) pericyclic reactions (Scheme 1.3 right part). This book reviews sulfur dioxide insertion reactions, with an emphasis on recent advances based on application of sulfur dioxide surrogates, and describes the detailed experimental procedures of these valuable reactions, as well as discusses the remaining challenges in this field. This book should be attractive and useful to a wide readership in organic chemistry and medicinal chemistry from both academia and industry. We hope this book could not only help readers comprehensively understand the sulfur dioxide insertion chemistry and the diverse reactivity and applications of sulfur dioxide, but also could inspire the readers to exploit new exciting reactivities of sulfur dioxide and realize its new applications.

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Chapter 2
Sulfur Dioxide Surrogates

Abstract The most significant driving force in the field of sulfur dioxide insertion has been the development of safe and bench-stable sulfur dioxide surrogates. To date, several sulfur dioxide surrogates have been developed and proved to be efficient in the processes of sulfur dioxide insertion. Among them, DABCO·$(SO_2)_2$ (named DABSO) and potassium metabisulfite ($K_2S_2O_5$) are two of the most commonly used sulfur dioxide surrogates, which have been identified and documented in various transformations. In this chapter, we will introduce these sulfur dioxide surrogates, with an emphasis on those utilized in sulfur dioxide insertion reactions.

Keywords Sulfur dioxide surrogates · Potassium metabisulfite · DABCO·$(SO_2)_2$ · Rongalite

Utilization of surrogates for sulfur dioxide is a practical and convenient method because it avoids the need of specialized pressure-resistant equipment and reduces the safety risks due to the toxic and gaseous properties of sulfur dioxide [1–4]. As the conditions with large excess of sulfur dioxide would cause catalyst sequestration in metal-catalyzed reactions, the loading of sulfur dioxide is also necessary to be controllable. Thus, the most significant driving force in the field of sulfur dioxide insertion has been the development of safe and bench-stable sulfur dioxide surrogates. Several sulfur dioxide surrogates, including metal sulfite salts, DABCO·$(SO_2)_2$ (named DABSO), $SOCl_2$ with water, and sodium formaldehyde sulfoxylate (named rongalite), have been demonstrated to be feasible in the processes of sulfur dioxide insertion (Scheme 2.1). In the meantime, there are also some other sulfur dioxide surrogates with some applications in organic synthesis and biological systems, although they have not been utilized in sulfur dioxide insertion reactions till now.

It is well established that treatment of metal sulfites/disulfites (M_2SO_3, $M_2S_2O_5$) with protonic acid would release sulfur dioxide gas (Scheme 2.2). These inorganic sulfites are commercially available, inexpensive and easy-to-handle, making them attractive and reliable as sulfur dioxide surrogates. Sodium sulfite (Na_2SO_3) has been used ex situ with the gas produced and being transferred into the sulfur

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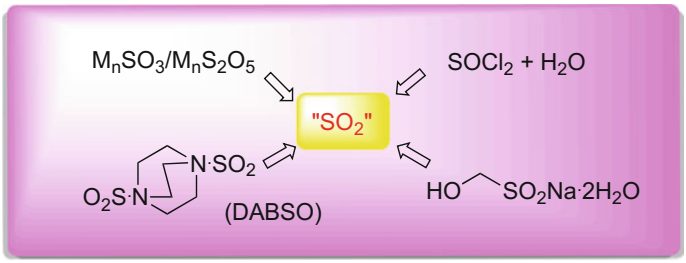
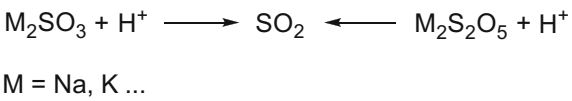


Scheme 2.1 Commonly used sulfur dioxide surrogates in sulfur dioxide insertion reactions



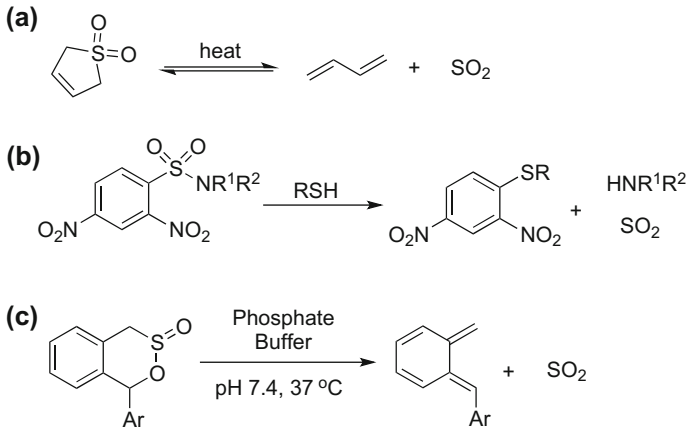
Scheme 2.2 Decomposition of metal sulfites/disulfites under acidic conditions

dioxide insertion reactions [5]. And $K_2S_2O_5$ has been particularly applied as a source of sulfur dioxide in a number of transformations, pioneered by the Wu group from Fudan University [6].

Sulfur dioxide could also be produced in situ through the reaction of thionyl chloride with water and participates in Sandmeyer sulfonyl chloride formation [7]. However, this rapid and exothermic reaction, together with the byproduct HCl, might lead to potential incompatibility. Thus, this procedure appears to be less attractive and practical, which only has a few limited applications in Sandmeyer reaction.

Rongalite (sodium formaldehyde sulfoxylate, with the chemical formula $HOCH_2SO_2Na{\cdot}2H_2O$) is commercially available and cheap, and has been widely used in a variety of synthetic transformations, which also provide approaches for symmetrical dialkyl sulfones [8]. Although this reagent introduces a $–SO_2–$ unit into molecules, we have to point out that it is a source of anion radical $SO_2^{-\cdot}$ as well as anion SO_2^{2-}, rather than a source of SO_2 [9]. Inspired by the recent progress in sulfur dioxide insertion reactions, the exploration of its novel reactivity in organic synthesis has come into notice. Considering these processes also introduce a sulfonyl unit into molecules, some representative examples will also be described in detail in Chap. 3.

The amine-SO_2 adducts have been exploited over a hundred of years ago, and early relevant studies mainly focused on the investigation of their structure and bonding, rather than application as a source of sulfur dioxide [10]. In 2010, the Willis group documented the utilization of DABCO·$(SO_2)_2$ (1,4-diazabicyclo[2.2.2] octane bis(sulfur dioxide), named by the authors as DABSO) as a reliable sulfur dioxide surrogate, which also represents the first utilization of a sulfur dioxide surrogate in organic chemistry [11]. This complex is a bench-stable, easy-to-handle white solid, and now represents the most commonly used sulfur dioxide surrogate.



Scheme 2.3 Other types of sulfur dioxide surrogates

General procedure for the synthesis of DABSO: A 50 mL round bottom flask was fitted with a condenser, attached to a Dreschel bottle bubbler system and flushed with argon for 10 min. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (2.00 g, 16.4 mmol) was added to the flask and the system flushed with argon for a further 5 min. Sulfur dioxide gas was introduced into the system (approx.1 bubble/sec) for 5 min. The reaction flask was cooled to −20 °C and the condenser to −78 °C and the sulfur dioxide was allowed to condense dropwisely onto the DABCO with stirring until the solid was completely covered with liquid sulfur dioxide (approx. 20 mL). The sulfur dioxide flow was stopped and the flask allowed to warm up to −10 °C and left stirring at reflux for 1 h. The condenser and bubbler were removed and the excess liquid sulfur dioxide was allowed to evaporate at room temperature under a flow of argon to reveal the complex as a white solid.

There are also some other procedures to access sulfur dioxide into necessary situations. 3-Sulfolene is another sulfur dioxide surrogate, it would release sulfur dioxide through a thermal cheletropic extrusion reaction (Scheme 2.3a) [12]. This process has been used for reduction of *N*-oxides, as well as isomerization of steroidal alkenes. Moreover, the application of sulfur dioxide surrogates including 2,4-dinitrobenzene sulfonamides [13] and 1-aryl-benzosultine derivatives [14] in biological systems has recently emerged (Scheme 2.3b, c).

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Chapter 3
Sulfur Dioxide Insertion Reactions

Abstract The area of sulfur dioxide insertion reactions has entered a new stage of renaissance in the last several years. In this chapter, we will summarize the reactions involved with the insertion of sulfur dioxide, with an emphasis on recent advances achieved by the application of sulfur dioxide surrogates. We will describe representative examples following the ideas of reaction design, and present the general experimental procedures. According to the types of transformation, these reactions are classified into four parts: (i) nucleophilic addition with organometallic reagents; (ii) transition metal catalysis; (iii) free radical reactions; and (iv) pericyclic reactions. These processes provide an efficient and practical route for the construction of sulfonyl-containing compounds.

Keywords Sulfur dioxide insertion · Reaction design · Nucleophilic addition · Transition metal catalysis · Free radical reactions

In this chapter, we will put an emphasis on the reaction development of sulfur dioxide insertion. According to the types of transformation, these reactions are mainly classified into four parts: (i) nucleophilic addition with organometallic reagents; (ii) transition metal catalysis; (iii) free radical reactions; and (iv) pericyclic reactions (Scheme 3.1). These transformations have emerged as an efficient and powerful strategy for the synthesis of sulfonamides, sulfones, and their derivatives thanks to the development of reliable sulfur dioxide surrogates. Particular attention will be paid to the reaction design and the advantages and restrictions of these processes.

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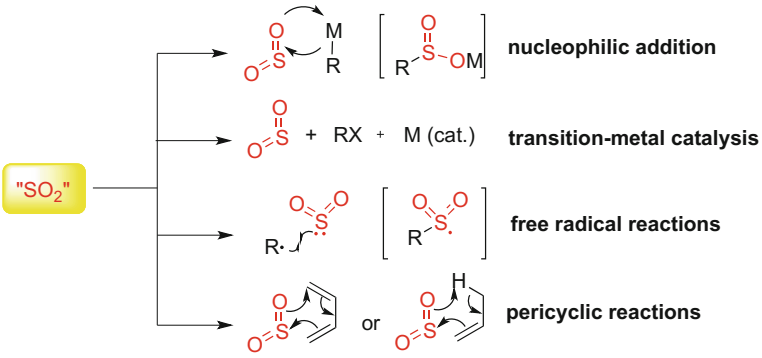


Scheme 3.1 Classification of sulfur dioxide insertion reactions

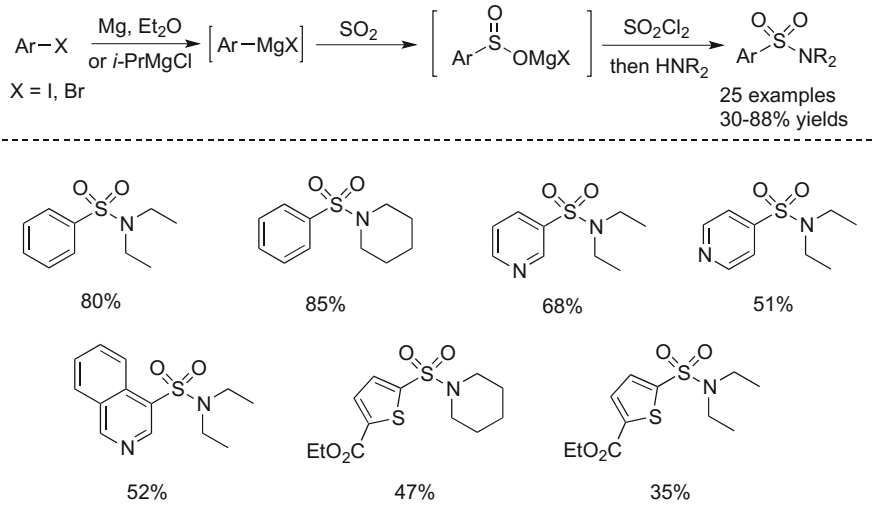
3.1 Nucleophilic Addition with Organometallic Reagents

Due to the electrophilic property of sulfur dioxide, the nucleophilic addition of organometallic reagents to sulfur dioxide gas has been well documented since a few decades ago [1]. A variety of organometallic species including Grignard reagents, organolithiums, organozincs, etc., can react with sulfur dioxide gas to give metal sulfinate salts [2–5]. The resulting metal sulfinate salts can be next trapped by electrophiles yielding sulfone derivatives. However, these processes have seldom applications in organic synthesis to produce important sulfonyl-containing compounds. Sulfur dioxide surrogates have also been proved as reliable equivalents of sulfur dioxide gas in these reactions recently.

3.1.1 Synthesis of Sulfonamides

Using sulfur dioxide gas, Barrett and co-workers reported a one-pot, relayed procedure for the preparation of sulfonamides directly from commercially available and inexpensive aromatic bromides and iodides in 2003 (Scheme 3.2) [6]. The *in situ* generated Grignard reagents could react with sulfur dioxide to give rise to the metal sulfinate intermediates, which could be converted into corresponding sulfonyl chlorides via the treatment of neat sulfuryl chloride at −40 °C. The resulting sulfonyl chlorides would finally react with secondary amines, leading to the desired sulfonamides. The key step was undoubtedly the formation of metal sulfinate salts. Both aryl and heteroaryl bromides could furnish this transformation, leading to a range of sulfonamides in moderate to good yields. However, an attempt of using alkyl bromide as the substrate was unsuccessful in this process.

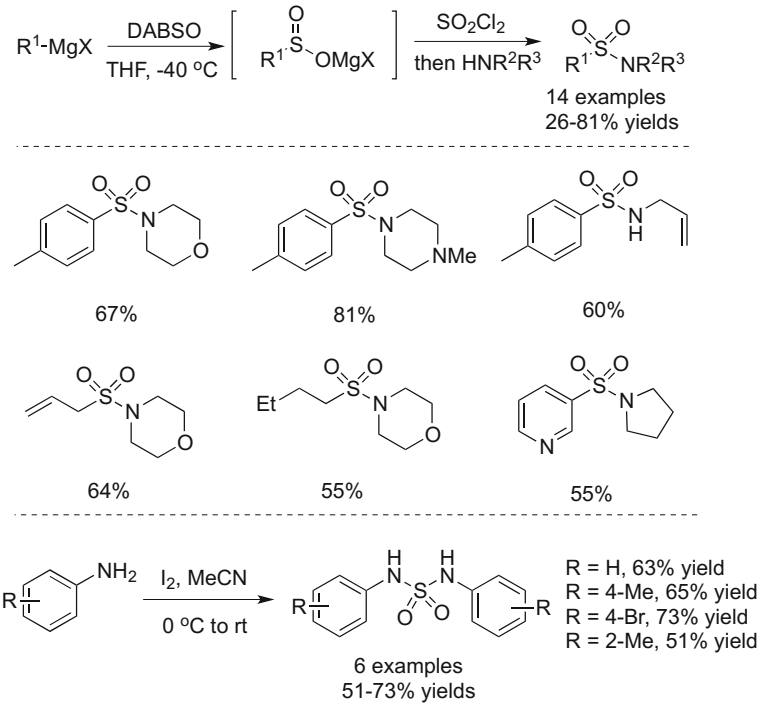
General procedure for the synthesis of sulfonamides starting from Grignard reagents and sulfur dioxide gas. General procedure (a) Mg turnings (540 mg, 22.40 mmol) were activated with I_2 (25 mg, 0.11 mmol) in THF (5.0 mL). The aryl



Scheme 3.2 Synthesis of sulfonamides via Grignard reagents and sulfur dioxide gas

bromide (11.2 mmol) in THF (15 mL) was added dropwisely and the mixture was heated to reflux for 1 h and recooled to −40 °C. SO_2 was bubbled through the solution for 5 min, and after 0.5 h, SO_2Cl_2 (0.90 mL, 11.20 mmol) was added. On warming to room temperature, the amine R_2NH (112 mmol, 10 equiv.) was added. After 3 h, the reaction mixture was quenched with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were combined and dried ($MgSO_4$), rotary evaporated, and chromatographed on silica to afford the sulfonamides; *General procedure (b) i*-PrMgCl in THF (2 M; 4.33 mmol) was added dropwisely with stirring over 5 min to the bromide or iodide (4.12 mmol) in THF (20 mL) at −30, −5 °C, or room temperature under argon. The resulting solution containing Grignard reagent was stirred for 30 min and allowed to react with SO_2, SO_2Cl_2, and R_2NH to provide the sulfonamide.

In 2011, the Willis group in Oxford University revealed that DABCO·$(SO_2)_2$ (1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide), named by the authors as DABSO) could be used as an excellent replacement for gaseous sulfur dioxide in the above transformation (Scheme 3.3) [7]. The easy-to-handle bench-stable DABSO was initially used in a palladium-catalyzed aminosulfonylation, which will be discussed in detail later in Sect. 3.2.1. Sulfinates could be smoothly produced through the reaction between Grignard reagents and DABSO. The addition of sulfuryl chloride would give rise to the corresponding sulfonyl chlorides, and subsequently be converted *in situ* to the desired sulfonamides. It was a one-pot, three-step process, similar to the above reaction. Aryl, allyl, alkyl, and heteroaryl-substituted Grignard reagents were all capable in this transformation. In addition, DABSO could react with anilines and iodine to produce a series of sulfamides under mild conditions. Moreover, cheletropic addition between DABSO



Scheme 3.3 One-pot preparation of sulfonamides and sulfamides using DABSO

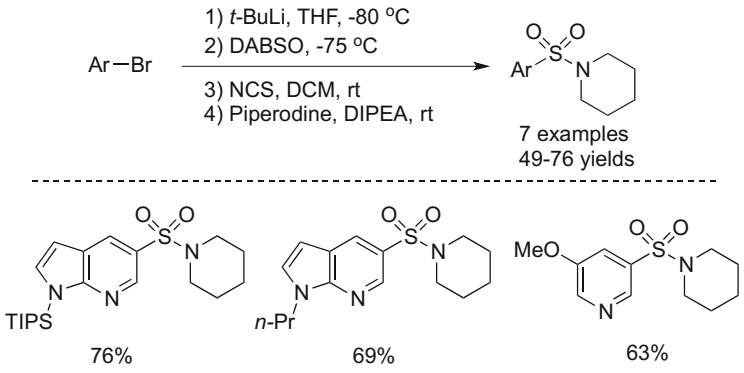
and 3-dimethylbutadiene under 120 °C would lead to the corresponding sulfolene. These transformations demonstrated that DABSO could serve as a superb surrogate for sulfur dioxide gas in certain established processes. It is noteworthy that the dosing of SO_2 equivalents was fully controllable.

General procedure for one-pot preparation of sulfonamides and sulfamides using DABSO. General procedure (a) Sulfonamide synthesis: A suspension of DABSO complex (151 mg, 0.63 mmol) in THF (3 mL) was cooled to −40 °C. The Grignard reagent (0.25 mmol) was added dropwisely and the mixture left for 1 h at −40 °C. Then sulfuryl chloride (0.02 mL, 0.25 mmol) was added at the same temperature and on warming to room temperature, the amine (2.5 mmol) was added to the mixture. After stirring for 3 h at room temperature, the reaction mixture was quenched with H_2O (3 mL) and extracted with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography on silica gel to afford the sulfonamide product. *General Procedure (b) Sulfamide synthesis*: A suspension of DABSO (240 mg, 1 mmol) in MeCN (5 mL) was cooled to 0 °C. Iodine (190 mg, 0.75 mmol) was then added and left to stir for 15 min at 0 °C until it was all dissolved. Then arylamine (0.5 mmol) was added and the reaction mixture was warmed to room temperature and stirred overnight. After 12 h, 10% aq NaOH (20 mL) were added and then the

pH of the solution was adjusted up to 6 using citric acid. The mixture was extracted with DCM (3 × 5 mL) and the combined organic layers were washed with 1 M aq HCl (1 × 5 mL), brine (1 × 5 mL) and then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash column chromatography afforded the sulfamide.

Subsequently, the Waldmann group applied the *in situ* generated organolithiums to the above transformation instead of Grignard reagents (Scheme 3.4) [8]. The one-pot synthesis of sulfonamides was developed, with an emphasis on the investigation of bromine–lithium exchange reaction between aryl bromides with *ter*t-butyllithium (*t*-BuLi). And *N*-chlorosuccinimide (NCS) was used as chlorinating reagent instead of sulfuryl chloride. They determined the exact molar amount of *t*-BuLi needed through a GC-MS assisted protonation assay for each substrate and significantly improved the previous protocol in terms of reproducibility and atom efficiency. A number of (hetero)aryl sulfonamides, notably of pyridine-core-substituted 7-azaindolyl sulfonamides, were synthesized under suitable conditions.

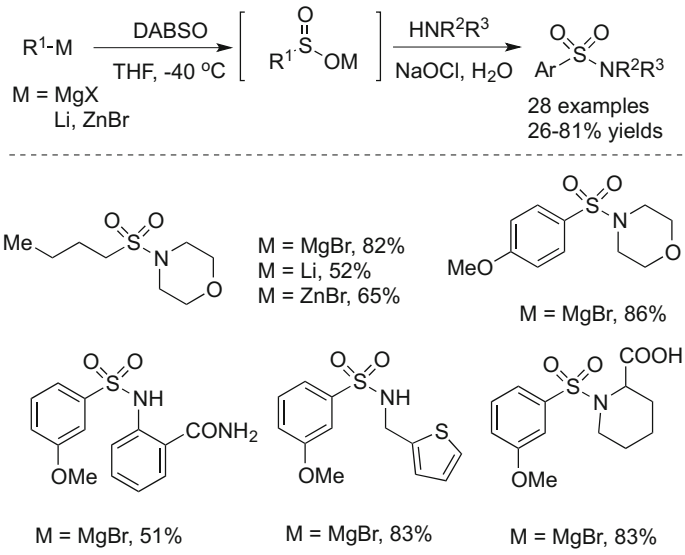
General procedure for the synthesis of sulfonamides using DABSO and in situ *generated organolithiums:* A 50 mL Schlenk tube was charged with the corresponding aryl bromide (0.5 mmol) and dry THF (5 mL) under argon. The solution was cooled to −80 °C in an ethanol/nitrogen cooling bath and the respective amount of *t*-BuLi (determined for any corresponding aryl bromide) was added dropwisely. After 10 min the reaction mixture was warmed up to −75 °C and DABCO-bis(sulfur dioxide) (120 mg, 0.5 mmol) was added at once. The cooling bath was removed after 30 min and the reaction mixture warmed up to room temperature. The THF solvent was removed under reduced pressure and dry DCM (8 mL) was added. NCS (80 mg, 0.6 mmol) was slowly added as a solution in dry DCM (2 mL). In a separate flask, piperidine (43 mg, 0.5 mmol) was dissolved in dry DCM (2 mL) and *N,N*-diisopropylethylamine (65 mg, 0.5 mmol) was added. This solution was then added to the reaction mixture directly. After the addition of water (20 mL), the mixture was extracted with DCM (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography.



Scheme 3.4 Synthesis of sulfonamides using DABSO and in situ generated organolithiums

To overcome the shortcomings imposed by the requirement of sulfuryl chloride in the previous reports, the Willis group developed a simple method for the synthesis of sulfonamides through the union of metal sulfinates and *N*-chloroamines in 2015 (Scheme 3.5) [9]. The in situ prepared metal sulfinates via the above-established method were combined with *N*-chloroamines, which were generated from amines and NaOCl, yielding the desired sulfonamides. This process shortened the reaction steps and avoided the use of sulfuryl chloride. Grignard reagents, organolithiums, organozinc reagents were all applied in this transformation. A broad reaction scope was observed under standard conditions. Alkyl, alkenyl, and (hetero)aryl sulfonamide were all accessible in moderate to good yields. Many sensitive functional groups including carboxyl, trimethylsilyl, and ester were compatible in this reaction. The authors further employed this method for the synthesis of a targeted 70 compound array, demonstrating the utility and efficiency of this sulfur dioxide insertion reaction for delivering sulfonamides with drug-like properties.

General procedure for the synthesis of sulfonamides via *the reaction of organometallic reagents, DABSO, and amines*: To a reaction tube was added DABSO (36 mg, 0.15 mmol) and THF (1 mL) and the resulting suspension flushed with nitrogen gas for 2 min. After cooling to −40 °C Grignard reagent (0.25 mmol) was added dropwisely and the mixture was stirred at this temp for 30 min. On warming to room temp a strong flow of nitrogen gas was applied to remove the solvent before addition of water (1.5 mL) and amines (1.25 mmol). The resulting mixture was cooled to 0–5 °C (ice water bath) and NaOCl (15.8% aqueous



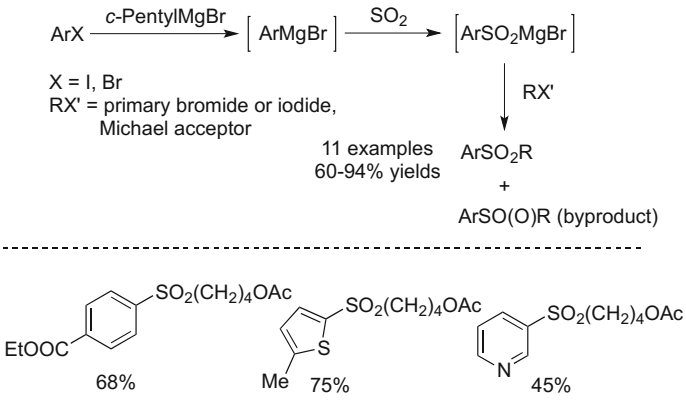
Scheme 3.5 Synthesis of sulfonamides via the reaction of organometallic reagents, DABSO and amines

solution, 296 μL, 0.75 mmol) was added dropwisely before allowing the reaction to warm to room temp (Note: addition of NaOCl to mixtures containing anilines results in colored oxidation products which could be flushed off with 100% CH_2Cl_2 on chromatography). After stirring for 16 h, NaS_2O_3 (aq, 10 mL) was added and the mixture was stirred for a further 20 min. The aqueous mixture was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were subsequently washed with 1 M HCl (aq) (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (petrol/Et_2O 3:2) afforded the titled sulfonamides.

