The Renaissance of Alkali Metabisulfites as SO_2 Surrogates

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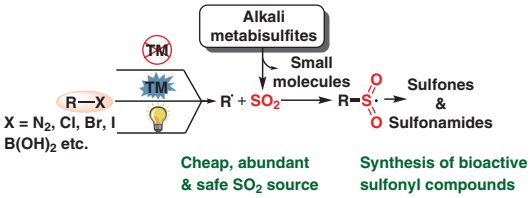

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Abstract The upsurge of interest in the development of methodologies for the construction of sulfur-containing compounds via the use of expedient reagents has established sustainable tools in organic chemistry. This review focuses on sulfonylation reactions using inorganic sulfites ($Na_2S_2O_5$ or $K_2S_2O_5$) as the sulfur dioxide surrogates. Compared to the bis-adduct with DABCO, which is an excellent surrogate of gaseous SO_2, the use of sodium or potassium metabisulfites as SO_2 surrogates are equally efficient. The objective of the current review is to exemplify recent sulfonylation reactions using inorganic sulfites. For better understanding, the review is categorized according to the mode of reactions: transition-metal-catalyzed SO_2 insertion, metal-free SO_2 insertion, and visible-light-mediated SO_2 insertion. All the reactions in each of the sections are illustrated with selected examples with a pertinent explanation of the proposed mechanism.

Key words DABCO·$(SO_2)_2$, sodium or potassium metabisulfite, SO_2 surrogate, sulfonylation reaction, SO_2 insertion

1 Introduction

In the past decades, the insertion of sulfone functionality into organic molecules has garnered much attention because of the versatile reactivity and enhanced properties of the generated moieties. Owing to their unique chemical and biological activity, compounds possessing a sulfone backbone are privileged structural motifs in many clinical drugs, natural products and agrochemicals (Figure 1).[1–3] In pharmaceuticals, the sulfone moiety has been explored extensively because of the biological activities that it can impart, such as anti-inflammatory, antimicrobial, anticancer, anti-HIV, and antimalarial action. In particular, Vismodegib® is an anti-cancer agent, Adociaquinone® is used for the treatment of breast cancer, and Tinidazole® and Amisulpride® are used as anti-inflammatory and anti-psychotic drugs, respectively (Figure 1).[4] Besides their use in the medicinal field, sulfone-containing compounds display a wide range of reactivity in the field of synthetic organic chemistry and the moiety can act as a leaving group; therefore, it has been designated as a 'chemical chameleon' by Trost.[5]

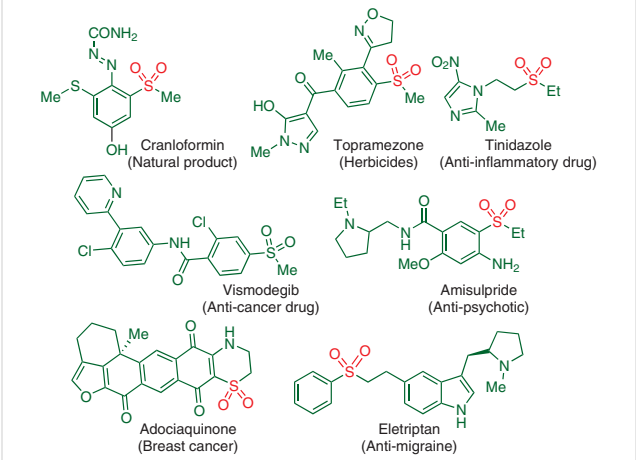

Figure 1 Representative active sulfone-containing molecules

Given the various applications of sulfones, synthetic chemists have long attempted to find new pathways to incorporate this important structural motif. Traditional methods used for the synthesis of such scaffold soften require multistep reactions and utilize pre-functionalized sulfonyl compounds such as sulfonyl halides,[6–9] sulfonyl

hydrazines,[10–13] and sodium sulfinates.[14–16] To overcome these shortcomings, chemists started to explore various sulfur dioxide surrogates as the source of sulfur dioxide in the sulfonylation reactions. With the use of sulfur dioxide surrogates, it is possible to avoid the problem of handling toxic, gaseous sulfur dioxide. The reagent 1,4-diazabicyclo-[2.2.2]octane-sulfur dioxide (DABSO or [DABCO·$(SO_2)_2$]) was reported by Willis et al. as the first sulfur dioxide