3.1.2 Synthesis of Sulfones

Besides the aminosulfonylative processes, alkylation of sulfinates also provides a convenient method for the construction of sulfones. The metal sulfinates generated from the addition of organometallic reagents to sulfur dioxide are powerful intermediates for sulfone synthesis. In 2005, Wu and co-workers described the synthesis of sulfones through the insertion of sulfur dioxide (Scheme 3.6) [10]. The magnesium sulfinates produced by the reaction of Grignard reagents with sulfur dioxide could combine with alkyl bromide smoothly to give the desired sulfones. Sulfur dioxide gas was used in this process, and sulfinate ester could be observed as a byproduct. Alkyl halides including primary iodides/bromides and allylic halides were all suitable under the standard reaction conditions. Michael accepter could also be used as alkylating reagents to generate the corresponding sulfones.

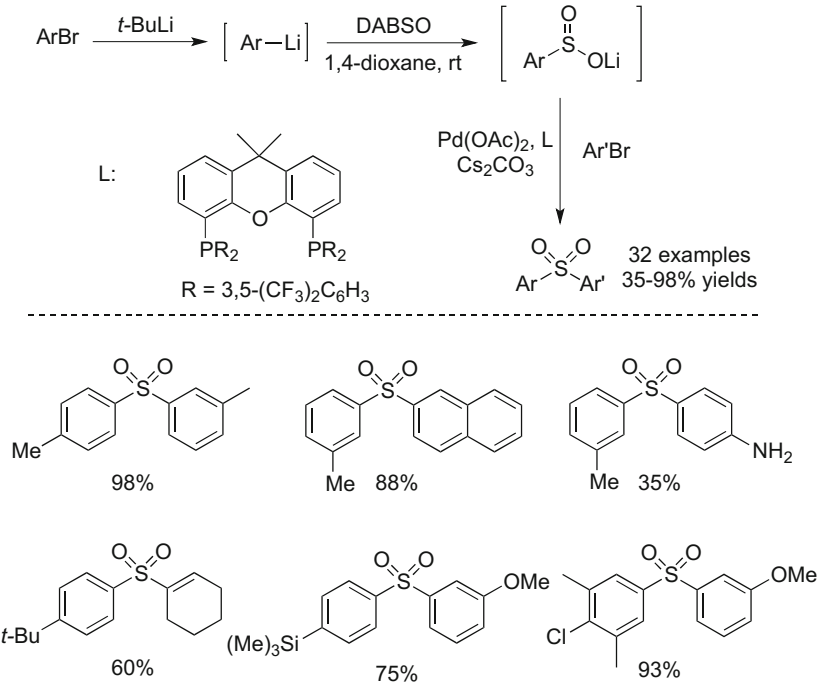
General procedure for alkylation of magnesium sulfinates: The reactions were typically carried out in 0.1–3 mmol scale (ArX). To a solution of an aromatic/heteroaromatic halide (ArX, 1.0 equiv.) in THF (0.2–0.4 mmol of ArX/mL) cooled to −40 °C was added cyclopentylmagnesium bromide (2.5 equiv.)



Scheme 3.6 Alkylation of magnesium sulfinates

dropwisely. The mixture was stirred at −40 °C for 40 min before SO_2 was introduced (SO_2 was condensed into the reaction flask for about 5 min). The mixture was stirred at −40 °C for 15 min then room temperature for 1 h. It was then concentrated. The residue was co-evaporated twice with dry THF to remove excess SO_2. The solid was dried under vacuum overnight. The solid thus obtained was dissolved in dry DMF (0.1–0.2 mmol of ArX/mL). To this solution was added K_2CO_3 followed by the alkylating reagent. The mixture was then heated at 70 °C overnight. After cooling to rt, water was added. The mixture was extracted EtOAc, dried over Na_2SO_4, and concentrated. Purification of the residue afforded the sulfones and sulfinates esters.

The application of sulfur dioxide surrogates in similar transformations was developed for sulfone synthesis recently. In 2013, the Willis group reported a palladium-catalyzed three-component reaction of organolithiums, DABSO, and aryl bromides for the synthesis of diaryl sulfones (Scheme 3.7) [11]. DABSO was used as the sulfur dioxide surrogate and led to the formation of sulfinates. The sulfination process via the reaction of organolithiums with sulfur dioxide was successfully combined with a relayed Pd-catalyzed sulfonation of aryl bromides to yield the desired diaryl sulfones. The electron-poor XantPhos-type ligand was found to be crucial to this transformation as it repressed the undesirable aryl-transfer from the ligand. A broad range of aryl, heteroaryl, and alkenyl sulfones could be accessed in

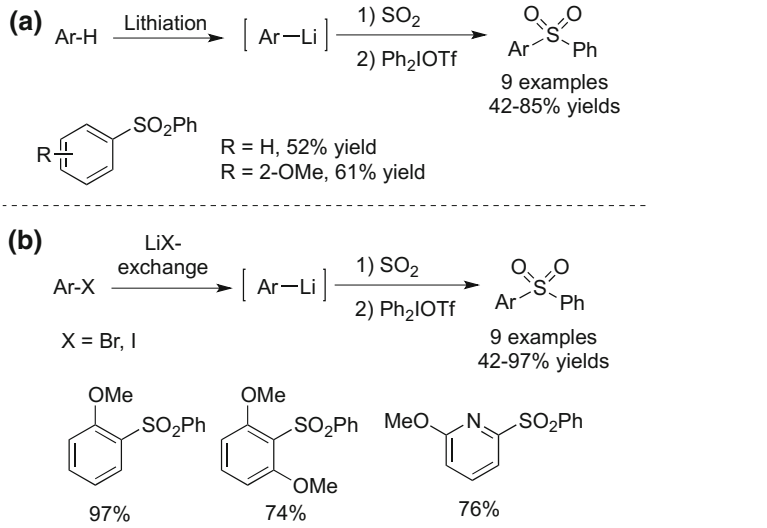


Scheme 3.7 A palladium-catalyzed three-component reaction of organolithiums, DABSO and aryl bromides

good to excellent yields. However, the substrate bearing a heterocycle such as heterocyclic lithium 2-thienylsulfinate or the substrate bearing an *ortho*-substitution such as *ortho*-substituted lithium 2-anisyl sulfinate failed in this reaction. The authors exploited the ability of the sulfone group to direct *ortho* metalation to realize *ortho* functionality.

General procedure for the palladium-catalyzed three-component reaction of organolithiums, DABSO, and aryl bromides: A stirred solution of arylbromide (ArBr, 28.9 mmol) in $^{n}Bu_2O$ (5 mL) in a 100 mL two-necked round-bottom flask was cooled to −10 °C and ^{t}BuLi solution in heptane (27.5 mL, titrated to 2.10 M, 57.7 mmol) was added dropwisely via syringe pump (0.25 mL/min) maintaining the external temperature between 0 and −10 °C. At the end of the addition the cooling bath was removed and the resultant suspension was stirred at room temperature for a further 1 h. The reaction mixture was filtered through a Schlenk-sinter into a 100 mL round-bottom Schlenk-flask and the filtrate stored in the freezer (−25 °C) under N_2 as a solution of 3-tolyl lithium in heptane/$^{n}Bu_2O$. All other aryl lithiums were prepared using the same procedure but on a reduced scale of aryl bromide (7 mmol), Bu_2O (3 mL) and ^{t}BuLi in heptane (14 mmol)—the resulting solution being stored in a 25 mL round-bottom Schlenk-flask. All aryl lithiums were titrated against a 1.0 M solution of 2-propanol in toluene with 0.2% 1,10-phenanthroline as the indicator prior to use. A glass reaction tube was charged with DABSO (63 mg, 0.26 mmol) and evacuated and filled with nitrogen once. 1,4-Dioxane (2 mL) was added and the resultant suspension stirred while the tube was flushed with nitrogen gas for 3 min. Aryl lithium solution (0.49 mmol) was added dropwisely to the vigorously stirred suspension at room temperature. The resulting suspension was stirred at room temperature for 2 h. Another glass reaction tube was charged with arylbromide (0.35 mmol), cesium carbonate (171 mg, 0.53 mmol), ligand (39 mg, 35 μmol) and palladium(II) acetate (8 mg, 35 μmol), sealed with a crimped cap and evacuated and filled with nitrogen three times. The lithium sulfinate slurry in dioxane was syringed across and the reaction heated at 110 °C with vigorous stirring for 16 h under sealed tube conditions. After cooling, the reaction mixture was diluted with DCM (10 mL) and filtered through a Celite pad which was washed with further DCM (20 mL). The combined filtrate was concentrated in vacuo. Flash column chromatography (10–25% Et_2O in petrol) afforded the desired product.

Using sulfur dioxide gas, Manolikakes and co-workers also developed a three-component reaction of organolithiums, sulfur dioxide, and diaryliodonium salts for the synthesis of diaryl sulfones (Scheme 3.8) [12]. Similarly, lithium sulfinates were generated via the reaction of organolithiums with sulfur dioxide. In this report, arylation of sulfinates with diaryliodonium salts was applied instead of the palladium-catalyzed sulfonylation. The combination of lithium sulfinates and diaryliodonium salts could proceed smoothly to give the desired sulfones in DMF at 90 °C. Alkyllithium reagents could also be applied in this reaction leading to alkyl aryl sulfones. Additionally, generation of the organolithium reagents in situ via exchange or deprotonation of hetero-(aromatic) halides or (hetero)arenes provided a more convenient route for the direct one-pot, three-step synthesis of sulfones.



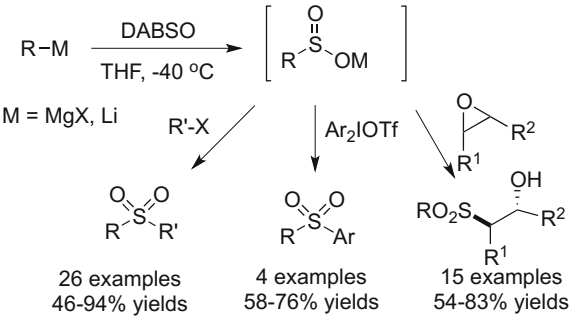
Scheme 3.8 Three-component reaction of organolithiums, sulfur dioxide and diaryliodonium salts

General procedure for the three-component reaction of organolithiums, sulfur dioxide, and diaryliodonium salts: (From anisole): To a solution of anisole (0.82 mL, 0.75 mmol, 1.5 equiv.) and TMEDA (0.22 mL, 1.5 mmol, 3.0 equiv.) in dry Et_2O (1.0 mL) in a dry, Ar-flushed Schlenk-flask equipped with a magnetic stirrer and a rubber septum was added *n*-BuLi (0.61 mL, 2.45 M in hexanes, 1.5 mmol, 3.0 equiv.) dropwisely. The mixture was allowed to stir at 25 °C for 30 min and then cooled to −78 °C and liquid SO_2 (0.1 mL, 5.0 mmol, 10.0 equiv.) was added. After warming to 25 °C within 90 min, excess SO_2 and solvents were removed. To the crude sulfinic acid, lithium salt was added diphenyliodonium triflate (215.1 mg, 0.5 mmol, 1.0 equiv.) and DMF (1.0 mL). The reaction mixture was heated to 90 °C and stirred at this temperature for 24 h. After cooling to 25 °C, sat. aqueous NH_4Cl-solution (10 mL) was added and the aqueous layer was extracted three times with CH_2Cl_2 (15 mL). The combined organic layers were washed with dist. H_2O (15 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. Purification by column chromatography (cyclohexane: EtOAc 20:1–4:1) yielded the product as a colorless solid. (*From 2-bromoanisole*): A dry, Ar-flushed Schlenk-flask equipped with a magnetic stirrer and a rubber septum was charged with *n*-BuLi (0.33 mL, 2.45 M in hexanes, 0.80 mmol, 1.6 equiv.) and cooled to −78 °C. Then 2-bromoanisole (0.1 mL, 0.75 mmol, 1.5 equiv.) was added dropwisely and the reaction mixture was stirred at this temperature for 1 h, before liquid SO_2 (0.1 mL, 5.0 mmol, 10.0 equiv.) was added. The mixture was allowed to warm to 25 °C within 90 min and then excess SO_2 and solvents were removed. To the crude sulfinic acid, lithium salt was added diphenyliodonium triflate (215.1 mg, 0.50 mmol, 1.0 equiv.) and DMF (1.0 mL).

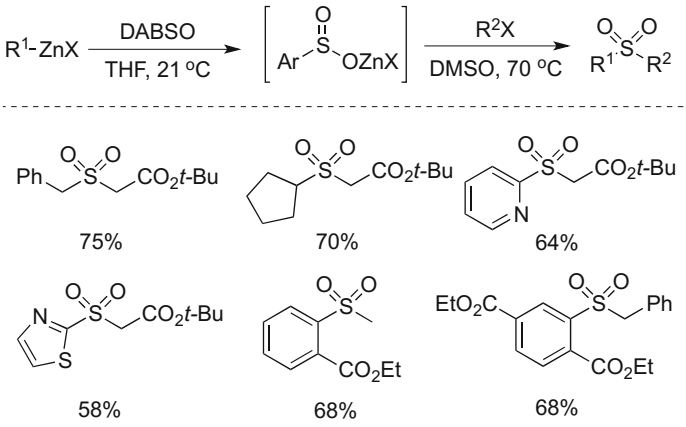
The reaction mixture was heated to 90 °C and stirred at this temperature for 24 h. After cooling to 25 °C, sat. aqueous NH_4Cl-solution (10 mL) was added and the aqueous layer was extracted three times with CH_2Cl_2 (15 mL). The combined organic layers were washed with dist. H_2O (15 mL), dried over Na_2SO_4 and the solvents were removed under reduced pressure. Purification by column chromatography (cyclohexane:EtOAc 9:1–4:1) yielded the product as a colorless solid.

With the above achievements, further application of the *in situ* generated sulfinates using sulfur dioxide surrogates could be expected. The Willis group reported a related process for the synthesis of sulfones (Scheme 3.9) [13]. They revealed that the in situ electrophilic trapping of metal sulfinates generated from the reaction of Grignard reagents or organolithium reagents with DABSO could give rise to the desired sulfones. Various electrophiles including alkyl, allyl, and benzyl halides, epoxides, and (hetero)aryliodoniums could react with the sulfinate intermediates leading to corresponding sulfones under suitable conditions. Using this one-pot process, a large number of sulfones could be synthesized in moderate to excellent yields. In the meantime, Rocke reported a similar transformation utilizing organozinc reagents as the substrates (Scheme 3.10) [14]. A wide range of structural motifs such as nitrile, secondary carbamates, and heterocyles were compatible with this process. The addition of organozinc reagents to sulfur dioxide could proceed at nearly room temperature, while the Willis's procedure required a much lower temperature of −40 °C. Moreover, 0.55 equivalent of DABSO was enough to conduct this reaction, leading to the desired sulfones in moderate to good yields.

General procedure for the DABSO-based, three-component one-pot sulfone synthesis: Procedure (a) for the synthesis of sulfones from organometallic reagent, DABSO, and alkyl halide/iodonium salt electrophiles as exemplified by the preparation of sulfone: To a reaction tube was added DABSO (60 mg, 0.25 mmol) and THF (1.0 mL) and the resulting suspension was flushed with nitrogen gas for 2 min. After cooling to −40 °C, organometallic reagent (0.25 mmol) was added dropwisely and the mixture was stirred at this temperature for 1 h. On warming to room temperature a strong flow of nitrogen gas was applied to remove the solvent before addition of DMF (2 mL) and alkyl halide/iodonium salt electrophiles (0.75 mmol). The mixture was subjected to microwave heating at 120 °C for 3 h. After cooling, Et_2O (20 mL) was added and the solids were filtered off before



Scheme 3.9 DABSO-based three-component one-pot synthesis of sulfones



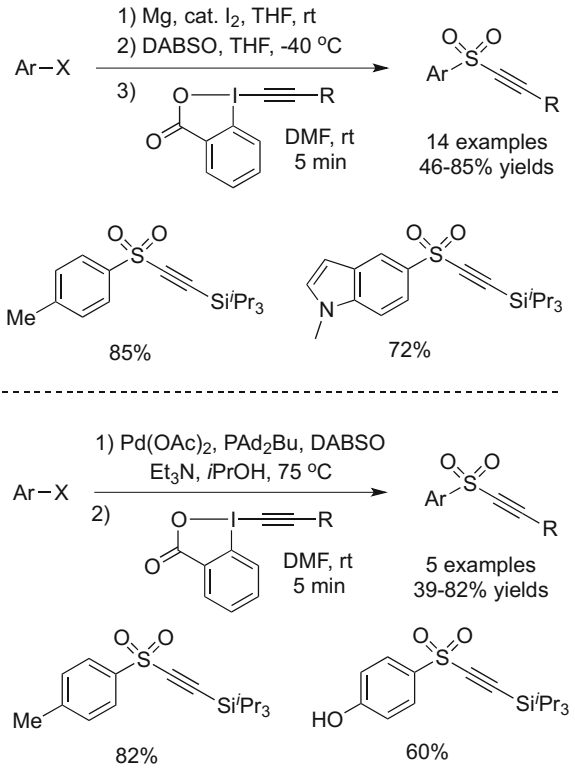
Scheme 3.10 Synthesis of sulfones from organozinc reagents, DABSO, and alkyl halides

removing the solvent in vacuo. Purification by flash column chromatography (petrol/Et_2O 3:2) afforded the titled sulfone. *General Procedure (b) for the synthesis of β-hydroxy sulfones from Grignard reagent, DABSO*: To a reaction tube was added DABSO (60 mg, 0.25 mmol) and THF (1.0 mL) and the resulting suspension was flushed with nitrogen gas for 2 min. After cooling to −40 °C Grignard reagents (0.25 mmol) was added dropwisely to the suspension which was stirred at this temperature for 1 h. On warming to room temperature, a strong flow of nitrogen gas was applied to remove the solvent before addition of H_2O (1.5 mL) and epoxides (1.25 mmol). The resulting mixture was heated to 90 °C and stirred at this temperature for 16 h. After cooling, sat. NH_4Cl (10 mL) and subsequently CH_2Cl_2 (10 mL) were added, the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (petrol/Et_2O 1:4) afforded the titled β-hydroxy sulfones.

General procedure for the synthesis of sulfones from organozinc reagents, DABSO, and alkyl halides: A dry, nitrogen-filled vial was charged with DABSO (66.1 mg, 0.55 equiv.) and heated under dynamic vacuum in a 40 °C aluminum block for 20 min. After the nitrogen atmosphere was restored and the vial was returned to room temperature, a 0.50 M solution of an organozinc reagent in THF (1.0 mL) was added in one portion. The resulting mixture was vortexed for 2 min to obtain a fine suspension and then stirred at room temperature for 15 min. DMSO (1.00 mL) and an alkylating agent were introduced to the reaction mixture, and the reaction mixture was placed in a 70 °C aluminum block for 1 h. The reaction mixture was then partitioned between MTBE (ca. 25 mL) and 1.0 M aq. HCl (ca. 25 mL). The MTBE layer was washed with brine, dried over sodium sulfate, and evaporated. Products were isolated from this crude material by MPLC (EtOAc/heptane gradient).

Alkynyl sulfones present an important class of sulfones due to their versatile reactivities. The strong electron-withdrawing property of the sulfonyl unit enhances the reactivity of the triple bond. Thus, sulfonyl alkynes possess wide applications in cycloadditions and conjugate addition reactions. In 2015, Waser and co-workers realized a one-pot three-component reaction of ethynyl-benziodoxolone (EBX) reagents, DABSO, and organomagnesium reagents for the preparation of arylsulfonyl alkynes (Scheme 3.11) [15]. The metal sulfinates generated from Grignard reagents and DABSO could react with ethynyl-benziodoxolone (EBX) reagents leading to the desired sulfones. The reaction was accomplished in 5 min in DMF at room temperature. This transformation took place under mild conditions. A broad range of aryl and heteroarylalkynyl sulfones could be accessed in 46–85% yields. However, the substituents attached to the triple bond were restricted to triisopropylsilyl and tertiary butyl. Attempts with Me-EBX, Ph-EBX, and *n*-Hex-EBXX all failed to deliver the desired products. Additionally, the palladium-catalyzed sulfination of aryl iodine with DABSO could also be compatible in this transformation. The sulfinates generated under palladium catalysis proceeded through the alkynylation with ethynyl-benziodoxolone reagents to yield sulfonyl

Scheme 3.11 Synthesis of alkynyl sulfones via one-pot three-component reaction



alkynes. This transition-metal-catalyzed sulfination using sulfur dioxide surrogates was previously developed by Willis, and it will be discussed in detail later in Sect. 3.2.

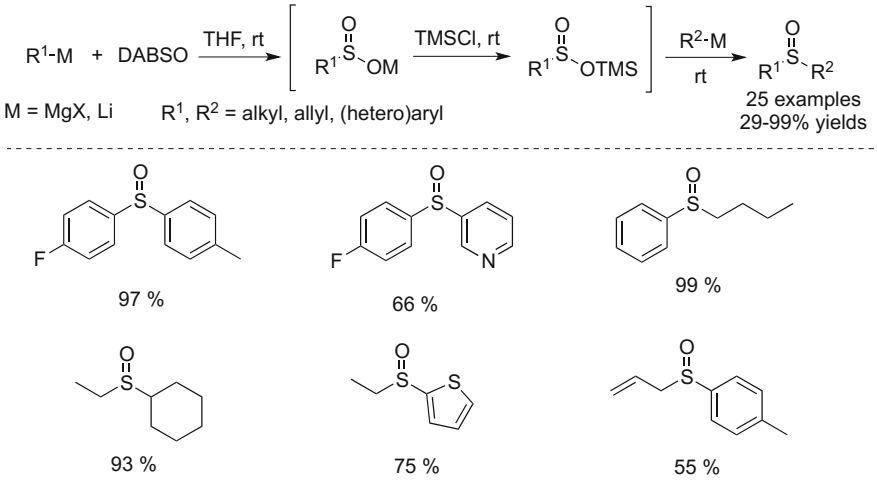
General procedure of one-pot, three-component reaction for the synthesis of alkynyl sulfones: General Procedure (a) for one-pot preparation of alkynyl sulfones using Grignard reagents: A stirring bar was placed in a 7.5 mL microwave tube with a cap (not sealed at this moment), and flamed dry under high vacuum. After cooling down to room temperature and filled with nitrogen, DABSO (48 mg, 0.20 mmol) was added into the microwave tube. The tube was sealed, evacuated, and filled with nitrogen four times. Anhydrous THF (0.65 mL) was added, and the tube was replaced in a −40 °C (MeCN + dry ice) bath for 10 min. The corresponding Grignard reagent (0.20 mL, 0.20 mmol) was added, and the reaction mixture was stirred for 1 h. The cooling bath was then removed, and the resulting solution was stirred at room temperature for another 1 h. The sealed cap was removed, and DMF (0.65 mL) and TIPS-EBX (103 mg, 0.240 mmol) or other R-EBX (0.24 mmol) were subsequently added to the resulting solution and stirred for further 5 min. The reaction was quenched by adding 1.0 M HCl (2.0 mL). The resulting layers were separated and the aqueous layer was extracted with EtOAc (3 × 5.0 mL). All of the organic layers were combined, washed with (sat.) $NaHCO_3$, dried over $MgSO_4$, and filtrated. The organic solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography to afford the desired product. The yields given are based on the indicated concentration for commercial Grignard reagents and on the used bromide starting material for self-made Grignard reagents. *General procedure (b) for one-pot preparation of alkynyl sulfones using palladium catalysis*: A 7.5 mL microwave tube was charged with a stirring bar, $Pd(OAc)_2$ (2.2 mg, 10 mol), CataCXium (5.4 mg, 15 mol), DABSO (48 mg, 0.20 mmol), and aryl iodide (0.20 mmol), sealed with a cap and evacuated and filled with nitrogen three times. Anhydrous triethylamine (84 μL, 0.60 mmol) and anhydrous 2-propanol (1.7 mL) were added and the resulting solution was stirred in a steel tube holder at 75 °C for 16 h. After cooling to room temperature, anhydrous DMF (0.65 mL) and TIPS-EBX (103 mg, 0.240 mmol) were subsequently added to the resulting solution and stirred for further 5 min. The reaction was quenched by adding 1.0 M HCl (2.0 mL). The resulting layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). All of the organic layers were combined, washed with (sat.) $NaHCO_3$, dried over $MgSO_4$, and filtrated. The organic solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography to afford the desired product.

3.1.3 Synthesis of Sulfoxides

It is well known that the sulfoxide unit is an important functional group widely existed in a number of biologically active compounds [16]. They are usually

prepared from the oxidation of corresponding sulfides or nucleophilic displacement on sulfinyl derivatives. In 2016, a one-pot process for the synthesis of unsymmetrical sulfoxides via insertion of sulfur dioxide was reported by the Willis group. Initially, the sulfinate intermediate was formed from the organometallic reagent (Scheme 3.12) [17]. Subsequent treatment with TMS-Cl (trimethylsilyl chloride) would lead to sulfinate silyl esters, which would accept the addition from a second organometallic reagent to give the desired sulfoxides. This protocol took advantage of the in situ generated sulfinates using DABSO as the sulfur dioxide surrogate and synthesized a variety of sulfoxides in good to excellent yields. Moreover, this multistep reaction could be entirely proceeded at room temperature.

General procedure for the one-pot synthesis of unsymmetrical sulfoxides via insertion of sulfur dioxide: To a 25 mL two-neck round-bottom flask was added DABSO (240.3 mg, 1.0 mmol, 0.5 equiv.) and anhydrous THF (4.0 mL), and the resulting suspension was flushed with nitrogen gas for 3 min. Under a constant flow of nitrogen gas, organometallic reagent (R^1M, 2.0 mmol, 1.0 equiv.) was added dropwisely and the reaction mixture was left to stir for 45 min (t_1) at room temperature. Subsequently, chlorotrimethylsilane (0.38 mL, 3.0 mmol, 1.5 equiv.) was added and the reaction mixture was left to stir for 45 min (t_2) at room temperature before adding another organometallic reagent (R^2M, 1.50 mmol, 0.75 equiv.). After stirring at room temperature for another 45 min (t_3), the reaction mixture was quenched with sat. aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The desired product was isolated from the obtained crude material by flash column chromatography using the indicated solvents and gradient.



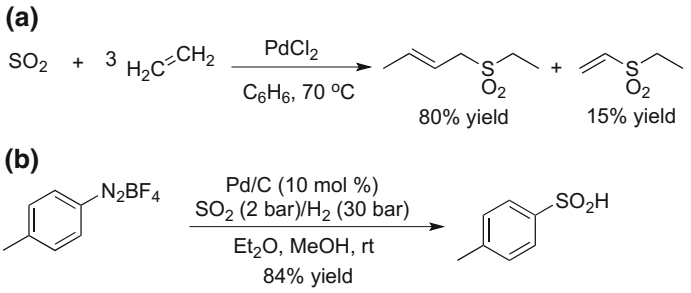
Scheme 3.12 One-pot synthesis of unsymmetrical sulfoxides via insertion of sufur dioxide

3.2 Transition Metal Catalysis

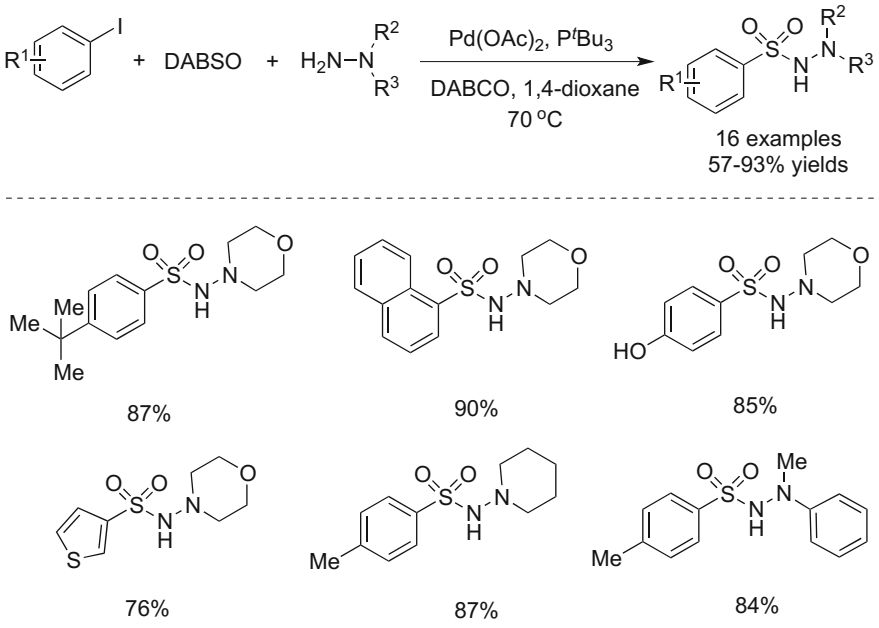
Compared with the well-established carbon monoxide chemistry, the application of sulfur dioxide in transition metal catalysis is still limited, although the coordination between sulfur dioxide with metal centers has been well recognized [18]. In 1968, Klein and co-workers reported the first transition-metal-catalyzed insertion reaction of sulfur dioxide (Scheme 3.13a) [19]. They revealed that the reaction of ethylene with sulfur dioxide in the presence of $PdCl_2$ catalyst could afford *trans*-but-2-enyl sulfone and ethyl vinyl sulfone. However, this area has rarely been noticed since then [20]. In 1999, Keim and co-workers reported a palladium-catalyzed generation of sulfinic acids from aryldiazonium salts, sulfur dioxide, and hydrogen (Scheme 3.13b) [21]. This reaction took place under high pressure at room temperature, and represented the first coupling reaction of sulfur dioxide insertion. Until the Willis group [22] utilized DABSO as a source of sulfur dioxide in a palladium-catalyzed aminosulfonylation of aryl halides, the rapid development of transition-metal-catalyzed sulfur dioxide insertion reactions has been witnessed.

3.2.1 Synthesis of Sulfonamides

As mentioned above, the Willis group pioneered the first palladium-catalyzed aminosulfonylation of aryl iodides (Scheme 3.14) [22]. Initially, they were inspired by the carbon monoxide chemistry and explored the possibility of the aminosulfonylation process of aryl halides using sulfur dioxide gas. A variety of nucleophiles and catalysts were investigated, however, these attempts turned out to be unsuccessful. Finally, they discovered that the key of C–SO_2–N linkages could be formed utilizing a hydrazine nucleophile and DABSO as the sulfur dioxide source. This three-component reaction of aryl iodides, DABSO, and hydrazines in the presence of a palladium catalyst could deliver a variety of *N*-aminosulfonamides in good to excellent yields. It is noteworthy that only a slight excess amount of DABSO was employed in this transformation. The controllable equivalent of sulfur



Scheme 3.13 Early studies of transition-metal-catalyzed insertion reaction of sulfur dioxide

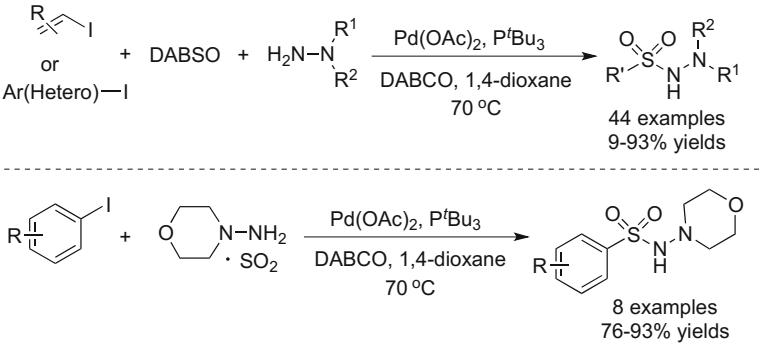


Scheme 3.14 Palladium-catalyzed aminosulfonylation of aryl halides with DABSO and hydrazines

dioxide might avoid the catalyst poisoning, and this was considered to be the key to success. Unfortunately, the nucleophiles were restricted to hydrazines and the reason remained to be undiscovered.

General procedure for the palladium-catalyzed aminosulfonylation of aryl halides with DABSO and hydrazines: A glass reaction tube was charged with 4-iodoanisole (50 mg, 0.21 mmol), 4-aminomorpholine (31 μl, 0.32 mmol), DABCO·$(SO_2)_2$ complex (31 mg, 0.13 mmol), 1,4-diazabicyclo[2.2.2]octane (12 mg, 0.11 mmol), palladium(II) acetate (5 mg, 21 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (12 mg, 42 μmol) and sealed under argon gas. 1,4-Dioxane (1.6 mL) was added and the tube was heated at 70 °C for 16 h. After cooling, the reaction mixture was filtered through Celite and washed sequentially with dichloromethane (10 mL) and diethylether (5 mL) before being concentrated in vacuo. Purification by flash column chromatography (50–100% diethylether in petrol) afforded the *N*-aminosulfonamide.

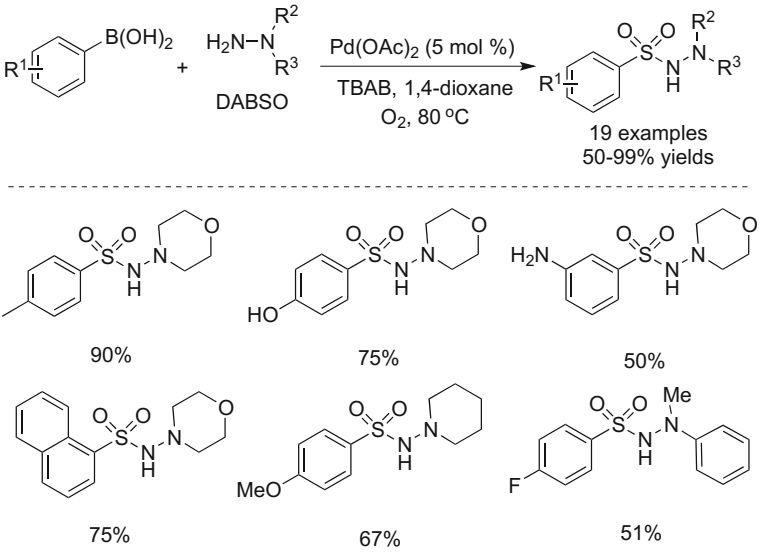
The reaction scope of this palladium-catalyzed aminosulfonylation was next extended by the same group via applying a variety of aryl-, heteroaryl, and alkenyl iodides as coupling partners (Scheme 3.15) [23]. A broad functional group tolerance was observed under the standard reaction conditions, highlighting the generality of this transformation. Moreover, *N*-aminomorpholine-SO_2 complex could function as both nucleophile and sulfur dioxide donor to deliver the corresponding *N*-aminosulfonamides.



Scheme 3.15 Scope exploration of the palladium-catalyzed aminosulfonylation

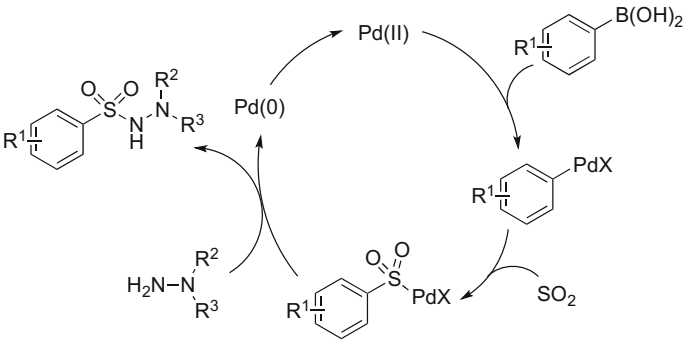
General procedure for the palladium-catalyzed aminosulfonylation: General procedure (a) for palladium-catalyzed aminosulfonylation of aryl iodides using DABSO, exemplified by the preparation of aminosulfonamide: A glass reaction tube was charged with 4-iodotoluene (50 mg, 0.23 mmol), 4-aminomorpholine (33 μl, 0.34 mmol), DABCO·$(SO_2)_2$ complex (33 mg, 0.14 mmol), 1,4-diazabicyclo [2.2.2]octane (13 mg, 0.11 mmol), palladium(II) acetate (5 mg, 21 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (13 mg, 42 μmol) and sealed under N_2 gas. 1,4-Dioxane (1.6 mL) was added and the tube was heated at 70 °C for 16 h. After cooling, the reaction mixture was filtered through Celite and washed sequentially with dichloromethane (10 mL) and diethylether (5 mL) before being concentrated in vacuo. Purification by flash column chromatography (50–100% diethylether in petrol) afforded the *N*-aminosulfonamide. *General procedure (b) for the formation of N-morpholinosulfonamides using 4-aminomorpholine-sulfur dioxide complex, exemplified by the preparation of 4-methyl-N-morpholinobenzenesulfonamide*: A glass reaction tube was charged with 4-iodotoluene (50 mg, 0.23 mmol), 4-aminomorpholine-sulfur dioxide complex (57 mg, 0.34 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO) (28 mg, 0.25 mmol), palladium(II) acetate (5 mg, 23 μmol) and tri-*tert*-butylphosphonium tetrafluoroborate (13 mg, 46 μmol) and sealed under N_2. 1,4-Dioxane (1.6 mL) was added and the tube was heated at 70 °C with stirring for 16 h. After cooling, the reaction mixture was filtered through Celite. The Celite pad was washed sequentially with CH_2Cl_2 (10 mL) and Et_2O (5 mL) and the combined organic extracts concentrated in vacuo. Purification by flash column chromatography (50–100% Et2O in petrol) afforded the *N*-aminosulfonamide.

Inspired by these elegant works, the Wu group in Fudan developed a palladium-catalyzed coupling of arylboronic acids, DABSO, and hydrazines in the presence of dioxygen to deliver *N*-aminosulfonamides (Scheme 3.16) [24]. The authors utilized arylboronic acids as arylated reagents instead of aryl iodides. The reaction took place smoothly under oxidative conditions using dioxygen as the oxidants. Tetrabutylammonium bromide (TBAB) was applied as a base and the



Scheme 3.16 Palladium-catalyzed coupling of arylboronic acids, DABSO and hydrazines

ligand was unnecessary in this process. A number of sensitive functional groups including free-amino and hydroxyl could be tolerated under the reaction conditions. A possible mechanism was proposed (Scheme 3.17). The authors hypothesized that a Pd(II) species would be generated via the transmetallation of Pd(II) with arylboronic acid. The subsequent insertion of sulfur dioxide and nucleophilic attack of hydrazine would take place to give the desired product and Pd(0). The Pd(II) catalyst could be regenerated via the oxidation of Pd(0) by dioxygen, which reentered the catalytic cycle.

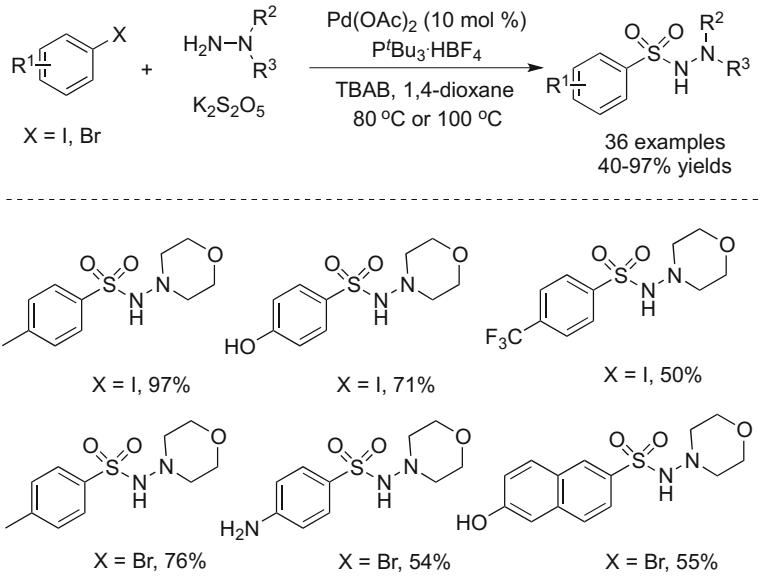


Scheme 3.17 A plausible mechanism of the palladium-catalyzed coupling of arylboronic acids, DABSO and hydrazines

General procedure for the palladium-catalyzed coupling of arylboronic acids, DABSO, and hydrazines: Hydrazine (0.5 mmol) in 1,4-dioxane (2.0 mL) was added to a mixture of arylboronic acids (1.0 mmol), DABCO·$(SO_2)_2$ (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and TBAB (0.75 mmol) under a balloon of O_2. The reaction was stirred at 80 °C for 12 h. After completion of the reaction as indicated by TLC, the residue was purified directly by flash chromatography on silica gel to afford aryl *N*-aminosulfonamides.

Subsequently, the Wu group revealed that potassium metabisulfite could also be used as an excellent equivalent of sulfur dioxide in the palladium-catalyzed aminosulfonylation (Scheme 3.18) [25]. This discovery is exciting and attractive since sulfites are more easily accessible and environment benign. Potassium metabisulfite was used as a replacement of DABSO in Willis's report, and was proved to be efficient in the palladium-catalyzed aminosulfonylation process. Both aryl iodides and aryl bromides were good partners in this transformation while aryl bromides gave lower yields. However, aryl chlorides were inert during the reaction process. It was found that the addition of HBF_4 was conducive to the reaction, suggesting the control of pH value was crucial in the reaction system.

General procedure for the palladium-catalyzed reaction of aryl halides, potassium metabisulfite, and hydrazines: Hydrazine (0.6 mmol) was added to a mixture of aryl iodide (0.5 mmol), potassium metabisulfite (0.5 mmol), $Pd(OAc)_2$ (5 mol%), $P^tBu_3.HBF_4$ (10 mol%), HBF_4 (20 mol%), and TBAB (0.75 mmol) in 1,4-dioxane (2.0 mL). The reaction was stirred at 80 °C for 12 h. After completion



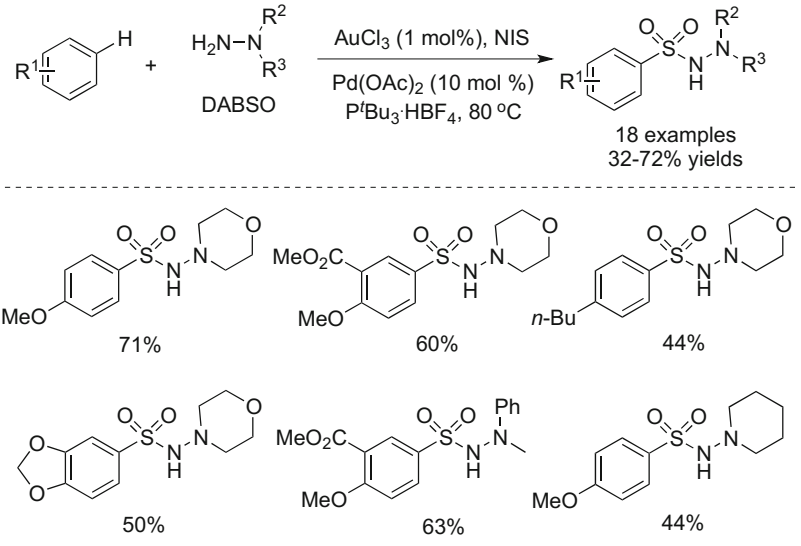
Scheme 3.18 Palladium-catalyzed reaction of aryl halides, potassium metabisulfite, and hydrazines

of the reaction as indicated by TLC, the residue was purified directly by flash chromatography on silica gel to afford aryl *N*-aminosulfonamides.

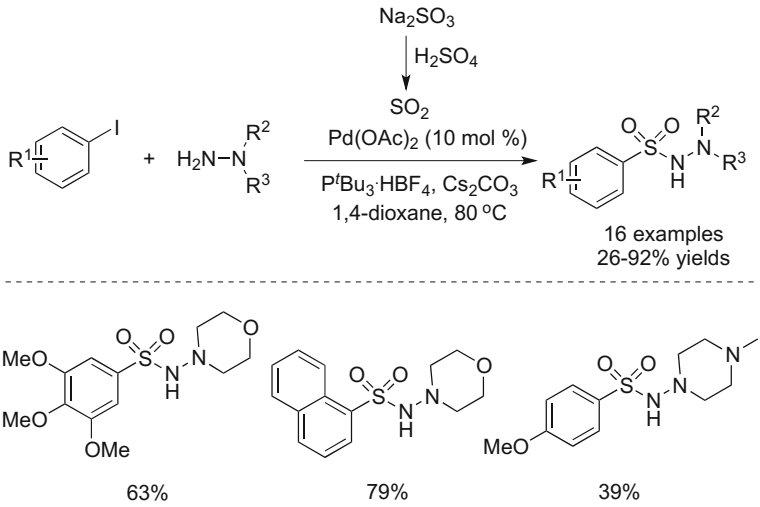
The palladium-catalyzed aminosulfonylation could also combine with a C–H functionalization process of arenes (Scheme 3.19) [26]. The arenes could be *in situ* converted to aryl iodides in the presence of gold(III) catalysts and NIS, and would next undergo the aminosulfonylation through coupling with DABSO and hydrazines. This one-pot, two-step process enabled the direct conversion of arenes to the corresponding *N*-aminosulfonamides. The employment of simple arenes as substrates was attractive and moderate yields could be obtained in most cases. Electron-rich arenes were favorable in this transformation, due to the distinct electronic effect of the iodization step.

General procedure for aminosulfonylation of arenes, sulfur dioxide, and hydrazines: Arene (0.5 mmol) was added to a mixture of NIS (0.5 mmol) and $AuCl_3$ (1 mol%) in DCE (1.0 mL). The reaction mixture was stirred at room temperature for 1 h. Then DABCO·$(SO_2)_2$ (1.5 equiv.), hydrazine (1.5 equiv.), Pd $(OAc)_2$ (10 mol%), P(^{t}-Bu)$_3$·HBF_4 (20 mol%), and 1,4-dioxane (1.0 mL) were added. The solution was stirred at 80 °C for 12 h. After completion of the reaction as indicated by TLC, the residue was purified directly by flash column chromatography on silica gel to afford aryl *N*-aminosulfonamides.

Further investigation found that the *ex situ* generated sulfur dioxide gas could also accomplish the palladium-catalyzed aminosulfonylation to deliver the desired *N*-aminosulfonamides (Scheme 3.19) [27]. The Wu group in Germany utilized a two-chamber reactor to introduce the sulfur dioxide gas. Sodium sulfite (Na_2SO_3) reacted with concentrated sulfuric acid (H_2SO_4) to produce sulfur dioxide in one



Scheme 3.19 Aminosulfonylation of arenes, sulfur dioxide, and hydrazines

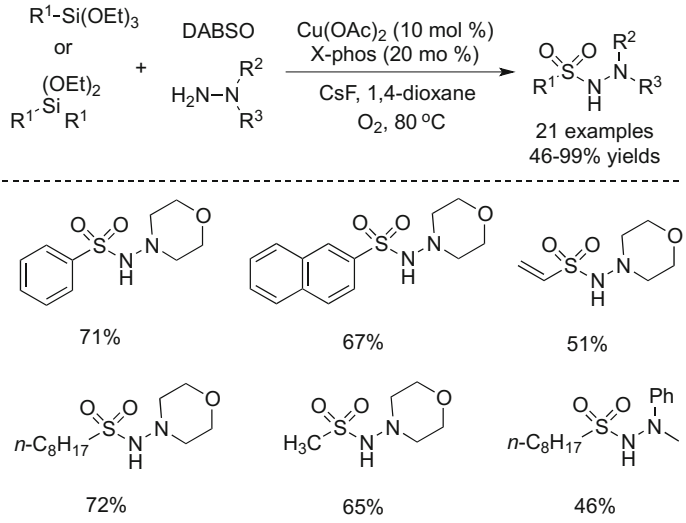


Scheme 3.20 Palladium-catalyzed aminosulfonylation of aryl iodides by using Na_2SO_3 as the SO_2 source

chamber. The *ex situ* generated sulfur dioxide gas was conducted to the reaction system in the other chamber via a poly(propene) pipe. Similar yields were obtained compared with the procedures using DABSO as the sulfur dioxide source.

General procedure for the palladium-catalyzed aminosulfonylation of aryl iodides by using Na_2SO_3 as the SO_2 source: Two Schlenk tubes (10 mL) were connected by a short plastic pipe through their side arms. Concentrated sulfuric acid (0.5 mL) was added into tube A and Na_2SO_3 (500 mg) was put in the funnel. The air in the funnel was excluded by argon flow. Then, the whole system was vacuumed through the Schlenk line, and the stopcock of Schlenk tube B was closed. Next, the aryl iodide (0.25 mmol), $Pd(OAc)_2$ (5.61 mg, 25 μmol), P(^{t}Bu)$_3$HBF$_4$(14.51 mg, 50 μmol), Cs_2CO_3 (171 mg, 0.525 mmol), and 1,4-dioxane (1 mL) were added under an atmosphere of argon. Then, 4-aminomorpholine (36 μL, 0. 375 mmol) was added, and the argon gas in tube B was carefully removed by the Schlenk line. Finally, the stopcocks of the funnel and Schlenk tube B were opened slowly, and the whole system was filled with SO_2. Schlenk tube B was immersed in an oil bath, and the contents were stirred at 80 °C for 16 h. After cooling to room temperature, the mixture was filtered through Celite and then purified by flash column chromatography to give the pure product.