Biographical Sketches

Bhisma Kumar Patel (born in August 1965) received his B.Sc (Hons) and M.Sc degrees from Sambalpur University, Odisha, India. He was admitted to IIT Kanpur for his PhD in the research group of Prof. S. Ranganathan (FNA) (1988–1994). After three years of post-doctoral tenure with Prof. Dr Fritz Eckstein at the Max-Planck Institute for Experimental Medicine (1994–1997), he joined the Department of Chemistry, Indian Institute of Technology Guwahati as an Assistant Professor in April 1997, where he was elevated to the post of Full Professor in August 2005, and HAG Professor in September 2011 and continued as the Head of the Department. His current research interests include green chemistry, C–H activation, cross dehydrogenative coupling, metal-catalyzed/metal-free oxidative functionalization, multi-component reactions and hypervalent iodine mediated organic transformations. Altogether 25 students have been awarded PhD degrees under his supervision and his research work has resulted in the publication of 162 research papers in journals of international repute, and three patents.

Ashish Kumar Sahoo was born in 1994 in Odisha, India. He received his BSc. from Utkal University and M.Sc. and M.Phil. both from North Orissa University, Odisha. He qualified for the CSIR National Eligibility Test & GATE in 2016 and is currently pursuing his doctoral research under the supervision of Prof. Bhisma K. Patel at the Indian Institute of Technology in Guwahati (India). His research primarily focuses on photoredox catalysis and radical-based C–H functionalization.

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Amitava Rakshit was born in 1993 in West Bengal, India. He received his B.Sc. (Hons.) degree from Bankura Christian College, The University of Burdwan in 2014 and MSc. degree from IIT Kharagpur in 2016. He qualified for the CSIR National Eligibility Test & GATE in 2016 and is currently pursuing his doctoral research under the supervision of Prof. Bhisma K. Patel at the Indian Institute of Technology in Guwahati (India). His research focuses primarily on nitrile-triggered access of *N*-heterocycles via thermal and photochemical processes.

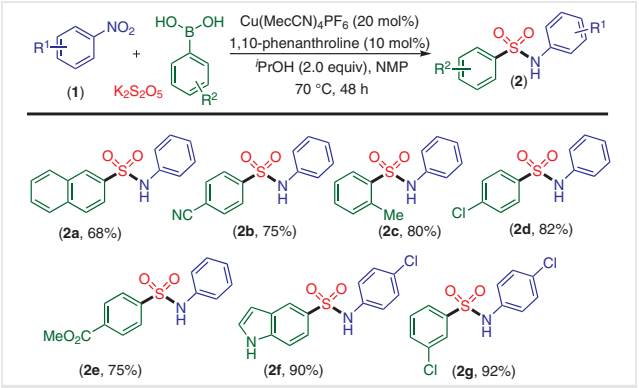
surrogate in a palladium-catalyzed amino sulfonylation reaction.[17] In 1988, Santos and Mello reported DABCO·$(SO_2)_2$ as a stable and innocuous reagent.[18] However, the synthesis of DABCO·$(SO_2)_2$ is performed at –78 °C using gaseous sulfur dioxide. Moreover, the process is neither atom-economic nor cost-effective as a large excess of 1,4-diazabicyclo-[2.2.2]octane (DABCO) is used during the reaction. Although the application of DABCO·$(SO_2)_2$ in sulfonylation reactions has developed rapidly in the past few years, chemists still strive to find an alternative to DABSO, which can be utilized as a better sulfur dioxide surrogate.[19] In this perspective, the use of inorganic sulfites such as $K_2S_2O_5$ or $Na_2S_2O_5$ is demonstrated to be attractive and to offer suitable alternative sulfur dioxide surrogates for the synthesis of sulfonylated compounds. Such inorganic sulfites are inexpensive, readily available, and environmentally benign, providing an atom-economic route for the synthesis of an array of sulfonyl compounds, including sulfones and sulfonamides. Indeed, more reports using inorganic sulfites as the source of sulfur dioxide have started appearing.[20] Sulfonylation reactions utilizing these alkali metabisulfites could be performed under transition-metal catalysis or through a radical process under metal or additive-free conditions. In some cases, a photocatalyst is necessary to promote the reaction under visible-light irradiation. Although some aspects of this fast-developing area has been covered in a few reviews, the primary objective of the present review is to bring the latest uses of alkali metabisulfites to the fore.[21,22] For convenience, this review is divided into three categories based on the SO_2 insertion strategy during the sulfonylation reaction: (i) transition-metal-catalyzed SO_2 insertion; (ii) transition-metal-free SO_2 insertion; and (iii) visible-light-mediated SO_2 insertion.