Compared with the palladium catalysts, other metal catalysts were rarely used in the above aminosulfonylation processes. In 2014, Wang and co-workers revealed a copper-catalyzed aminosulfonylation of triethoxysilanes in the presence of DABSO and hydrazines (Scheme 3.21) [28]. This represents the first example of copper-catalyzed sulfur dioxide insertion reaction. It is noteworthy that both triethoxy(aryl) silanes and triethoxy(alkyl)silanes were compatible in this transformation, while the



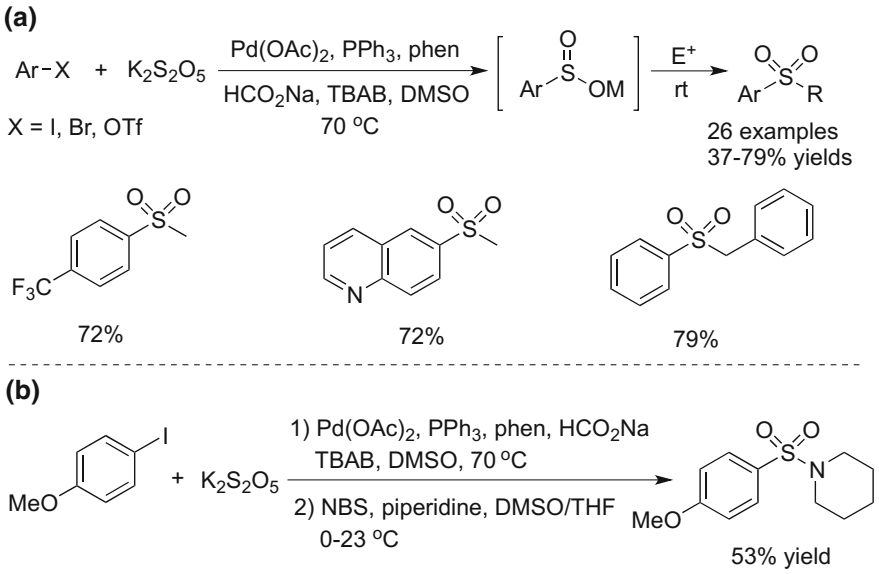
Scheme 3.21 A copper-catalyzed three-component reaction of triethoxysilanes, DABSO and hydrazines

alkyl groups were commonly not acceded in previous reports. Not only aryl *N*-aminosulfonamides but also alkyl *N*-aminosulfonamides could be synthesized during this procedure. In addition, application of diethoxydiarylsilanes also succeeded to yield the desired products.

General procedure for copper-catalyzed three-component reaction of triethoxysilanes, DABSO, and hydrazines: Organosilicon reagents (0.3 mmol) was added to a solution of DABCO·$(SO_2)_2$ (2.0 equiv.), copper acetate (10 mol%), X-Phos (20 mol%), CsF (2.0 equiv.) in 1,4-dioxane (1.0 mL). Then hydrazine (2.0 equiv.) and 1,4-dioxane (1.0 mL) were added. The mixture was stirred at 80 °C under O_2 atmosphere. After completion of reaction as indicated by TLC, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether, 1:2) to provide the product.

3.2.2 Synthesis of Sulfones

The palladium-catalyzed process has also been applied to synthesize a variety of sulfones. And sulfinates are considered as the key intermediates in most cases, similar to the nucleophilic addition processes of organometallic reagents to sulfur dioxide. In 2013, Shavnya and co-workers reported a palladium-catalyzed sulfination of aryl and heteroaryl halides with potassium metabisulfite (Scheme 3.22) [29]. The authors discovered that the sulfinates could be directly produced from aryl and heteroaryl halides and potassium metabisulfite in the presence of palladium



Scheme 3.22 Palladium-catalyzed sulfination of aryl and heteroaryl halides with potassium metabisulfite

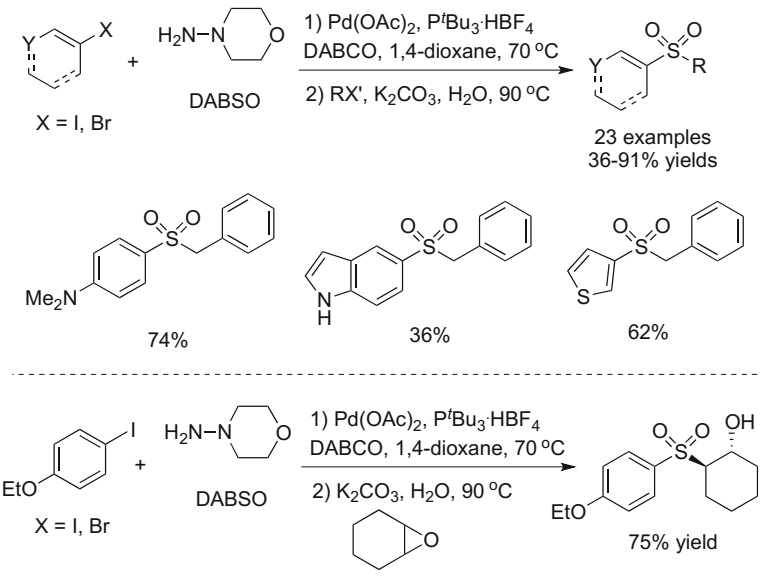
catalysts and sodium formate (HCO_2Na). Further reaction with electrophiles such as alkyl halides could lead to corresponding sulfones. A number of sulfones were obtained under the reaction conditions in moderate to good yields. Nitrogen-containing heterocycles were well tolerated in this transformation. Moreover, treatment of *N*-bromosuccinimide (NBS) and amines with the in situ generated sulfinates could lead to corresponding sulfonamides. Several examples for sulfonamide synthesis were revealed in the report, and the parallel synthesis of derivatives of the drug Viagra was accessible with this method.

General procedure for the palladium-catalyzed sulfination of aryl and heteroaryl halides with potassium metabisulfite: *General procedure (a) synthesis of (hetero)aryl methyl sulfones:* Step 1: A microwave vial equipped with a magnetic stir bar was charged with the starting aryl or heteroaryl halide or triflate (0.58 mmol), potassium metabisulfite (266 mg, 1.16 mmol, 2 equiv.), tetrabutylammonium bromide (210 mg, 0.640 mmol, 1.1 equiv.), sodium formate (89 mg, 1.3 mmol, 2.2 equiv.), palladium acetate (6.5 mg, 0.029 mmol, 5 mol%), triphenylphosphine (23 mg, 0.087 mmol, 15 mol%), 1,10-phenanthroline (16 mg, 0.087 mmol, 15 mol%), and DMSO (1.6 mL). The mixture was degassed by bubbling nitrogen gas under stirring for 10 min, stirred at 70 °C (external temperature) for 3 h and then cooled to room temperature. Step 2: Iodomethane (0.054 mL, 0.87 mmol, 1.5 equiv.) was added and the resulting mixture was stirred at room temperature for 18 h. The mixture was diluted with water (4 mL), extracted with EtOAc (2 × 3 mL), the combined organic extract was washed with brine,

dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column, eluting with a gradient from 15 to 50% of EtOAc in heptane to afford the desired sulfone product. *General procedure (b) synthesis of sulfonamides*: Step 1: A microwave vial equipped with a magnetic stir bar was charged with the starting aryl or heteroaryl halide (0.58 mmol), potassium metabisulfite (266 mg, 1.16 mmol, 2 equiv.), tetrabutylammonium bromide (210 mg, 0.640 mmol, 1.1 equiv.), sodium formate (89 mg, 1.3 mmol, 2.2 equiv.), palladium acetate (6.5 mg, 0.029 mmol, 5 mol%), triphenylphosphine (23 mg, 0.087 mmol, 15 mol%), 1,10-phenanthroline (16 mg, 0.087 mmol, 15 mol%), and DMSO (1.5 mL). The mixture was degassed by bubbling nitrogen gas under stirring for 10 min, the mixture was stirred at 70 °C (external temperature) for 2 h (for iodides) or 3 h (for bromides), and then cooled to room temperature. Step 2: A solution of amine (2.0 equiv.) in THF (3 mL) was added and the mixture was cooled to 0 °C (external temperature) with an ice bath. A solution of NBS (206 mg, 1.16 mmol, 2.0 equiv.) in THF (2.5 mL) was added dropwisely at this temperature and the reaction mixture was warmed to room temperature over 30 min. The mixture was diluted with brine (4 mL), water (2 mL), and extracted with EtOAc (5 mL); the organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column, eluting with a gradient from 10 to 40% of EtOAc in heptane to afford the desired sulfonamide product.

As *N,N′,N′*-trialkyl aminosulfonamides could be converted into sulfinates with the treatment of a suitable base, Willis and co-workers applied the palladium-catalyzed aminosulfonylation process to a one-pot, three-component reaction for sulfone synthesis (Scheme 3.23) [30]. The aminosulfonamides delivered under the palladium catalysis as they previously reported, could be transferred to the sulfinates, which would next combine *in situ* with electrophiles to give the corresponding sulfones. The electrophilic coupling partner could be a benzylic, allylic, or alkyl halide, as well as an electron-poor arene, or a cyclic epoxide. This one-pot, two-step process enabled the preparation of a variety of sulfones featuring various functional groups. The drawback was the requirement of a hydrazine as the additive.

General procedure for the synthesis of sulfones through palladium-catalyzed aminosulfonylation of aryl halides: An oven-dried tube was charged with tri-*tert*-butylphosphonium tetrafluoroborate (20 mol%), palladium(II) acetate (10 mol%) and the halogenated substrate (1 equiv.). Either bis(sulfur dioxide)-1,4-diazabicyclo [2.2.2]octane (DABSO) (1.1 equiv.) or (DABSO) (0.6 equiv.) and 1,4-diazabicyclo [2.2.2]octane (DABCO) (0.5 equiv.) were then added as specified. The solid reagents were weighed out in air. The tube was then evacuated and backfilled with N_2. The hydrazine (1.2 equiv.) and 1,4-dioxane (0.30 M) were added via microsyringe. The reaction mixture was stirred at 70 °C for 16 h. Either Method I or Method II was then followed as stated (*Method I*: K_2CO_3 (aq) (2.40 M, 2.5 equiv.) and the electrophile (2.5 equiv.) were added and the reaction mixture was stirred at 90 °C for the specified length of time. *Method II*: K_2CO_3 (aq) (2.40 M, 2.5 equiv.) and benzyl bromide (0.95 equiv.) were added and the

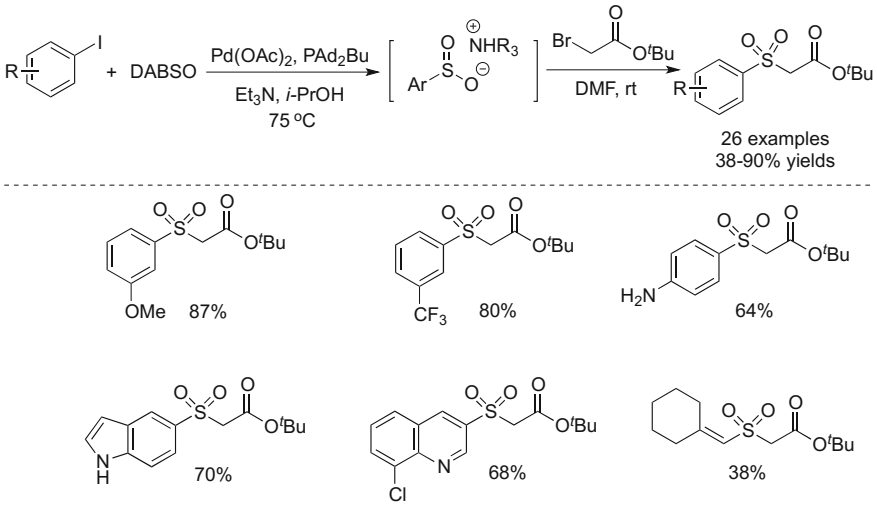


Scheme 3.23 Synthesis of sulfones through palladium-catalyzed aminosulfonylation of aryl halides

reaction mixture was stirred at 90 °C for 1 h. The second electrophile (2 equiv.) was then added and the reaction mixture stirred at 90 °C for 19 h. After cooling to room temperature, the suspension was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification via column chromatography yielded the corresponding sulfone.

Similar to the Shavnya's work, the Willis group reported a palladium-catalyzed sulfination of aryl halides with DABSO in the meantime (Scheme 3.24) [31]. A milder reaction condition was applied. Aryl and heteroaryl halides could be converted into the corresponding ammonium sulfinates with DABSO and trimethylamine in the presence of palladium catalysts. Isopropanol was used as both reductant and solvent in this transformation. The ammonium sulfinates were able to combine with electrophiles to give the corresponding sulfones. Other sulfone derivatives such as sulfonyl chlorides, and sulfonamides could also be synthesized via the ammonium sulfinate intermediates.

General procedure for synthesis of ammonium sulfinates from aryl halides and DABSO: A glass reaction tube was charged with DABSO (43 mg, 0.18 mmol), palladium(II) acetate (4 mg, 15 μmol), and CataCXium (8 mg, 23 μmol), sealed with a rubber septum and evacuated and filled with nitrogen four times. 1-Iodo-3,5-dimethylbenzene (44 μL, 0.30 mmol), anhydrous triethylamine (125 μL, 0.9 mmol) and anhydrous 2-propanol (1.5 mL) were added sequentially

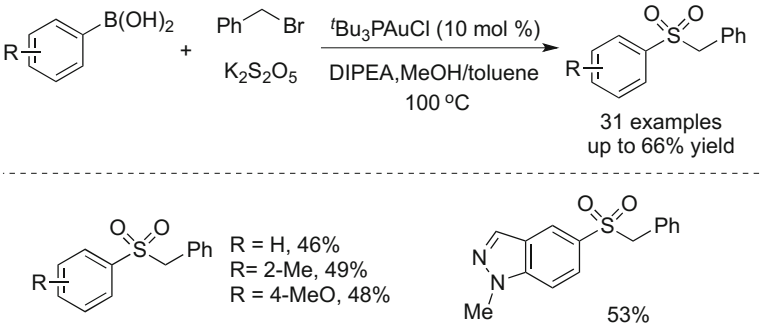


Scheme 3.24 Synthesis of ammonium sulfinates from aryl halides and DABSO

through the septum and the reaction mixture was stirred under positive pressure of nitrogen in a preheated oil bath at 75 °C for 16 h. After cooling to room temperature, a solution of *tert*-butyl bromoacetate (89 μL, 0.6 mmol) in anhydrous DMF (0.5 mL) was added dropwisely and the resultant solution was stirred at the same temperature for 3 h or until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was poured onto water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (5–20% Et_2O in petrol) afforded the sulfone.

The above transformations utilizing aryl halides were initiated by Pd(II) and extra or readily available reductants were usually required. Considering the change of valence states, application of other arylated reagents such as aryl boronic acids might provide a redox-neutral route to access sulfinates. In 2014, the Toste group reported a gold(I)-catalyzed sulfination of aryl boronic acids (Scheme 3.25) [32]. Potassium metabisulfite ($K_2S_2O_5$) was used as the source of sulfur dioxide and the multistep process was not necessary. This three-component reaction of arylboronic acids, $K_2S_2O_5$ and alkyl halides in the presence of gold catalyst and diisopropylethylamine (DIPEA) as base would directly deliver the desired sulfones. The in situ generated metal sulfinates could also be converted to sulfonamides with the treatment of *N*-chlorosuccinimide (NCS) and amines in a one-pot, three-step process. However, only moderate yields were obtained in most cases. A mechanism exploiting the reactivity of gold(I)–heteroatom bonds to generate sulfinates was proposed.

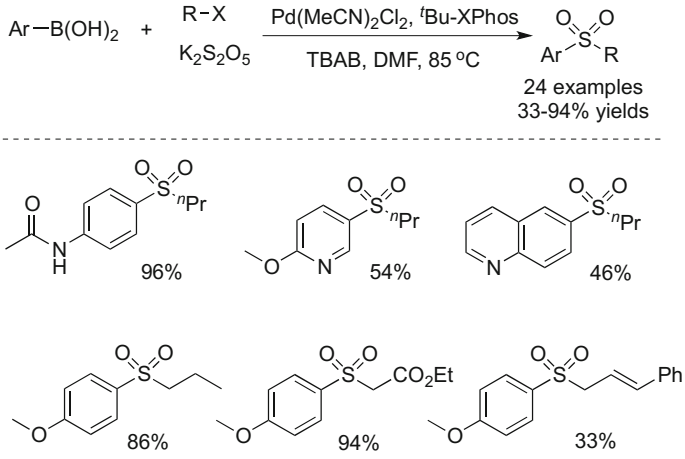
General procedure for the gold-catalyzed synthesis of sulfinate derivatives: A 2-dram vial with stir bar was charged with boronic acid (0.37 mmol), $K_2S_2O_5$ (167 mg, 0.74 mmol), and *t*-Bu_3PAuCl (16 mg, 0.037). The reagents were



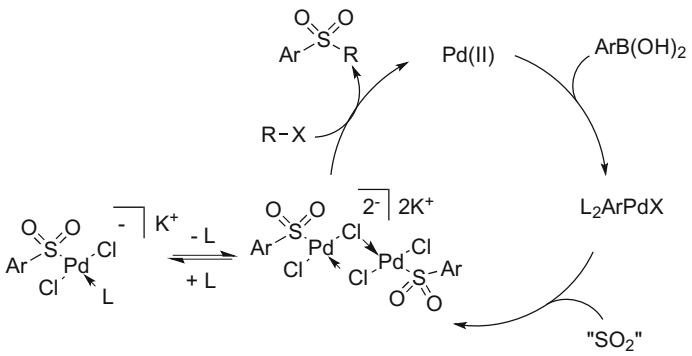
Scheme 3.25 Gold-catalyzed synthesis of sulfinate derivatives

suspended in 1:1 $PhCH_3$/MeOH (2 mL) and treated with DIPEA (128 μL, 0.74 mmol) and benzyl bromide (88 μL, 0.74 mmol). The reaction vessel was capped with a septum-lined cap and heated in an aluminum block at 100 °C for 18 h. The reaction mixture was cooled to room temperature and the volatile materials were removed on the rotary evaporator. The resultant solids were partitioned between EtOAc (30 mL) and water (30 mL) and treated with sat. aq. NH_4Cl (3 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The resultant crude product was purified by flash chromatography (0–60% EtOAc/heptanes gradient, 4 g silica gel) to yield the desired product.

Inspired by the Toste's work, Shavnya and co-workers subsequently developed a palladium-catalyzed sulfination of arylboronic acids with potassium metabisulfite ($K_2S_2O_5$) (Scheme 3.26) [33]. The transformation was similar to the previous report. It is noteworthy that higher yields and broader scope was achieved in this



Scheme 3.26 Palladium-catalyzed sulfination of aryl boronic acids for sulfone synthesis

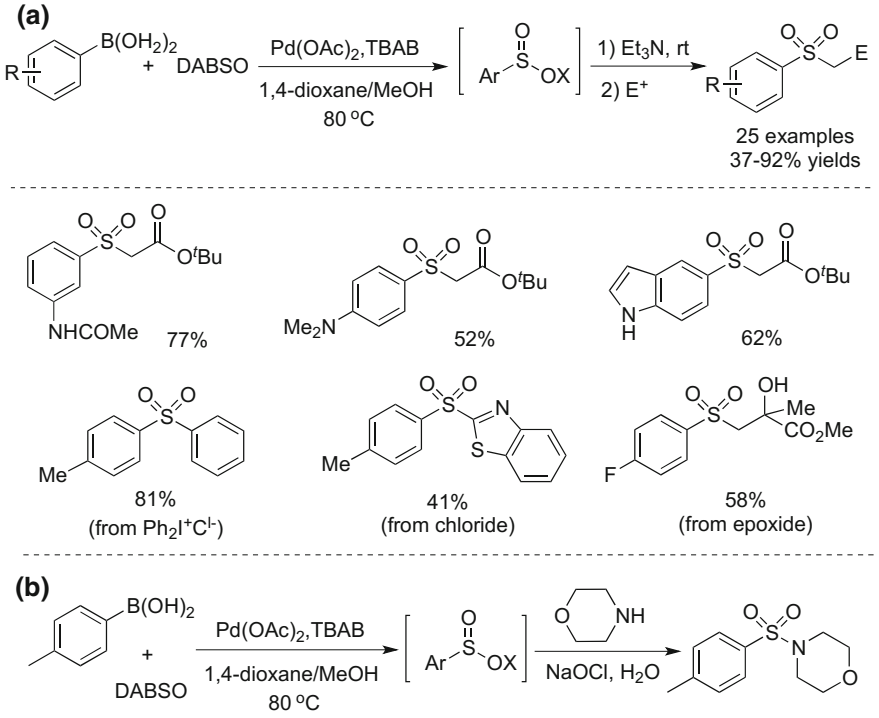


Scheme 3.27 A plausible mechanism for the palladium-catalyzed sulfination of aryl boronic acids

work. Both unactivated and activated alkyl halides were capable of affording the desired sulfone products in moderate to good yields. Treatment of stoichiometric palladium catalyst with boronic acid and $K_2S_2O_5$ led to a dimeric palladium sulfinate complex, which was isolated and characterized by X-ray diffraction analysis. Based on the experimental observations, a possible mechanism was proposed (Scheme 3.27). It was postulated that the reaction was initiated by the transmetallation of arylboronic acid and Pd(II) catalyst. Subsequent sulfur dioxide insertion would bring the dimeric palladium sulfinate complex, which would undergo alkylation with alkyl halides to give the desired sulfone products.

General procedure for the synthesis of sulfones through a palladium-catalyzed sulfination of arylboronic acids: A vial equipped with a magnetic stir bar was charged with the starting aryl or heteroaryl boronic acid (0.52 mmol), potassium metabisulfite (260 mg, 1.13 mmol, 2.2 equiv.), tetrabutylammonium bromide (184 mg, 0.567 mmol, 1.1 equiv.), dichlorobis(acetonitrile)palladium(II) (14 mg, 0.052 mmol, 10 mol%), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (23 mg, 0.052 mmol, 10 mol%), and DMF (1.5 mL). The mixture was degassed by bubbling nitrogen gas under stirring for 10 min, electrophile (RX) was added, the vial was capped, and the mixture was stirred at 85 °C (external temperature) using conventional heating for 22 h. The resulting mixture was cooled to room temperature, diluted with water (4 mL), extracted with EtOAc (2 × 3 mL); the combined organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on a silica gel column, eluting with a gradient from 10 to 40% of EtOAc in heptane to afford the desired sulfone product.

In the meantime, the Willis group reported a similar palladium(II)-catalyzed sulfination from boronic acids and DABSO (Scheme 3.28a) [34]. The sulfinate intermediates could be trapped by electrophiles to yield the desired sulfones under a one-step process or a two-step process. Ligand was free in this reaction. A variety of electrophilic partners were employed, with an emphasis on activated alkyl halides. Other C-based electrophiles such as aryl iodonium salts, electron-poor aryl



Scheme 3.28 Palladium-catalyzed sulfination from boronic acids and DABSO

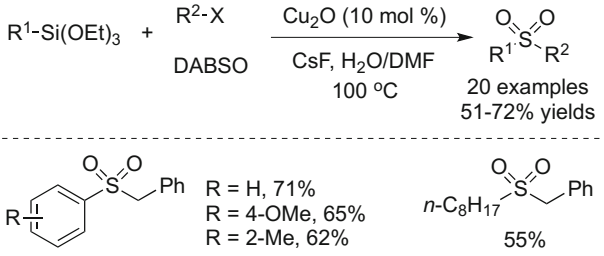
chlorides, or cyclic epoxides could also be utilized in this transformation to give the corresponding sulfones. Treatment of the sulfinate intermediates with *N*-electrophiles enabled the synthesis of sulfonamides in a one-pot, two-step process (Scheme 3.28b).

General procedure for the palladium-catalyzed sulfination from boronic acids and DABSO: General procedure (a) synthesis of sulfones: To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL), the resulting mixture was heated at 80 °C and stirred at this temperature for 30 min. The reaction was then allowed to cool to room temperature, Et_3N (70 μL, 0.50 mmol) was added and the mixture was stirred for 1 min. Electrophile was then added and the reaction was heated at 80 °C and stirred at this temperature for 30 min. The reaction mixture was allowed to cool to room temperature and filtered through a plug of silica before removing the solvent in vacuo. Purification by flash column chromatography (petrol/Et_2O 3:2) afforded the titled sulfone. *General procedure (b) synthesis of sulfonamides*: To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL), the resulting mixture was heated at 80 °C and stirred at this temperature

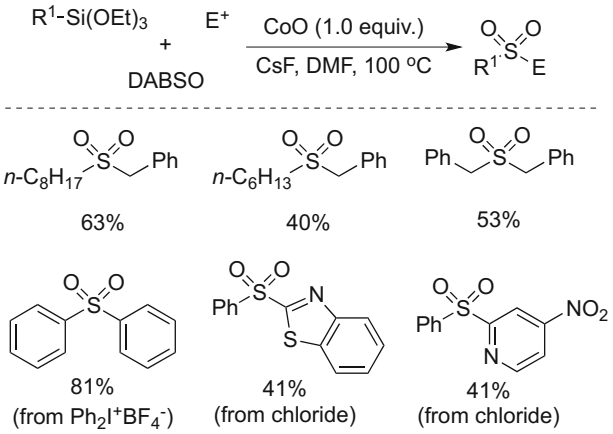
for 30 min. The reaction was then allowed to cool to room temperature, Et_3N (70 μL, 0.50 mmol) was added and the mixture was stirred for 1 min. Following this, the solvents were removed in vacuo and water (1.5 mL) and amines (1.25 mmol) were added. NaOCl (14.5% aqueous solution, 320 μL, 0.75 mmol) was added to the mixture at 0 °C and the reaction was allowed to warm to room temperature and stirred at this temperature for 16 h. NaS_2O_3 (aq) (10 mL) was added and the mixture was stirred for a further 20 min. The aqueous mixture was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were subsequently washed with 1 M HCl (aq) (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (petrol/Et_2O 1:1) afforded the titled sulfonamide.

A copper(I)-catalyzed three-component reaction of triethoxysilanes, DABCO·$(SO_2)_2$, and alkyl halides was revealed by the Wu group in Fudan almost in the meantime (Scheme 3.29) [35]. This transformation provided an alternative approach for sulfone synthesis under ligand-free conditions. Copper(I) oxide was found to be the best copper catalyst and enabled the efficient insertion of sulfur dioxide. A broad range of sulfones were synthesized applying various triethoxysilanes and alkyl halides. A possible mechanism involved with the sulfinate intermediates was proposed, supported by DFT theoretical calculations. The same group subsequently discovered that the cobalt salts could also promote the sulfination process (Scheme 3.30) [36]. This represents the first application of cobalt salts in sulfur dioxide insertion reactions. However, the cobalt catalyst was not efficient enough and a stoichiometric amount of cobalt salts was required. Electrophiles including activated and unactivated alkyl halides, electron-poor aryl chlorides and aryl iodonium salts were all compatible in this transformation. In most cases, only moderate yields could be obtained. Despite of these limitations, the utilization of earth-abundant and non-precious metal salts in the insertion of sulfur dioxide is attractive and still remained to be widely explored. This process opened a new window to these adventures.

General procedure for the copper(I)-catalyzed sulfination from triethoxysilanes and DABSO for sulfone synthesis: Triethoxysilanes (0.3 mmol) and alkyl halides (0.6 mmol) were added to a solution of Cu_2O (0.03 mmol), CsF (0.6 mmol), and



Scheme 3.29 Copper(I)-catalyzed sulfination from triethoxysilanes and DABSO for sulfone synthesis

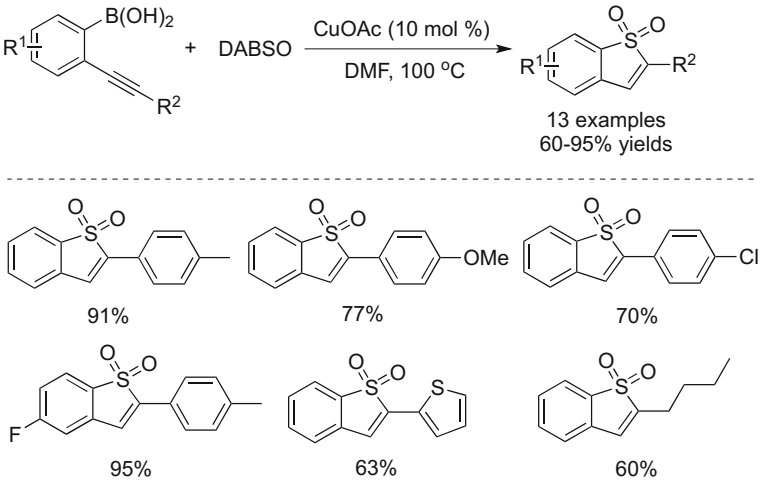


Scheme 3.30 Cobalt(I)-promoted sulfination from triethoxysilanes and DABSO for sulfone synthesis

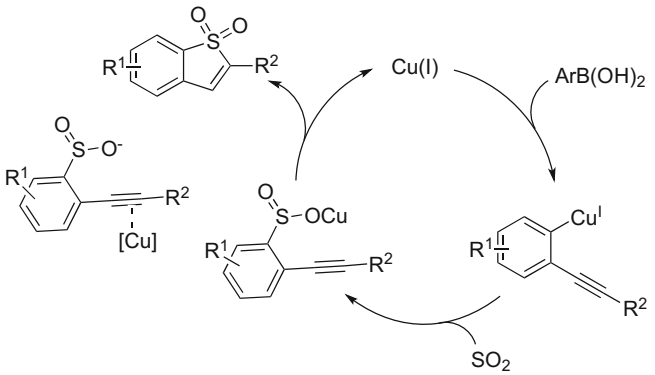
DABCO·$(SO_2)_2$ (0.3 mmol) in H_2O/DMF (0.1/2.0 mL). The mixture was stirred at 100 °C for 10–15 h. After completion of reaction as indicated by TLC, the mixture was extracted with ethyl acetate. The combined organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:6) to give the desired product.

General procedure for the cobalt(I)-promoted sulfination from triethoxysilanes and DABSO for sulfone synthesis: To a test tube was added CoO (0.3 mmol), CsF (0.6 mmol), and DABCO·$(SO_2)_2$ (0.3 mmol). The tube was evacuated and back filled with N_2 three times. DMF (2.0 mL) was added through a syringe, followed by the addition of triethoxysilane (0.3 mmol) and electrophile (0.6 mmol) (the electrophiles should be added previously if they are solids). The mixture was stirred at 100 °C for 10-15 h. After completion of reaction as indicated by TLC, The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:6) to give the desired product.

Further investigations revealed that the copper catalyst was also efficient for the sulfination of boronic acids. The copper-catalyzed sulfination combining with intramolecular cyclization was reported by the Wu group in 2016 (Scheme 3.31) [37]. The copper(I)-catalyzed insertion of sulfur dioxide into (2-alkynylaryl)boronic acids would afford the desired benzo[*b*]thiophene 1,1-dioxides. The reaction proceeded smoothly in the presence of copper catalysts in DMF at 100 °C without requirement of ligands. A number of benzo[*b*]thiophene 1,1-dioxides were obtained in good to excellent yields. This transformation was highly efficient and atom economical and provided a reliable route to the useful benzo[*b*]thiophene 1,1-dioxide derivatives. A plausible mechanism was proposed (Scheme 3.32). The



Scheme 3.31 Copper(I)-catalyzed sulfonylation of (2-alkynylaryl)boronic acids with DABSO



Scheme 3.32 A plausible mechanism of the copper(I)-catalyzed sulfonylation of (2-alkynylaryl) boronic acids with DABSO

initial transmetallation of (2-alkynylaryl)boronic acids with the copper catalyst would result in the copper species intermediates. Subsequent insertion of sulfur dioxide would lead to the sulfinates, which could next undergo the intramolecular 5-*endo* cyclization via the activation of the triple bonds by the copper catalyst to give the desired benzo[*b*]thiophene 1,1-dioxides.

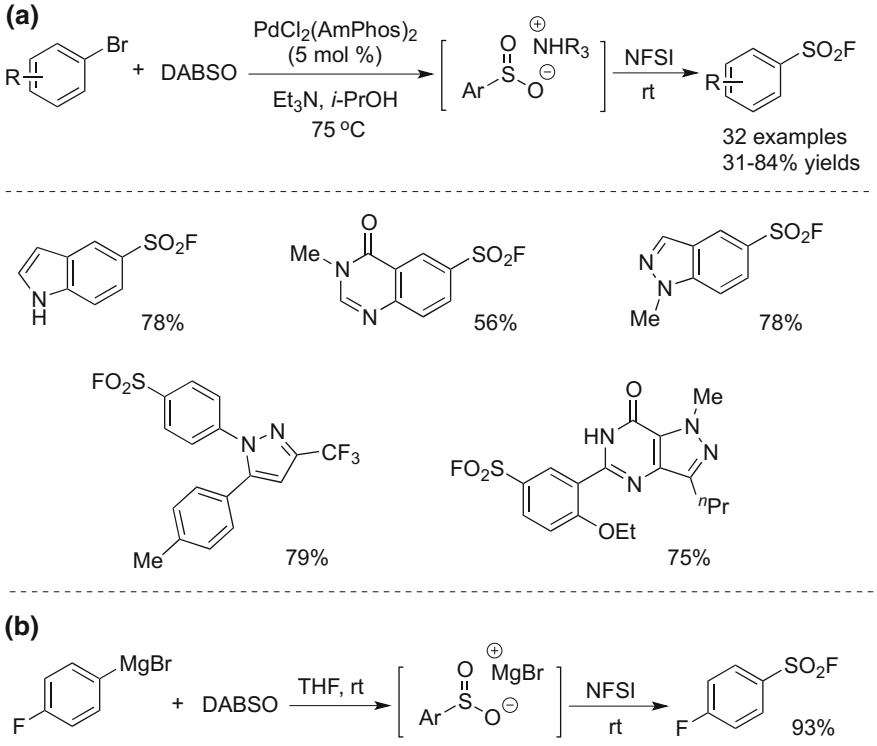
General procedure for the copper(I)-catalyzed sulfonylation of (2-alkynylaryl) boronic acids with DABSO: Copper (I) acetate (10 mol%) was added to a solution of (2-alkynyaryl)boronic acid (0.2 mmol) and DABCO·$(SO_2)_2$ (0.4 mmol) in DMF (2.0 ml) under N_2. The mixture was stirred at 100 °C for 10–15 h. After completion of reaction as indicated by TLC, The mixture was poured into water and extracted with

ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EtOAc/*n*-hexane) to give the desired product.

3.2.3 Synthesis of Sulfonyl Fluorides

Recently, the Willis group applied their previously established palladium-catalyzed sulfination of aryl bromides for the synthesis of biologically active sulfonyl fluorides (Scheme 3.33a) [38]. They described a one-pot, three-component reaction of aryl bromides, DABSO and the electrophilic fluorine source of NFSI to afford sulfonyl fluorides. As similar as the previous procedures, the sulfinate intermediates were produced through the palladium-catalyzed sulfination of aryl bromides in the presence of DABSO, and could *in situ* react with the electrophilic fluorine source of NFSI to give the desired sulfonyl fluorides. A variety of aryl and heteroaryl bromides featuring various functional groups were employed, leading to the sulfonyl fluorides in moderate to good yields. Several active pharmaceutical ingredients and their precursors were successfully synthesized through this transformation. Two peptide-derived sulfonyl fluorides were also constructed successfully. Additionally, the metal sulfinates generated from Grignard reagents and DABSO could also accomplish this fluorination process, giving rise to the sulfonyl fluorides in relative high yields (Scheme 3.33b).

General procedure for the palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides: General procedure (a) (from aryl bromides): A glass reaction tube was charged with DABSO (58 mg, 0.24 mmol, 0.6 equiv.), $PdCl_2(AmPhos)_2$ (14.2 mg, 0.020 mmol, 0.05 equiv.) and 4-bromobiphenyl (93 mg, 0.40 mmol, 1.0 equiv.), sealed with a rubber septum and evacuated and filled with N_2 four times. Anhydrous isopropanol (1.5 mL) and anhydrous triethylamine (167 μL, 1.2 mmol, 3.0 equiv.) were added sequentially through the septum and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminum heating block at 75 °C for 24 h. After cooling to room temperature, NFSI (189 mg, 0.6 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 3 h until completion. The reaction mixture was concentrated in vacuo, then dissolved in EtOAc and filtered through Celite. The filtrate was washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide the crude product, which was purified by column chromatography on silica (20% CH_2Cl_2 in pet. ether) to afford 4-phenylbenzenesulfonyl fluoride as a white crystalline solid. *General procedure (b) (from heteroaromatic bromides)*: A 8 mL microwave vial was charged with DABSO (96 mg, 0.4 mmol), $PdCl_2(AmPhos)_2$ (14.2 mg, 0.020 mmol) and 3-bromo-6-methoxypyridine (89 mg, 0.40 mmol). A solution of *N,N*-dicylclohexylmethylamine (257 μL, 1.2 mmol) in anhydrous isopropanol (1.6 mL) was added, the vial was sealed with a Teflon cap, sparged for 5 min with N_2 and subject to microwave conditions at 110 °C for 1 h. After cooling to room temperature, NFSI (189 mg, 0.6 mmol) was added and the reaction mixture was stirred for 2 h until



Scheme 3.33 Palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides

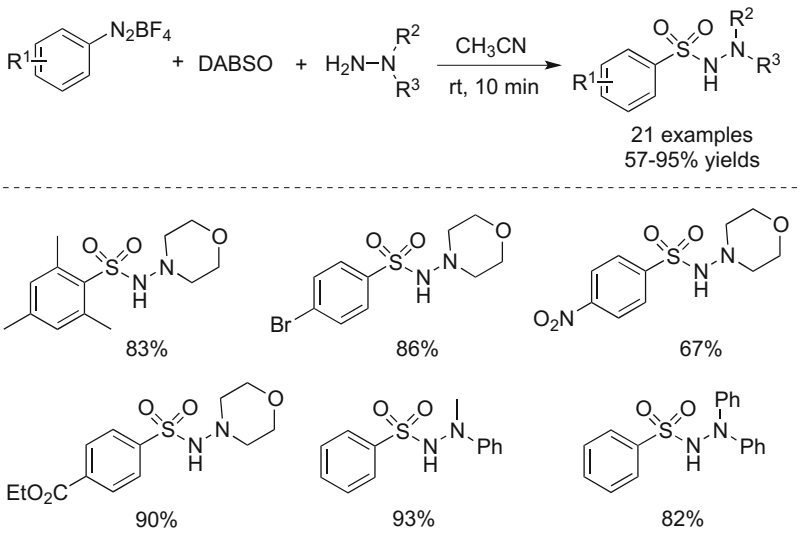
completion. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to produce the crude product, which was purified by column chromatography on silica (0–30% EtOAc in heptane) to provide 6-methoxypyridine-3-sulfonyl fluoride as a white solid. *General procedure (c) (from Grignard reagents)*: DABSO (240 mg, 1.0 mmol, 0.5 equiv.) was suspended in anhydrous THF (4 mL) and the suspension was purged with N_2 for 3 min. 4-Fluorophenylmagnesium bromide solution (1.84 mL, 2.0 mmol, 1.0 equiv., 0.92 M in THF) was added dropwisely and the mixture was stirred at room temperature for 45 min. The solution was cooled to 0 °C, then NFSI (946 mg, 3.0 mmol, 1.5 equiv.) was added portionwisely at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The mixture was quenched with sat. aq. NH_4Cl and partitioned between EtOAc and brine, washed with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to produce the crude product, which was purified by column chromatography on silica (10% CH_2Cl_2 in pet. ether) to provide 4-fluorobenzenesulfonyl fluoride as a colorless oil.

3.3 Free Radical Reactions

The radical chemistry has recently flourished, especially in the field of visible-light-induced photoredox catalysis [39]. Radical-based insertion of sulfur dioxide is destined to be an attractive and promising strategy for the construction of sulfonyl-containing compounds. Mild conditions, fast conversion, and good reactivity can be expected via the radical process. Actually, the research in radical-based insertion of sulfur dioxide emerged decades of years ago [40]. However, only a dearth of methods has been developed and the limited examples mainly focused on the Sandmeyer-type reaction for sulfonyl chloride synthesis. Moreover, these transformations require the use of sulfur dioxide gas and have seldom been utilized in modern organic synthesis. This type of reactions will be discussed in detail in Sect. 3.3.3.

3.3.1 Synthesis of Sulfonamides

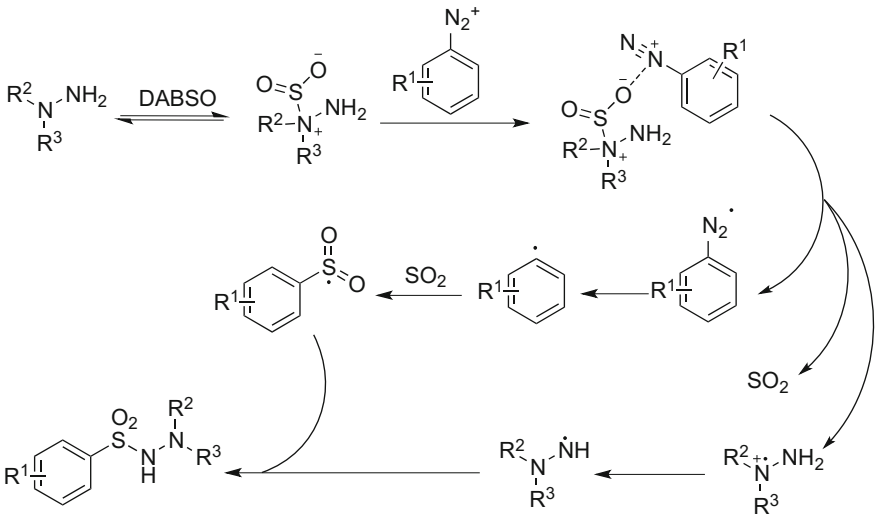
A significant breakthrough was contributed by the Wu group from Fudan in 2014. Inspired by the palladium-catalyzed aminosulfonylation established by the Willis group, the Wu group discovered a metal-free coupling of aryldiazonium tetrafluoroborates, the sulfur dioxide surrogate of DABSO and hydrazines for the generation of *N*-aminosulfonamides (Scheme 3.34) [41]. This was pioneered from a serendipitous result achieved in a control experiment in the absence of a palladium



Scheme 3.34 Metal-free coupling of aryldiazonium tetrafluoroborates, DABSO and hydrazines

catalyst. The reaction took place under extremely mild conditions and accomplished in 10 minutes. This highly efficient process enabled a wide range of aryldiazonium tetrafluoroborates to be converted into *N*-aminosulfonamides in the presence of DABSO and hydrazines. A broad range of functional groups including ethers, esters, halo, amino, hydroxyl, and nitro groups were compatible in this transformation, leading to the desired *N*-aminosulfonamides in good to excellent yields. Based on the experimental observations and the DFT computational studies, the authors proposed a plausible mechanism (Scheme 3.35). They supposed that the hydrazine-SO_2 complex generated from the hydrazines and DABSO would combine with the arydiazonium cation through electrostatic interaction. Subsequent single electron transfer and release of N_2 would lead to the aryl radicals, SO_2 and hydrazine radical cations. The aryl sulfonyl radicals were formed via the attack of aryl radicals to SO_2, and the hydrazine radicals could be formed via the deprotonation of hydrazine radical cations. Final combination of aryl sulfonyl radicals and hydrazine radicals would give rise to the desired products. In this proposed mechanism, the hydrazine was considered to be involved in the generation of aryl radicals and initiated the reaction. This might explain the restriction of the substrate scope to hydrazines.

General procedure for the metal-free coupling of aryldiazonium tetrafluoroborates, DABSO, and hydrazines: Aryldiazonium tetrafluoroborate (0.30 mmol) in CH_3CN (1.0 mL) was added dropwisely to a solution of DABCO·$(SO_2)_2$ (0.18 mmol) and hydrazine (0.36 mmol) in CH_3CN (3.0 mL) under N_2 in 10 min. The mixture was stirred at room temperature for another 10 min. The solvent was



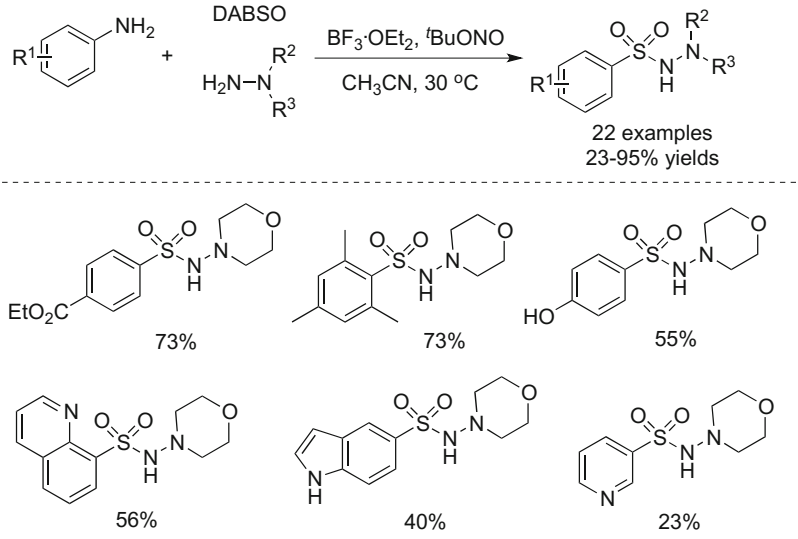
Scheme 3.35 A plausible mechanism of the metal-free coupling of aryldiazonium tetrafluoroborates, DABSO and hydrazines

evaporated and the residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:2) to give the desired product.

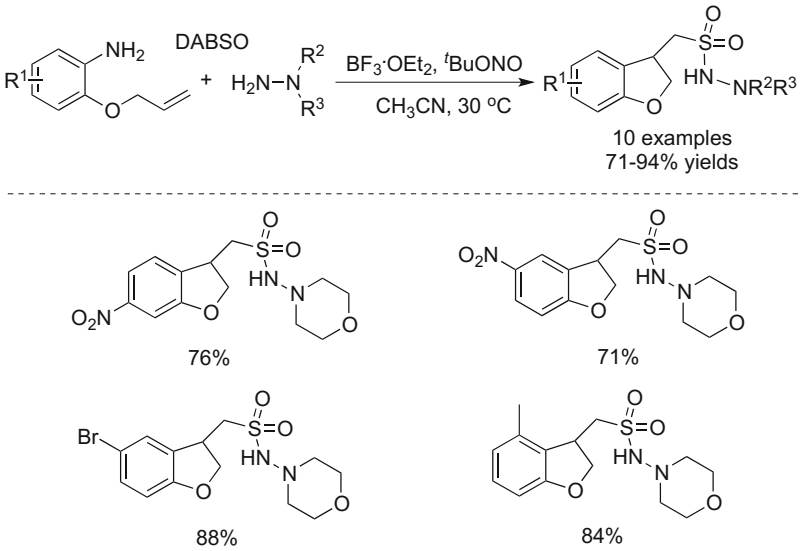
The *in situ* diazotization allowed the direct use of aromatic amines in the insertion reaction of sulfur dioxide. The same group reported a coupling reaction of aryl and heteroaryl amines, DABSO, and hydrazines to generate *N*-aminosulfonamides (Scheme 3.36) [42]. The aromatic amines could be converted to the corresponding aryldiazonium salts with the treatment of *t*-BuONO in the presence of $BF_3{\cdot}Et_2O$. The in situ generated aryldiazonium salts would accomplish the aminosulfonylation process with DABSO and hydrazines, delivering the corresponding *N*-aminosulfonamides in moderate to excellent yields. A broad reaction scope was observed and heteroaryl amines could also undergo this transformation to give the desired products. This one-pot, two-step reaction is attractive since it avoids the use of unstable aryldiazonium salts and the starting materiel amines are simple and easily available.

General procedure for the aminosulfonylation of aromatic amines, sulfur dioxide and hydrazines: ^{t}BuONO (0.54 mmol) was added to a solution of aniline (0.45 mmol) and $BF_3{\cdot}OEt_2$ (0.54 mmol) in CH_3CN (1.0 mL) dropwisely at 0 °C. After 5 min, the solution was slowly added into a mixture of $DABCO{\cdot}(SO_2)_2$ (0.18 mmol) and hydrazine (0.30 mmol) in CH_3CN (3.0 mL) at 30 °C The mixture was stirred at 30 °C for another 10 min. The solvent was then evaporated and the residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:2) to give the desired product.

The Wu group subsequently revealed a three-component coupling reaction of 2-(allyloxy)anilines, DABSO and hydrazines [43] (Scheme 3.37). In this report,



Scheme 3.36 Aminosulfonylation of aromatic amines, sulfur dioxide and hydrazines

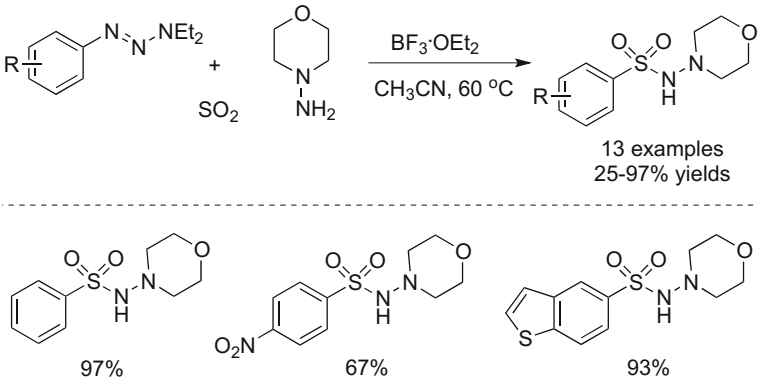


Scheme 3.37 A three-component coupling reaction of 2-(allyloxy)anilines, DABSO and hydrazines

2-(allyloxy)aryldiazonium salts were initially applied and the corresponding 1-(2,3-dihydrobenzofuran-3-yl)-methanesulfonohydrazides could be delivered in relative high yields. They further discovered that the in situ diazotization could also be applied in this process. The 2-(allyloxy)aryldiazonium salts generated in situ from 2-(allyloxy)anilines with *t*-BuONO in the presence of $BF_3{\cdot}Et_2O$ could undergo the radical aminosulfonylation and intramolecular 5-*exo*-cyclization, leading to the desired 1-(2,3-dihydrobenzofuran-3-yl)-methanesulfonohydrazides. This process enabled the formation of a heterocycle benzofuran and sulfonamide in the meantime.

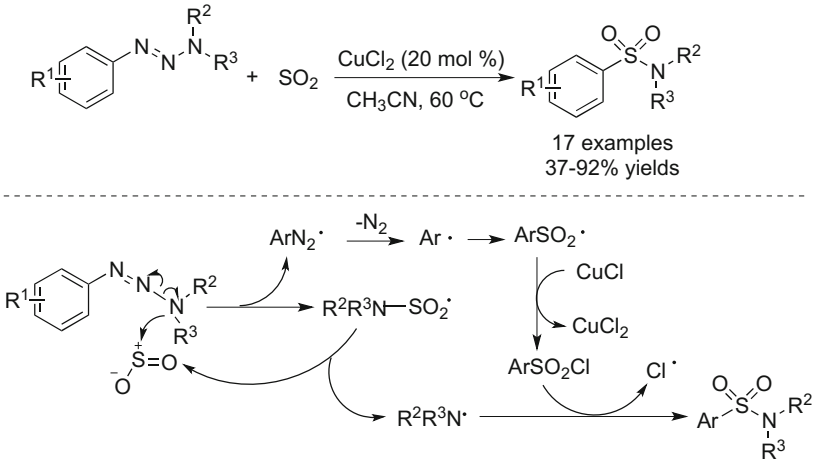
General procedure for the three-component coupling reaction of 2-(allyloxy) anilines, DABSO, and hydrazines: Allyloxyaryldiazonium tetrafluoroborate (0.20 mmol) in CH_3CN (1.0 mL) was added dropwisely to a solution of DABCO·$(SO_2)_2$ (0.12 mmol) and hydrazine (0.24 mmol) in CH_3CN (3.0 mmol) under N_2 in 10 min. The mixture was stirred at room temperature for another 10 min. Then the solvent was evaporated and the residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:2) to give the desired product.

Using sulfur dioxide gas, the Wu group from Germany developed a similar route to generate *N*-aminosulfonamides from trizazenes and hydrazines (Scheme 3.38) [44]. This three-component reaction of trizazenes, sulfur dioxide, and hydrazines would lead to the *N*-aminosulfonamides in good to excellent yields in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$. The authors considered that this route might be more practical since the trizazenes were usually stable than the equivalent



Scheme 3.38 A three-component reaction of trizazenes, sulfur dioxide and hydrazines

diazonium salts. A mechanism involved with a sulfonyl radical and a hydrazine radical was also proposed. In the meantime, they discovered that treatment of trizazenes with sulfur dioxide in the presence of copper catalysts would deliver the corresponding sulfonamides (Scheme 3.39). A variety of sulfonamides could be accessed in good to excellent yields under the reaction conditions. A possible mechanism was proposed and presented in Scheme 3.38. The trizazenes would react with sulfur dioxide to generate the diazo aryl and dialkylamino sulfonyl radicals via the homolysis of N–N bonds. The diazo aryl radicals would release a molecule of nitrogen and further attack the sulfur dioxide to give the sulfonyl radicals, which could be further converted into sulfonyl chlorides catalyzed by CuCl. The dialkylamino sulfonyl radicals would produce the amino radicals via a



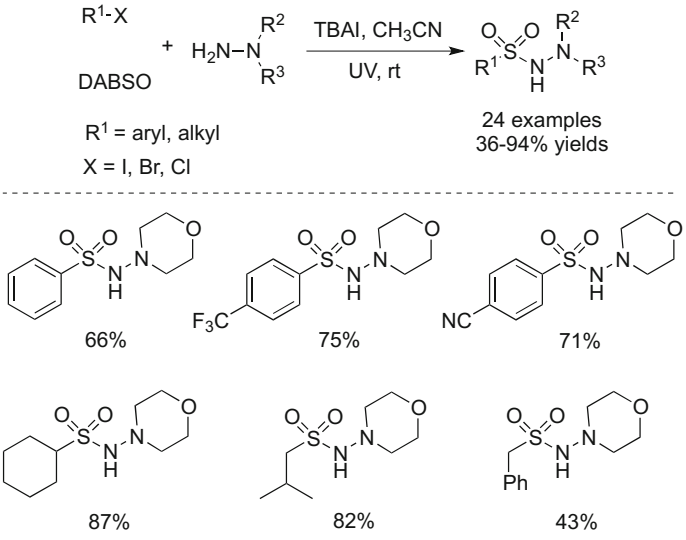
Scheme 3.39 Synthesis of sulfonamides from trizazenes and sulfur dioxide

decomposition process. The reaction of amino radicals with sulfonyl chlorides would finally give rise to the desired sulfonamides.

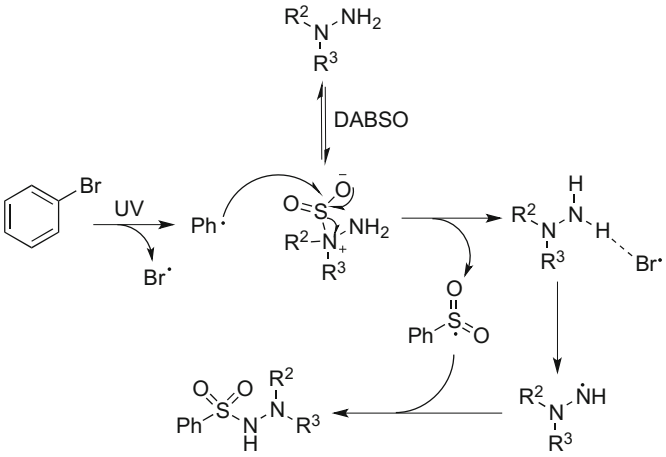
General procedure for the three-component reaction of trizazenes, sulfur dioxide, and hydrazines: To a dried Schlenk tube (10 mL), triazene substrate (0.2 mmol) was added under Ar, then 1.0 mL of SO_2 solution in MeCN was added. After which the hydrazine (0.3 mmol) and $BF_3{\cdot}OEt_2$ (0.3 mmol) were added through syringe. The mixture was stirring at 60 °C for the indicated time. Cooled to room temperature and column chromatography gave the desired products.

General procedure for the synthesis of sulfonamides from trizazenes and sulfur dioxide: To a dried Schlenk tube (10 mL), triazene substrate (0.2 mmol) and $CuCl_2$ (0.02 mmol) was added under Ar, then 1.0 mL of SO_2 solution in MeCN was added. The mixture was stirring at 70 °C for 18 h. Cooled to room temperature and column chromatography gave the desired products.

Inspired by the photo-induced radical processes, the Wu group from Fudan developed a three-component reaction of aryl/alkyl halides, DABSO, and hydrazines under ultraviolet irradiation, delivering the corresponding *N*-amino-sulfonamides in moderate to good yields (Scheme 3.40) [45]. The reaction condition was extremely mild and no metals or photo-redox catalysts were required. A wide range of *N*-aminosulfonamides featuring various functional groups could be afforded under the reaction conditions. Aryl iodides, bromides, and chlorides were all good reactants in this transformation. More importantly, alkyl halides were also good coupling partners in this sulfur dioxide insertion reaction. The authors proposed a possible mechanism involving a radical process (Scheme 3.41). They supposed that the hydrazine-SO_2 complex would be initially generated. In the



Scheme 3.40 A three-component reaction of aryl/alkyl halides, DABSO and hydrazines under ultraviolet irradiation

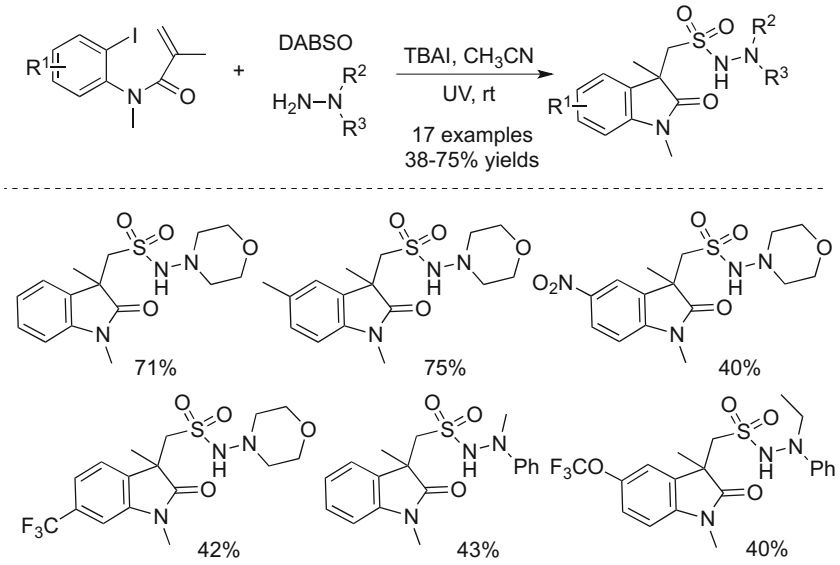


Scheme 3.41 A plausible mechanism for the three-component reaction of aryl/alkyl halides, DABSO and hydrazines under ultraviolet irradiation

meantime, treatment of aryl halide with ultraviolet irradiation could produce the aryl radical and halo radical. The attack of aryl radical to the hydrazine-SO_2 complex would occur to give the sulfonyl radical and release the hydrazine. The halo radical would integrate with the hydrazine and led to the hydrazine radical. The combination of the sulfonyl radical and the hydrazine radical would finally give rise to the corresponding product. This proposed mechanism was supported by the DFT theoretical calculations as well.

General procedure for the three-component reaction of aryl/alkyl halides, DABSO, and hydrazines under ultraviolet irradiation: In a quartz tube, TBAI (112 mg, 0.3 mmol) and DABCO·$(SO_2)_2$ (38.4 mg, 0.16 mmol) were added. The flask was evacuated and backfilled with N_2 three times, before a solution of aryl/alkyl halide (0.2 mmol) and hydrazine (0.3 mmol) in CH_3CN (4.0 mL) was added. The mixture, placed around the mercury lamp (purchased from Yuming, Shanghai) with a distance of 10 cm, was stirred under UV irradiation (0.67 W cm^{-1}) for 10 h at room temperature. After completion of reaction as indicated by TLC, the mixture was directly purified by flash column chromatography (EtOAc/Petroleum, 1:2) to give the desired product.

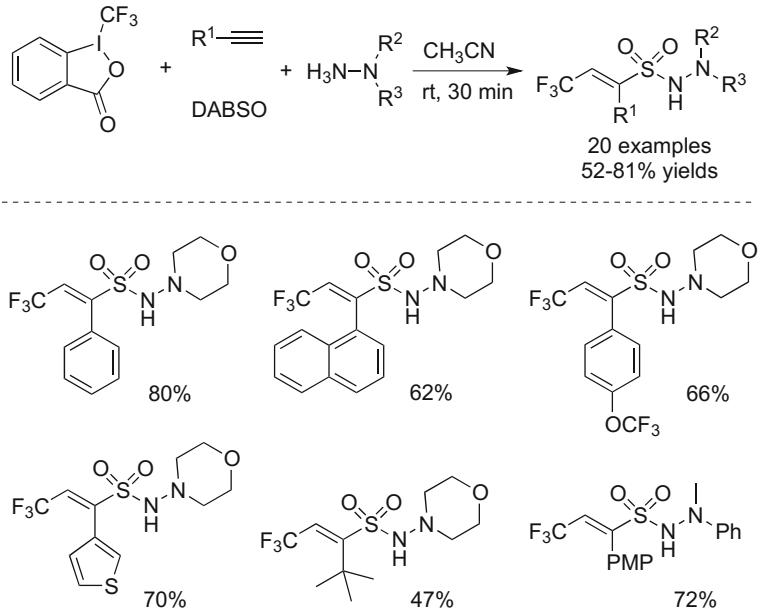
Subsequently, the same group extended the photo-induced aminosulfonylation to the synthesis of (2-oxoindolin-3-yl)methanesulfonohydrazides (Scheme 3.42) [46]. The three-component reaction of *N*-(2-iodoaryl)acrylamides, DABSO, and hydrazines would lead to the formation of the oxindole core and sulfonyl hydrazines at the same time. In this process, the aryl radical generated from *N*-(2-iodoaryl)acrylamides under ultraviolet irradiation would undergo the 5-*exo* radical cyclization to produce an alkyl radical intermediate, which would further accomplish the aminiosulonylation to yield the desired (2-oxoindolin-3-yl) methanesulfonohydrazides.



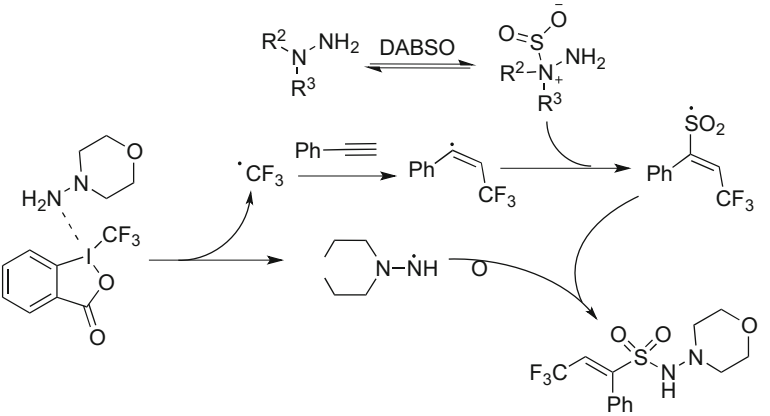
Scheme 3.42 A three-component reaction of *N*-(2-iodoaryl)acrylamides, DABSO and hydrazines

General procedure for the three-component reaction of N-(2-iodoaryl)acrylamides, DABSO, and hydrazines: In a quartz tube, TBAI (0.3 mmol) and hydrazine (0.3 mmol) were added to a mixture of *N*-(2-iodoary)acrylamide (0.2 mmol) and DABCO·$(SO_2)_2$ (0.16 mmol) in MeCN (4 mL) under N_2. The mixture, placed around the mercury lamp (purchased from Yuming, Shanghai) with a distance of 10 cm, was stirred under UV irradiation (0.67 W cm^{-1}) for 10 h at room temperature. After completion of reaction as indicated by TLC, the mixture was directly purified by flash column chromatography to give the desired product.

A catalyst-free four-component reaction of Togni's reagent, alkynes, DABSO, and hydrazines was discovered by the Wu group (Scheme 3.43) [47]. The vicinal difunctionalization of alkynes led to the generation of (*E*)-3,3,3-trifluoroprop-1-ene-1-sulfonohydrazides. This transformation took place smoothly under room temperature without the requirement of catalysts or additives. This multicomponent reaction combined with the trifluoromethylation of alkynes and insertion of sulfur dioxide with excellent stereoselectivity and regioselectivity. A wide range of (*E*)-3,3,3-trifluoroprop-1-ene-1-sulfonohydrazides was synthesized in moderate to good yields. The introduction of the trifluoromethyl group and the sulfonyl group into the small molecule in the meantime was efficient and attractive. A proposed mechanism was presented in Scheme 3.44. Initially, the reaction between hydrazine and the Togni's reagent would produce the trifluoromethyl radical and the hydrazine radical. The trifluoromethyl radical subsequently attacked the alkyne to give rise to the alkenyl radical, which would further react with the hydrazine-SO_2 complex to generate the sulfonyl radical. The sulfonyl radical would combine with the hydrazine radical to deliver the final product.



Scheme 3.43 A catalyst-free four-component reaction of Togni's reagent, alkynes, DABSO and hydrazines

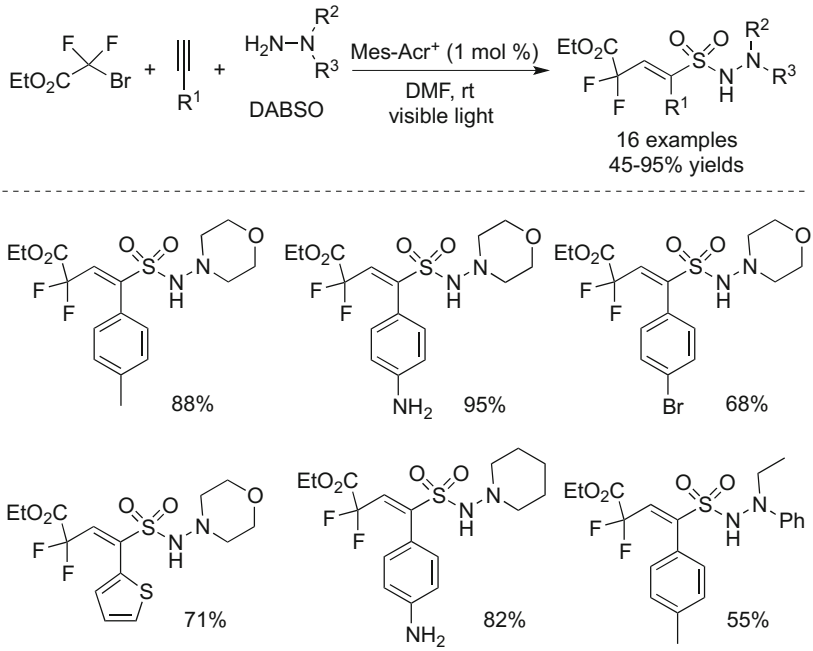


Scheme 3.44 A plausible mechanism of the catalyst-free four-component reaction of Togni's reagent, alkynes, DABSO and hydrazines

General procedure for the catalyst-free four-component reaction of Togni's reagent, alkynes, DABSO, and hydrazines: Alkyne (0.2 mmol) was combined with Togni reagent (0.3 mmol) and DABSO (0.16 mmol) in a tube. The tube was evacuated and backfilled with N_2 three times before the addition of CH_3CN

(4.0 mL). Subsequently, hydrazine (1.5 equiv.) was added dropwisely to the solution. After completion of reaction as indicated by TLC, the mixture was washed with saturated sodium bicarbonate and brine. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate three times. The combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by flash column chromatography (EtOAc/*n*-hexane, 1:4) to give the desired product.

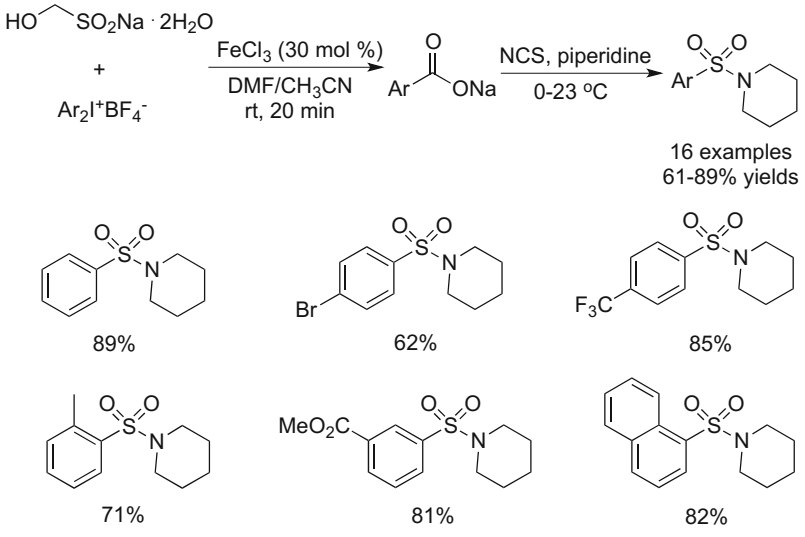
Very recently, the Wu group extended the above transformation to vicinal difluoroalkylation and aminosulfonylation of alkynes under photocatalysis (Scheme 3.45) [48]. They revealed a four-component reaction of ethyl 2-bromo-2,2-difluoroacetate, alkynes, DABSO, and hydrazines for the construction of (*E*)-ethyl 2,2-difluoro-4-aryl-4-sulfamoylbut-3-enoates. Compared with the previously reported trifluoromethylation process, the visible-light catalysis in this reaction was used to activate the ethyl 2-bromo-2,2-difluoroacetate to produce the difluoroalkyl radical. 9-Mes-10-methyl acridinium perchlorate was demonstrated to be essential as a photocatalyst. Considering the importance of CF_2R groups in biologically active molecules, this transformation might attract further applications. Moreover, this process represents the first example of sulfur dioxide insertion reaction promoted by the visible-light-induced photoredox catalysis.



Scheme 3.45 A four-component reaction of ethyl 2-bromo-2,2-difluoroacetate, alkynes, DABSO and hydrazines

General procedure for the four-component reaction of ethyl 2-bromo-2,2-difluoroacetate, alkynes, DABSO, and hydrazines: Alkyne (0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (0.4 mmol), and hydrazine (0.24 mmol) were combined with DABSO (0.16 mmol, 38.40 mg) and 9-Mes-10-methyl acridinium perchlorate (1 mol%) in a flask. The flask was evacuated and backfilled with Ar_2 three times before DMF (3.0 mL) was added. The mixture was then placed around the visible light bulb (CLF, 11w) with a distance of 10 cm, and was stirred under visible light irradiation for 12 h at room temperature. After completion of reaction as indicated by TLC, the mixture was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:4) to provide the desired product.

Commercially available rongalite ($HOCH_2SO_2Na{\cdot}2H_2O$) was applied in a radical coupling reaction to deliver arylsulfinates, by Luo and co-workers (Scheme 3.46) [49]. The rongalite was able to introduce the sulfonyl unit, as a source of sulfur dioxide. It should be pointed out that the anion radical SO_2 was the key intermediate rather than sulfur dioxide. Aryl radicals were generated from diaryliodoniums via a single electron transfer in the presence of iron-catalysts. The combination of aryl radicals with sulfoxylate anion radicals would lead to arylsulfinates efficiently. Further treatment with *N*-chlorosuccinimide (NCS) and piperidine enabled to convert arylsulfinates into the corresponding sulfonamides. This transformation took place at room temperature, leading to a variety of sulfonamides in good yields. The application of rongalite to fix the sulfonyl motif into small molecules is attractive and promising since the rongalite is commercially available and cheap. Recently, Shavnya and co-workers extended this process to a reaction of alkyl halides with rongalite to synthesize alkyl sulfinates. The in situ

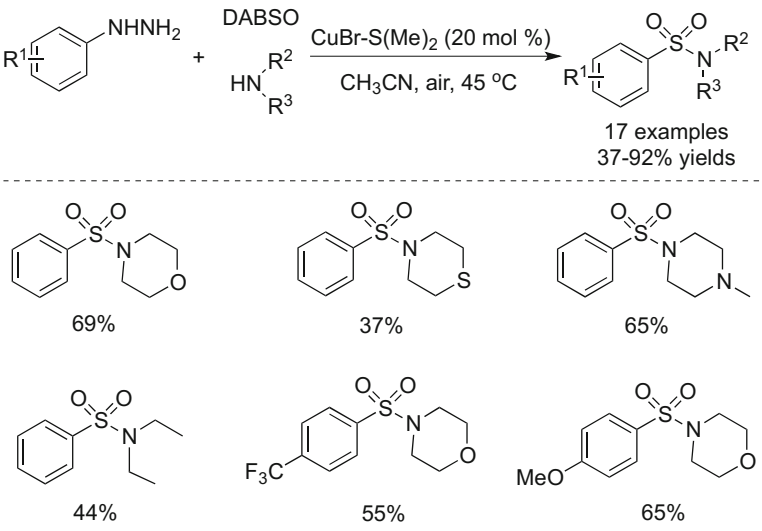


Scheme 3.46 Iron-catalyzed synthesis of arylsulfinates through radical coupling reaction

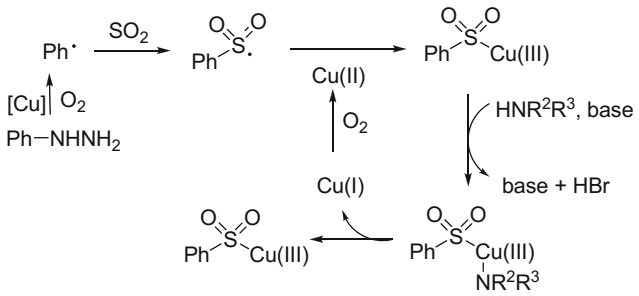
generated alkyl sulfinates were utilized to produce a variety of sulfonamides, sulfonyl fluorides, and unsymmetrical sulfones [50].

General procedure for the iron-catalyzed arylsulfinate synthesis through radical coupling reaction: A mixture of diaryliodonium tetrafluoroborate (0.3 mmol), rongalite (0.45 mmol), $FeCl_3$ (30 mol%) in DMF/MeCN (0.5/0.5 mL) were stirred at room temperature for 20 min in a tube under air atmosphere. Then the suspension was dissolved in DMF (10 mL). Piperidine (0.6 mmol) and triethylamine (0.1 mmol) were then added, followed by dropwise addition of *N*-chlorosuccinimide (0.6 mmol) at 0 °C in 30 min. The reaction mixture was warmed to room temperature and stirred for 2 h before water (8 mL) was added. The aqueous solution was extracted with dichloromethane (3 × 10 mL), and the combined extracts were dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was separated by column chromatography on silica gel to afford the pure sulfonamide product.

Very recently, the Pan group reported a copper-catalyzed three-component reaction of hydrazines, DABSO, and amines in the presence of oxygen to deliver sulfonamides (Scheme 3.47) [51]. The hydrazine was applied as the source of aryl radical. This radical coupling process took place under mild conditions, which directly produced a variety of sulfonamides. A possible mechanism was proposed (Scheme 3.48). The aryl hydrazines could be converted into aryl radicals in the presence of oxygen. The assistant of copper catalyst might speed up this oxidative process. The sulfonyl radicals were subsequently generated through the insertion of sulfur dioxide, and further reacted with the copper(II) catalysts to give the copper (III) species. Further combination with amines and reductive elimination would lead to the final products. For the previously reported aminosulfonylation processes,



Scheme 3.47 Copper-catalyzed three-component reaction of hydrazines, DABSO and amines



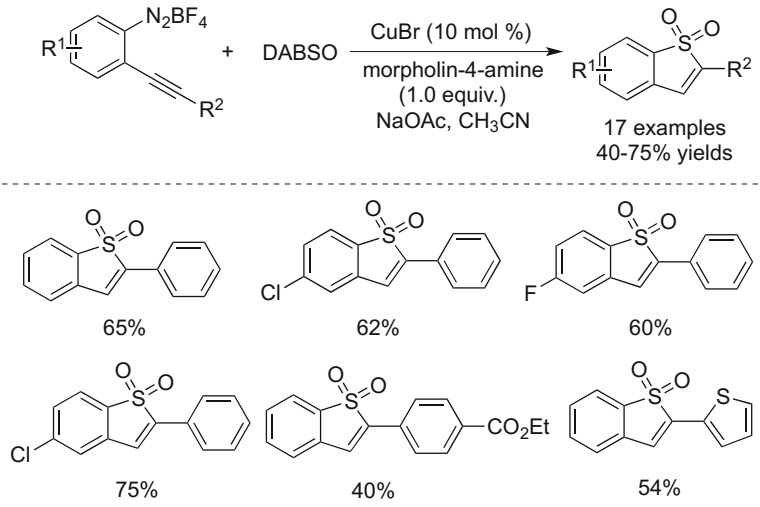
Scheme 3.48 A plausible mechanism for the copper-catalyzed three-component reaction of hydrazines, DABSO and amines

only sulfonyl hydrazines could be obtained in most cases. This new discovery might open a new window for sulfonamide synthesis via the insertion of sulfur dioxide. The shortcomings were also obvious: the limited source of hydrazine as the starting material and only moderate yields could be obtained in most cases.

General procedure for the copper-catalyzed three-component reaction of hydrazines, DABSO, and amines: Hydrazines (0.25 mmol), DABCO·$(SO_2)_2$ (0.25 mmol), amines (1.0 mmol), CuBr-S$(Me)_2$ (0.05 mmol) were added to a Schlenk tube (25 mL) under dry air balloon, followed by addition of CH_3CN (3 mL). The mixture was stirred at 45 °C for 15 h, then filtered and the solid was washed with ethyl acetate. The organic solution was dried over Na_2SO_4 and concentrated under vacuo. Then, the crude product was purified by flash chromatography to afford the desired product.

3.3.2 Synthesis of Sulfones

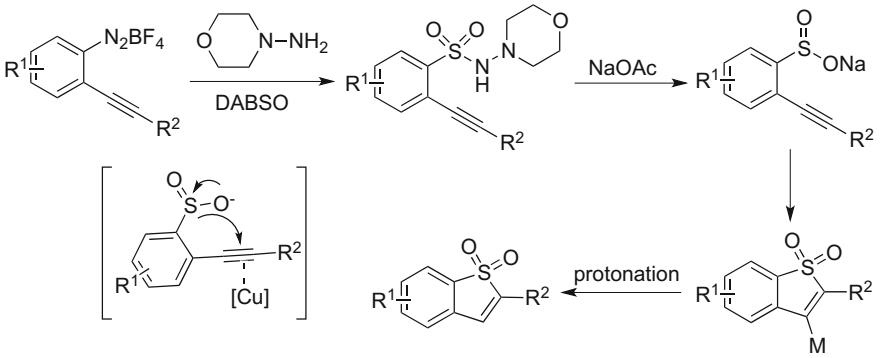
It is well known that *N,N′,N′*-trialkyl aminosulfonamides can be converted into sulfinates in the presence of base and the sulfinates can undergo nucleophilic addition or substitution to provide sulfones [30]. Thus, the application of the radical-based aminosulfonylation for sulfone synthesis can be expected. In 2014, the Wu group explored the further utilization of the *N*-aminosulfonamides generated through their previously established radical process to synthesize sulfonyl-containing heterocycles (Scheme 3.49) [52]. They designed and conducted the three-component reaction of 2-alkynylaryldiazonium tetrafluoroborates, DABSO, and hydrazines. It was expected that the in situ generated *N*-aminosulfonamide would undergo a 6-*endo* cyclization with nucleophilic addition of the nitrogen atom to the tripe bond in the presence of a metal catalyst. However, the benzo[*b*]thiophene 1,1-dioxide derivative was obtained instead of the expected 2*H*-benzo[*e*] [1,2] thiazine 1,1-dioxide. This copper-catalyzed reaction proceeded well in the presence of a copper catalyst using sodium acetate (NaOAc) as the base, delivering a number of 2*H*-benzo[*e*][1,2] thiazine 1,1-dioxides



Scheme 3.49 A three-component reaction of 2-alkynylaryldiazonium tetrafluoroborates, DABSO and hydrazines

in moderate to good yields. A possible mechanism was proposed (Scheme 3.50). The radical-based aminosulfonylation of aryldiazonium tetrafluoroborates would initially occur to give the corresponding *N*-aminosulfonamides. The subsequent decomposition of *N*-aminosulfonamides with the treatment of a base would lead to the sulfinates, which would further undergo 5-*endo* cyclization catalyzed by a copper catalyst to deliver the final products.

General procedure for the three-component reaction of 2-alkynylaryldiazonium tetrafluoroborates, DABSO, and hydrazines: 2-Alkynylphenyldiazonium (0.48 mmol) in CH_3CN (2.0 mL) was added dropwisely to a solution of DABCO-bis(sulfur dioxide) (0.24 mmol) and morpholin-4-amine (0.40 mmol) in

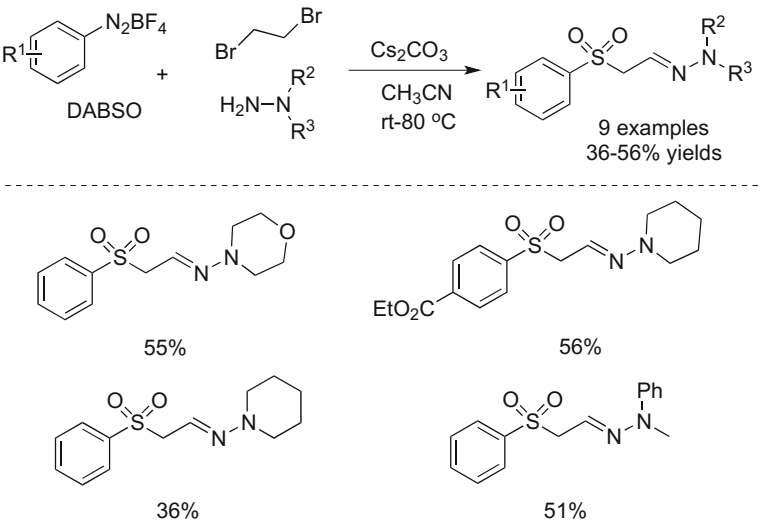


Scheme 3.50 A plausible mechanism for the three-component reaction of 2-alkynylaryldiazonium tetrafluoroborates, DABSO and hydrazines

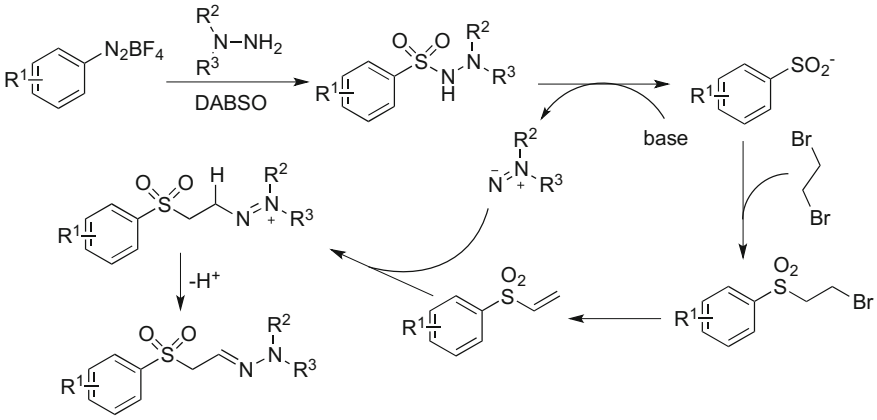
CH_3CN (5.0 mL) in 10 min. After the mixture was stirred at room temperature for another 15 min, NaOAc (1.20 mmol) and CuBr (0.04 mmol) were added to the suspension. The mixture was allowed to stir under reflux overnight. After completion of the reaction as indicated by TLC, the solvent was evaporated and the residue was purified directly by flash column chromatography (*n*-hexane/ethyl acetate = 6:1) to give the desired product.

Subsequently, the same group discovered that the treatment of *N*-aminosulfonamides with 1,2-dibromoethane in the presence of a base could provide an efficient approach to 2-arylsulfonyl hydrazones (Scheme 3.51) [53]. They revealed that the decomposition of *N*-aminosulfonamide produced a diazene and a sulfinate salt. The diazene and sulfinate salt would further be bridged by 1,2-dibromoethane to deliver the corresponding 2-arylsulfonyl hydrazones. The one-pot, two-step process could synthesize a number of 2-arylsulfonyl hydrazones under mild conditions. Based on a cross-over experiment, they considered that the vinylsulfone would be the key intermediate in this transformation. Accordingly, a plausible mechanism was proposed (Scheme 3.52). They supposed the sulfinate salt decomposed from the *N*-aminosulfonamide would react with 1,2-dibromoethane to give the sulfonated intermediate, which would next undergo elimination to afford vinylsulfone. Further addition of the diazene to vinylsulfone and isomerization would deliver the final product.

General procedure for the four-component reaction of aryldiazonium tetrafluoroborates, DABSO, 1,2-dibromoethane and hydrazines: Aryldiazonium tetrafluoroborate (0.30 mmol) in CH_3CN (1.0 mL) was added dropwisely to a solution of DABCO·$(SO_2)_2$ (0.18 mmol) and hydrazine (0.36 mmol) in CH_3CN



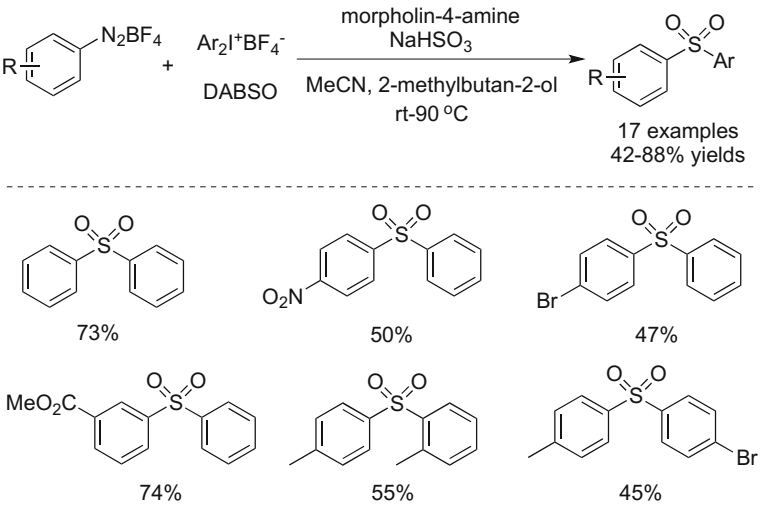
Scheme 3.51 A four-component reaction of aryldiazonium tetrafluoroborates, DABSO, 1,2-dibromoethane and hydrazines



Scheme 3.52 A possible mechanism for the four-component reaction of aryldiazonium tetrafluoroborates, DABSO, 1,2-dibromoethane and hydrazines

(2.0 mL) under N_2 in 10 min. The mixture was stirred at room temperature for another 10 min. Then 1,2-dibromoethane (5 equiv.) and Cs_2CO_3 (3 equiv.) were added to the above mixture. The mixture was stirred at 80 °C for 5 h. After completion of reaction as indicated by TLC, the mixture was directly purified by flash column chromatography (EtOAc/*n*-hexane, 1:1) to give the desired product.

Wu group also reported a reaction of aryldiazonium tetrafluoroborates, DABSO, hydrazines, and aryliodonium tetrafluoroborates to deliver the sulfones (Scheme 3.53) [54]. Again, the radical-based aminosulfonylation of aryliodonium

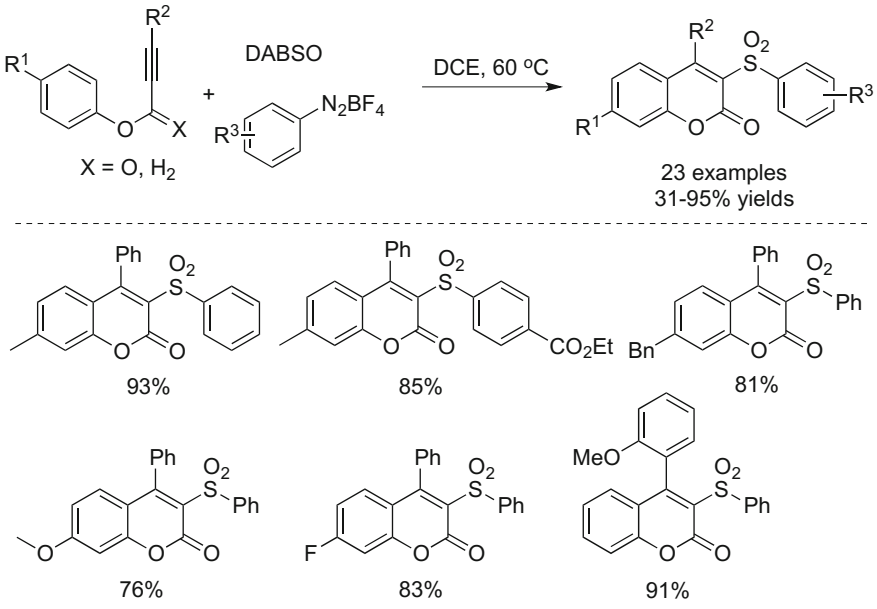


Scheme 3.53 Reaction of aryldiazonium tetrafluoroborates, DABSO, hydrazines and aryliodonium tetrafluoroborates

tetrafluoroborates was utilized. This time, the *in situ* generated sulfinate intermediates would react with aryliodonium tetrafluoroborates, giving rise to the corresponding sulfones. Sodium hydrogen sulfite was used as the base in this report.

General procedure for the reaction of aryldiazonium tetrafluoroborates, DABSO, hydrazines, and aryliodonium tetrafluoroborates: Aryldiazonium tetrafluoroborate (0.30 mmol) in CH_3CN (1.0 mL) was added dropwisely to a solution of DABCO·$(SO_2)_2$ (0.18 mmol) and morpholin-4-amine (0.36 mmol) in CH_3CN (3.0 mL) under N_2 in 10 min. The mixture was stirred at room temperature for another 10 min. Then aryliodonium tetrafluoroborate (0.36 mmol), $NaHSO_3$ (0.90 mmol), and 2-methylbutan-2-ol (2.0 mL) were added. The mixture was stirred at 90 °C until completion of the reaction. The solvent was evaporated and the residue was purified directly by flash column chromatography to give the desired product.

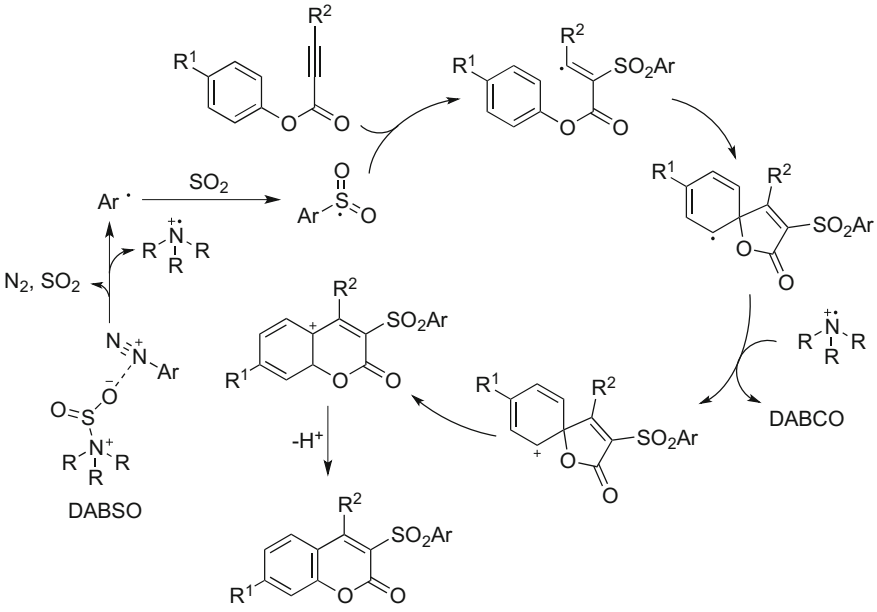
Another significant breakthrough in the radical-based process for sulfur dioxide insertion was achieved by the Wu group in 2016 [55]. In their previously established radical aminosulfonylation process [41], the nucleophile was still restricted to the hydrazine. They suspected that the hydrazine was involved in the initiation of the aryl radical and sulfonyl radical, and considered this might explain the substrate limitation. However, they finally discovered that treatment of aryliodonium tetrafluoroborates with DABSO would directly lead to the sulfonyl radicals under suitable conditions (Scheme 3.54). The resulting sulfonyl radicals could be trapped



Scheme 3.54 Generation of 3-sulfonated coumarins from aryldiazonium tetrafluoroborates, DABSO and aryl propiolates

by aryl propiolates to afford 3-sulfonated coumarins. This reaction proceeded under extremely mild conditions and no catalysts or additives were required. A broad reaction scope was also observed and various 3-sulfonated coumarins could be synthesized in good to excellent yields. Based on the experimental observations, they proposed a possible mechanism (Scheme 3.55). They reasoned that arydiazonium cation would integrate with DABSO through electrostatic interaction. The subsequent homolytic cleavage of N–S bond through a single electron transfer would lead to the tertiary amine radical cation, SO_2 and aryl radical (with the release of N_2). The insertion of sulfur dioxide to the aryl radical would provide the arylsulfonyl radical, which would attack the triple bond of aryl propiolates. Further spiro-cyclization, oxidation by the tertiary amine radical cation, 1,2-ester migration and aromatization would give rise to the desired 3-sulfonated coumarins. The introduction of in situ diazotization of aryl amines also provided a one-pot, two-step process to access 3-sulfonated coumarins. The success of this transformation might lead to the revolution of the radical-based sulfur dioxide insertion reactions, although the generality of the introduction of sulfonyl radicals with this process remained to be explored. The oxidative ability of the tertiary amine radical cation might be the key problem.

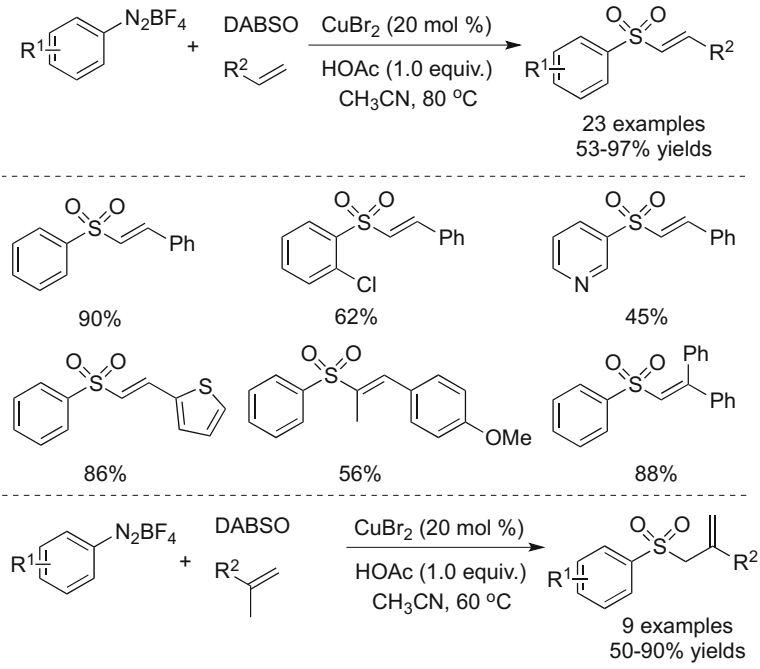
General procedure for the generation of 3-sulfonated coumarins from aryldiazonium tetrafluoroborates, DABSO, and aryl propiolates: A solution of aryl propiolate (0.2 mmol), DABCO·$(SO_2)_2$ (0.4 mmol) and aryldiazonium tetrafluoroborate



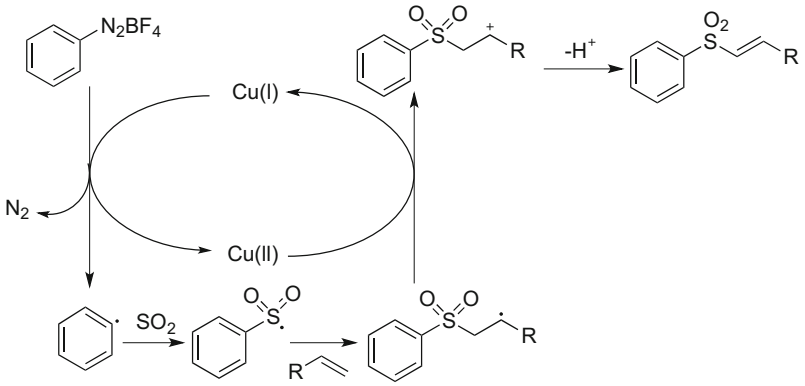
Scheme 3.55 A plausible mechanism for the generation of 3-sulfonated coumarins from aryldiazonium tetrafluoroborates, DABSO, and aryl propiolates

(0.24 mmol) in DCE (1.5 mL) was heated to 60 °C under Ar protection. The mixture was stirred at 60 °C for 30 min. After completion of reaction as indicated by TLC, the solvent was evaporated and the residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:3) to give the desired 3-sulfonated coumarin.

In the meantime, the Wu group revealed a three-component coupling reaction of aryldiazonium tetrafluoroborates, DABSO, and alkenes in the presence of a copper catalyst (Scheme 3.56) [56]. This Heck-type sulfonylation reaction led to a variety of (*E*)-alkenyl sulfones or allylic sulfones in good to excellent yields. In fact, Feng and co-workers previously reported the coupling of aryldiazonium tetrafluoroborates, DABSO, and alkenes in the presence of iodide-catalysts and *tert*-Butyl hydroperoxide (TBHP) [57]. However, in Wu's paper, the authors declared that some results could not be reproducible. Only a trace amount of product could be detected under the conditions reported by Feng. Moreover, the utilization of several alkyldiazonium tetrafluoroborates which were extremely unstable was implausible. This copper-catalysis enabled the smooth coupling of aryldiazonium tetrafluoroborates, DABSO, and alkenes to yield sulfones. In the proposed mechanism (Scheme 3.57), the authors supposed that the aryl radicals was generated via a singer electron transfer between Cu(I) and aryldiazonium salts. Subsequent insertion of sulfur dioxide would lead to the sulfonyl radicals, which would next add to



Scheme 3.56 A three-component coupling reaction of aryldiazonium tetrafluoroborates, DABSO and alkenes



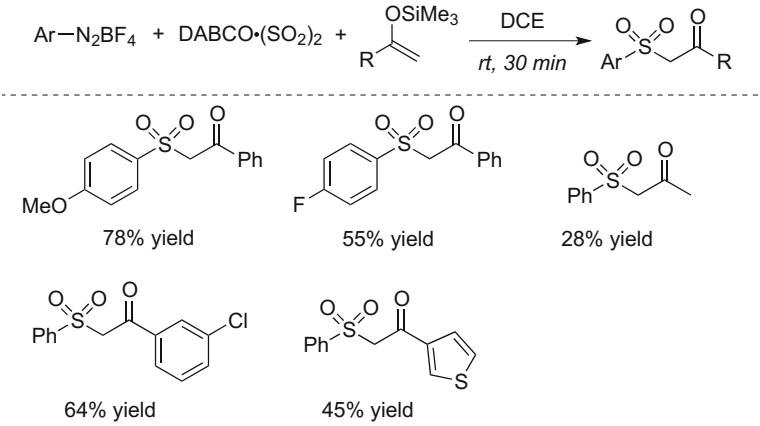
Scheme 3.57 A plausible mechanism for the three-component coupling reaction of aryldiazonium tetrafluoroborates, DABSO, and alkenes

the alkenes. The resulting alkyl radicals could be oxidized by Cu(II) to alkyl cations, followed by elimination to produce the final products. Only a small quantity of products could be detected in the absence of the copper catalysts, indicating the previously reported metal-free sulfonylation was not efficient enough in this Heck-type transformation. Maybe the tertiary amine radical cation was inefficient to oxidize the alkyl radical intermediate to the corresponding alkyl cation, impeding the successful conversion of starting materials. This copper-catalysis provides an important supplement to the metal-free sulfonylation process and further applications can be expected.

General procedure for the three-component coupling reaction of aryldiazonium tetrafluoroborates, DABSO, and alkenes: Alkene (0.4 mmol) and acetic acid (0.2 mmol) were added to a solution of $CuBr_2$ (0.04 mmol), aryldiazonium tetrafluoroborate (0.2 mmol) and DABCO·$(SO_2)_2$ (0.5 mmol) in CH_3CN (1.0 mL). The mixture was stirred at 80 °C for about 30 min. After the reaction was completed (indicated by TLC), the solvent was evaporated and the residue was purified directly by flash column chromatography (EtOAc/*n*-hexane, 1:6) to provide the desired product.

Wu and co-workers further extended this approach to the reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, and silyl enol ethers [58]. Diverse β-keto sulfones were generated under catalyst- and additive-free conditions (Scheme 3.58). This transformation is green and proceeds efficiently at room temperature, and goes to completion in half an hour. Again, the combination of aryldiazonium tetrafluoroborate and DABCO·$(SO_2)_2$ would provide sulfonyl radical as the key intermediate during the reaction process. In this transformation, oxidants or metal catalysts are avoided, and the presence of DABCO acted as a carrier for single electron transfer in the reaction.

General procedure for the synthesis of β-keto sulfones via *the reaction of phenyldiazonium tetrafluoroborate, sulfur dioxide, and silyl enol ethers*: Silyl



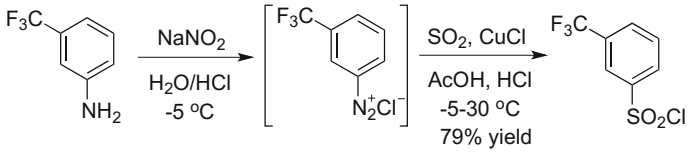
Scheme 3.58 A three-component coupling reaction of aryldiazonium tetrafluoroborates, DABSO, and silyl enol ethers

enolate (0.2 mmol) was added to a solution of aryldiazonium tetrafluoroborate (0.24 mmol), and DABCO·$(SO_2)_2$ (0.3 mmol) in DCE (2.0 mL). The mixture was stirred at room temperature for 30 min. After completion of reaction as indicated by TLC, the mixture was purified directly by flash column chromatograph (EtOAc/n-hexane, 1:4) to give the desired product.

3.3.3 *Synthesis of Sulfonyl Chlorides and Other Derivatives*

As mentioned above, the initial research in radical-based insertion of sulfur dioxide mainly focused on the Sandmeyer-type reaction for the synthesis of sulfonyl chloride. In 1957, Meerwein and co-workers reported the first chlorosulfonylation of diazonium salts catalyzed by $CuCl_2$ under acidic conditions [59]. Yale and Sowinski applied this reaction for the synthesis of a group of sulfonylureas via sulfonyl chlorides as the synthetic intermediates [60]. An example was shown in Scheme 3.59.

General procedure for the Sandmeyer sulfonylation reaction: α,α,α-Trifluoro-*o*-toluidine (48.6 g, 0.3 mol, conc. hydrochloric acid (105 mL), and glacial acetic



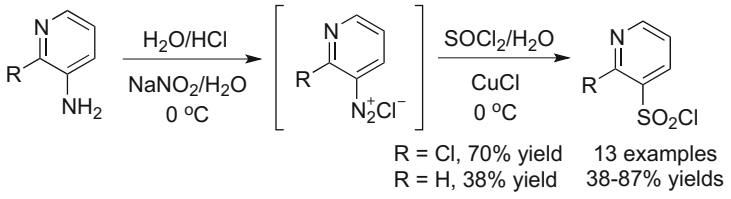
Scheme 3.59 An example of Sandmeyer sulfonylation reaction

acid (30 mL) at –5 to 0 °C were treated dropwisely, with a solution of sodium nitrite (22.8 g, 0.3 mol) in water (45 mL). The diazotized solution was allowed to warm to 4 °C and then added to 6 g of cuprous chloride in 400 mL of a saturated solution of sulfur dioxide in glacial acetic acid, also at 4 °C. The vigorous reaction accompanied by considerable frothing caused a rise in temperature to 27 °C. One and half hour later, the reaction mixture was poured into 1 L of ice water and the product was extracted with ether. The ether extract was washed until neutral with saturated aqueous sodium bicarbonate solution, then dried, concentrated, and distilled to give the sulfonyl chloride.

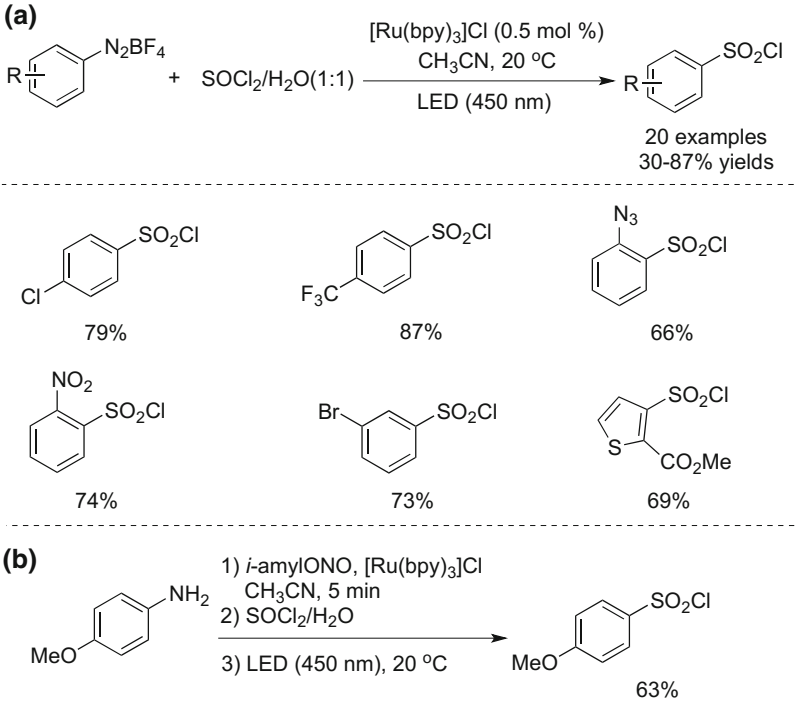
As the above reactions were usually conducted in acetic acid and gaseous sulfonyl dioxide would bring the handling trouble, Hogan and co-workers utilized $SOCl_2/H_2O$ as the sulfur dioxide source and reported an aqueous process for the preparation of sulfonyl chlorides (Scheme 3.60) [61]. The diazonium salts were generated from aryl amines and sodium nitrite in the presence of hydrochloric acid. Subsequent chlorofulfonylation of diazonium salts using $SOCl_2/H_2O$ as the sulfur dioxide source would yield a range of electron-deficient and electron-neutral aryl sulfonyl chlorides. Additionally, this process could be carried out on the multikilogram scale. Other reports also revealed that these transformations could be conducted in a flow reactor and *t*-BuONO was used instead of $NaNO_2$ [62].

General procedure for the Sandmeyer sulfonylation reaction using $SOCl_2/H_2O$ as the sulfur dioxide source: Hydrochloric acid (36% w/w, 20 mL) was added, with agitation, to 3,3′-dithiobis(2-chloropyridine) (2.0 g) at 20 °C to give a pale-yellow solution. Water (5 mL) was added, and chlorine gas bubbled through the solution for 1 h, maintaining the temperature of the mixture at 20–23 °C. Water (25 mL) was added dropwisely to the reaction mixture, maintaining the temperature at 20–29 °C. A white solid precipitated during this addition, and after cooling the mixture to 20 °C the suspended solid was collected by vacuum filtration, washed with water (3 × 25 mL), and dried under vacuum at below 35 °C to give 2-chloropyridine-3-sulfonyl chloride.

Recently, Wangelin and co-workers developed a chlorosulfonylation reaction of arenediazonium salts via visible-light-induced photoredox catalysis (Scheme 3.61) [63]. The combination of $SOCl_2/H_2O$ was used for the generation of sulfur dioxide and HCl. The photocatalytic three-component reaction of arenediazonium salts, sulfur dioxide and HCl would lead to the corresponding sulfonyl chlorides. A variety of sulfonyl chlorides were synthesized in good yields under mild



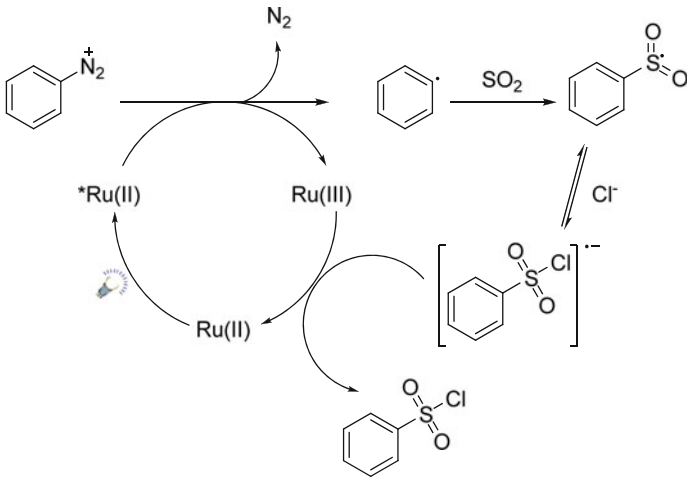
Scheme 3.60 Sandmeyer sulfonylation reaction using $SOCl_2/H_2O$ as the sulfur dioxide source



Scheme 3.61 Aromatic chlorosulfonylation under photoredox catalysis

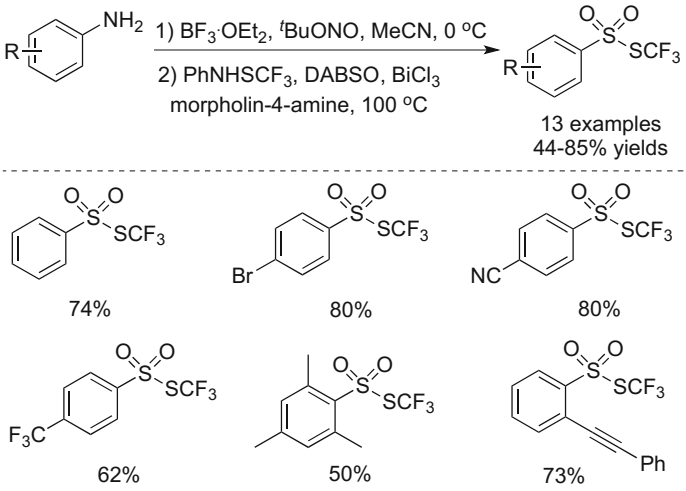
conditions with low catalyst loading. A broader reaction scope was observed compared to the results from the copper-catalyzed reaction. Both electron-deficient and electron-rich aryldiazonium salts could be applied, leading to the desired products smoothly. Various functional groups including halo, azide, nitro groups, CF_3, SF_5, esters, heteroarenes were all compatible in this transformation. A one-pot, two-step process was also developed enabling the direct conversion of aryl amines to sulfonyl chlorides via the in situ diazotization. A possible mechanism supported by theoretical and experimental studies was proposed (Scheme 3.62). Sulfur dioxide and HCl would be produced through the reaction of $SOCl_2$ and H_2O. The aryl radical was generated via a single electron transfer between aryldiazonium salt with the excited photocatalyst, and next trapped a molecular sulfur dioxide to deliver the sulfonyl radical. The sulfonyl radical reacted with the chloride anion to give a radical anion intermediate, which would be oxidized by the $[Ru(bpy)_3]^{3+}$ to afford the neutral sulfonyl chloride.

General procedure for the aromatic chlorosulfonylation via *photoredox catalysis: General procedure (a) from arenediazonium salts*: A vial (6 mL) was charged with a magnetic stir bar, the arenediazonium salt (1.0 mmol), and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.5 mol%). The vial was sealed with an aluminum cap with a



Scheme 3.62 A plausible mechanism for the aromatic chlorosulfonylation under photoredox catalysis

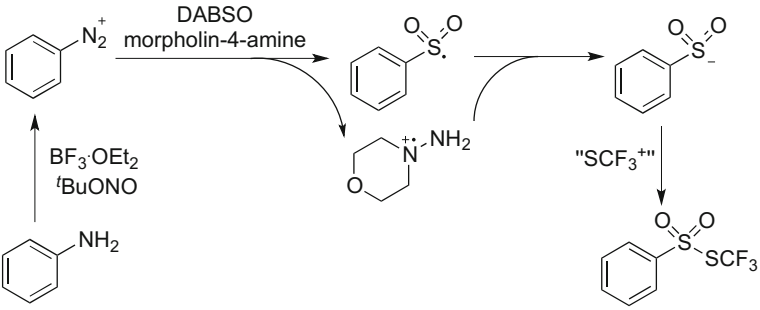
septum. Acetonitrile (1.5 mL) was added and the solution was purged with nitrogen gas stream for 5 min. Then water (90 μL, 5.0 mmol) and thionyl chloride (0.36 mL, 5.0 mmol) were added to the solution (careful! exothermic reaction between water and thionyl chloride). The reaction was irradiated with external LED (λ_{max} = 455 nm, 3.8 W) at room temperature for 20 h. After the irradiation was discontinued, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (10 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel using a mixture of pentane and ethyl acetate as a mobile phase. *General procedure (b) from anilines*: A vial (6 mL) was charged with a magnetic stir bar, the parent aniline (1.0 mmol), and $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (3.7 mg, 0.5 mol%). The vial was sealed with an aluminum cap with a septum. Acetonitrile (1.5 mL) was added and the solution was purged with nitrogen gas stream for 5 min. *Iso*-Amyl nitrite (0.16 mL, 1.2 mmol) was added, and the reaction mixture was stirred for 5 min at room temperature. Then water (90 μL, 5.0 mmol) and thionyl chloride (0.36 ml, 5.0 mmol) were added to the solution (careful! exothermic reaction between water and thionyl chloride). The reaction was irradiated with external LED (λ_{max} = 455 nm, 3.8 W) at room temperature for 20 h. After the irradiation was discontinued, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (10 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel using a mixture of pentane and ethyl acetate as a mobile phase.



Scheme 3.63 One-pot reaction of anilines, sulfur dioxide, and trifluoromethanesulfanylamide

A one-pot reaction of anilines, sulfur dioxide, and trifluoromethanesulfanylamide mediated by bismuth(III) chloride was reported by Qiu and co-workers, leading to the formation of antifungal trifluoromethyl thiolsulfonates (Scheme 3.63) [64]. *N*-Aminomorphine was applied as an additive to promote the coupling of aryldiazonium salts, sulfur dioxide, and trifluoromethanesulfanylamides. Bismuth (III) chloride was employed to facilitate the generation of "CF_3S^+". This transformation provided an alternative procedure for the synthesis of valuable trifluoromethyl thiolsulfonates. Although *N*-aminosulfonamides could be easily accessed via the reaction of aryldiazonium salts, DABSO, and hydrazines, the authors considered that *N*-aminosulfonamides were not the reaction intermediates. They directly applied a readily made *N*-aminosulfonamide to react with trifluoromethanesulfanylamide in the presence of bismuth(III) chloride, and no desired product was detected. In the proposed mechanism (Scheme 3.64), it was supposed that the hydrazine radical cation would reduce the sulfonyl radical to the corresponding sulfonyl anion, which would further undergo electrophilic trifluromethylthiolation to deliver the final product.

General procedure for the one-pot reaction of anilines, sulfur dioxide, and trifluoromethanesulfanylamide: Aniline (0.45 mmol) and $BF_3{\cdot}Et_2O$ (0.54 mmol) in CH_3CN (1.0 mL), followed by dropwise addition of *t*-BuONO (0.54 mmol) at 0 °C. After 5 min, the above mixture was slowly added into a mixture of DABCO·$(SO_2)_2$ (0.21 mmol), morpholin-4-amine (0.40 mmol), $PhNHSCF_3$ (0.39 mmol), and $BiCl_3$ (0.6 mmol) in CH_3CN (1 mL). Then the mixture was stirred at 100 °C for 6–12 h. After completion of the reaction as indicated by TLC, the reaction mixture was filtered by sand core funnel with silica gel and washed by CH_2Cl_2. The residue was concentrated in vacuo and purified by column chromatography on silica gel to provide the product.

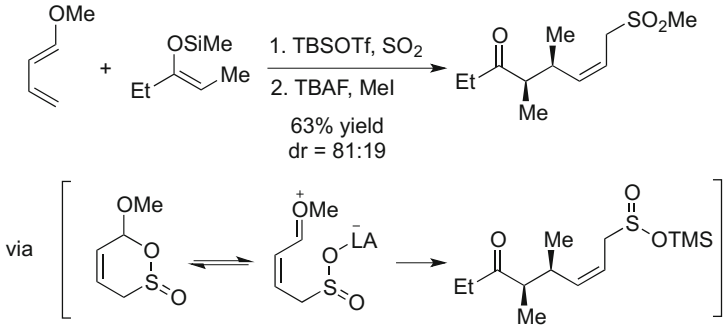


Scheme 3.64 A plausible mechanism for the one-pot reaction of anilines, sulfur dioxide, and trifluoromethanesulfanylamide

3.4 Pericyclic Reactions

There was a period of prosperity for the SO_2-based chemistry in the 1990s and 2000s. The versatilities of sulfur dioxide in the synthesis of complex poly-functionalized molecules have been achieved in pericyclic reactions [65–67]. Significant efforts were devoted to the investigation of [4 + 1] cheletropic—addition and [4 + 2] hetero-Diels–Alder reaction involving sulfur dioxide. The cycloadditions of sulfur dioxide with 1,3-dienes, ketenes, ketimines, and cyclic polyenes, etc., have been well established. Remarkably, the Vogel group was the first to explore the pericyclic reactions of sulfur dioxide. They have explored the SO_2-based chemistry extensively and developed a variety of transformations using gaseous or liquid sulfur dioxide. There was an account in this area published by the Vogel group in 2007 [65]. Since this book has an emphasis on recent advances based on the application of sulfur dioxide surrogates, we will not describe these pericyclic reactions as detailedly as other three types of reactions. In this section, the diverse use of sulfur dioxide in pericyclic reactions will be illustrated with several representative examples.

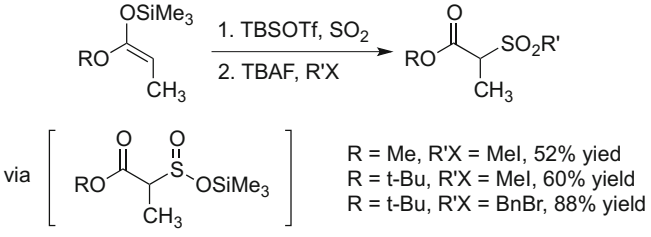
The Vogel group pioneered the use of sulfur dioxide to promote carbon–carbon bond formation mediated by Lewis acid. They revealed that a three-component reaction of electron-rich dienes, sulfur dioxide, and silyl enol ethers would lead to the sulfinates, which could be in situ converted into functionalized sulfones and sulfonamides. A typical example is presented in Scheme 3.65 [68]. Initially, the hetero-Diels–Alder cycloaddition between an electron-rich diene and sulfur dioxide catalyzed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at low temperature yielded a zwitterionic sulfinate, which would accept the nucleophilic attack from an enoxy silane to deliver the sulfinate. Further reaction with methyl iodide in the presence of tetrabutylammonium fluoride (TBAF) would afford the corresponding sulfone in 63% yield with high stereoselectivity. This transformation provided an efficient approach to polyfunctional sulfonyl derivatives and was applied successfully in the total synthesis of natural products.



Scheme 3.65 A four-component reaction of electron-rich diene, sulfur dioxide, silyl enol ether and MeI

Recent efforts in this area were mainly focused on the ene reactions of sulfur dioxide, developed by the same group. For instance, silyl enol ethers could react with sulfur dioxide via an ene reaction promoted by the Lewis acid of *t*-$BuMe_2SiOSO_2CF_3$ to give rise to the silyl sulfinates, which could be in situ trapped by a variety of electrophiles, delivering the corresponding polyfunctional sulfones (Scheme 3.66) [69]. Silyl enol ethers of esters, ketones, as well as allylstannanes and allylsilanes could undergo this one-pot three-component reaction, enabling the synthesis of various polyfunctional sulfones.

General procedure for the tree-component reaction of silyl enol ethers, sulfur dioxide, and electrophiles: *t*-$BuMe_2SiOSO_2CF_3$ (0.14 mmol, 0.05 equiv.) in anhydrous CH_2Cl_2 (2 mL) was degassed by freeze-thaw cycles on the vacuum line. Sulfur dioxide (1.2 mL, 27.4 mmol, 10 equiv.), dried by reaction with I_2 and quinolone (Karl-Fischer process), was transferred on the vacuum line to the CH_2Cl_2 solution frozen at –196 °C. The mixture was allowed to melt and to warm to –78 °C. After 30 min at this temperature the enoxysilanes (2.74 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (2 mL) were added slowly. The mixture was stirred at –78 °C for 2–5 h in a sealed tube. After cooling to –78 °C, the excess of sulfur dioxide and the solvent were evaporated under reduced pressure (0.001 Torr) to dryness (ca.

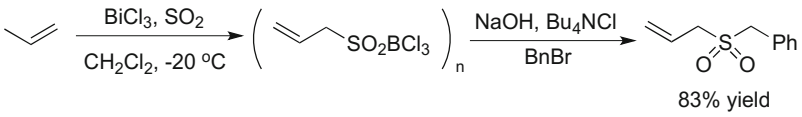


Scheme 3.66 A three-component reaction of silyl enol ethers, sulfur dioxide and electrophiles

1 h). A 1.0 M solution of Bu_4NF in THF (2.74 mL, 2.74 mmol, 1 equiv.) and electrophile (6.85 mmol, 2.5 equiv.) were added under Argon. The mixture was stirred at this temperature for 1 h, then at –40 °C for 1 h, and gradually allowed to reach 20 °C in about 10 h. After the addition of H_2O (20 mL), and neutralization with $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was eliminated under reduced pressure with a reflux. The residue was purified by flash column chromatography.

In 2010, the Vogel group reported the first ene reaction of unfunctionalized alkenes with sulfur dioxide mediated by BCl_3 [70]. The stable sulfinic acid.BCl_3 complex could be produced from unfunctionalized alkenes and sulfur dioxide in the presence of one equivalent of BCl_3. Further treatment with a base would lead to the corresponding sulfinates. The sulfinates could be in situ converted into sulfones via the reaction with electrophiles. An example was presented in Scheme 3.67. The desired (allylsulfonylmethyl)benzene could be obtained in 83% yield. Moreover, treatment of the sulfinic acid.BCl_3 complex with *N*-chlorosuccinimide (NCS) would give rise to the corresponding sulfonyl chloride, which could also be converted into a variety of sulfonyl-containing compounds.

General procedure for the ene reaction of unfunctionalized alkenes with sulfur dioxide mediated by BCl_3: To a solution of BCl_3 (10 mL, 10 mmol, 1.0 M) in CH_2Cl_2 frozen at −196 °C, sulfur dioxide (10 mL) was transferred through vacuum line. The solution was melt, warm to −20 °C and stirred for 30 min. The solution was again frozen at −196 °C and alkene (10 mmol) was added. The reaction mixture was stirred at −20 °C for 3 h. The excess of sulfur dioxide and CH_2Cl_2 were evaporated at −20 °C. So obtained crude products were used without purification for further transformations. Prop-2-ene-1-sulfinic acid/BCl_3 complex were dissolved in anhydrous CH_2Cl_2 (20 mL) and slowly added to NaOH (30 mL, 3.75 mmol, 5%) solution at 5 °C. The reaction mixture was warmed up to room temperature and mixed for 30 min. Benzyl bromide (2.05 g, 12 mmol) and Bu_4NCl (277 mg, 1 mmol) were added as a solution in CH_2Cl_2 (1 mL). The mixture was finally stirred at this temperature for 12 h, and poured into a mixture of water (30 mL). Crude product was extracted with CH_2Cl_2 (25 ml, 3 times) and dried (Na_2SO_4). The solvent was eliminated under reduced pressure. Purification by flash column chromatography (PE/EtOAc = 10/1) would provide the corresponding product.



Scheme 3.67 Ene reaction of unfunctionalized alkenes with sulfur dioxide mediated by BCl_3

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Chapter 4
Conclusions and Outlook

Abstract The above three chapters have overviewed the versatilities of sulfur dioxide in organic synthesis and described the commonly utilized sulfur dioxide surrogates. We classified and discussed the transformations in detail involving insertion of sulfur dioxide, with an emphasis on the reaction design and mechanisms, revealing the valuable insights of sulfur dioxide insertion reactions. In this chapter, we will summarize the book and look into the future of sulfur dioxide chemistry. We hope this book will help readers to review the field of sulfur dioxide chemistry, and ignite the interest of readers to solve the existing challenges and exploit new areas of sulfur dioxide chemistry.

Keywords Sulfur dioxide chemistry · Insight and outlook · New research areas

This book has highlighted the diverse use of sulfur dioxide in organic synthesis and described the commonly utilized sulfur dioxide surrogates. Recent progresses in the development of sulfur dioxide surrogates make the introduction of sulfur dioxide more accessible and efficient. A variety of sulfones and their derivatives can be achieved from these efficient transformations. Thus, sulfur dioxide insertion has become as a powerful strategy for the introduction of the sulfonyl motif into small molecules. The emerging new reactivities such as transition metal catalysis and radical process of sulfur dioxide make this strategy more attractive and promising. Moreover, the reaction design and mechanisms can provide the readers more valuable insights of the sulfur dioxide insertion reactions.

Although great progress in this field has been achieved, many challenges still remain in sulfur dioxide insertion chemistry, such as the scope restriction of nucleophiles in cross-coupling reactions, sulfonylation via C–H bond activation, applications in the total synthesis of nature products or drugs, combination with photoredox catalysis, and the development of more general, practical and green processes for the generation of sulfonyl radicals and their relevant applications.

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We believe more achievements in sulfur dioxide insertion reactions and their applications in organic synthesis and medicinal chemistry are forthcoming. We hope this book will help readers to review the field of sulfur dioxide chemistry, and ignite the interest of readers to solve the existing challenges and exploit new areas of sulfur dioxide chemistry.