2 Outlines of the Reactions Involving SO_2 Insertion

2.1 Transition-Metal-Catalyzed SO_2 Insertion

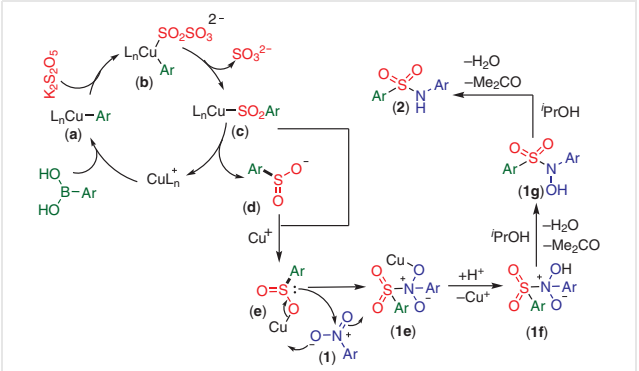
Although several methodologies have been developed for SO_2 insertions, the transition-metal-catalyzed SO_2 insertion is still in demand due to its remarkable catalytic activity and better selectivity.[23]

Sulfonamides are found in many pharmaceuticals and biologically active compounds and hence the development of new methodologies is deemed worthy.[24] A three-component reaction of an arylboronic acid, nitroarene (**1**), and potassium metabisulfite under copper catalysis was established by Wu et al. yielding a variety of sulfonamides. Various functional groups including hydroxy-, cyano-, amino- and carbonyl were well tolerated in this strategy (Scheme 1).[25]



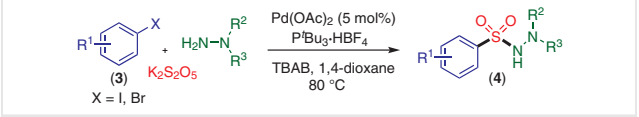
Scheme 1 Synthesis of phenyl *N*-aryl sulfonamides using nitrobenzene and boronic acids

According to the mechanism (Scheme 2), the copper-catalyzed addition of $K_2S_2O_5$ with an aryl boronic acid generates an arylsulfinate intermediate (**d**). Further, a copper-assisted nucleophilic interaction of intermediate (**e**) with nitroarene (**1**) gives rise to intermediate (**1e**) followed by protonation to afford intermediate (**1f**). The intermediate (**1f**) undergoes reduction with isopropanol, producing a sulfonyl hydroxylamine (**1g**), which, on further reduction, affords the final product **2**.



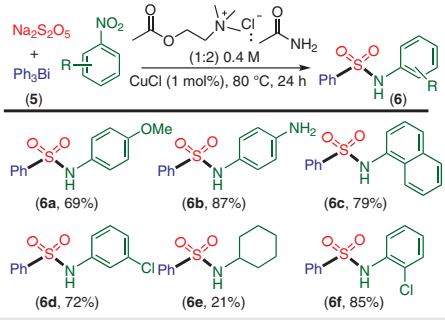
Scheme 2 Proposed mechanism for the formation of phenyl *N*-aryl sulfonamide derivatives

A similar approach was reported by Wu et al. for the synthesis of sulfonamides **4**, which proceeds via a Pd-catalyzed coupling of aryl halides **3**, hydrazines, and potassium metabisulfite. Both aryl iodides, as well as aryl bromides, reacted smoothly under identical reaction conditions. However, aryl chlorides and alkyl halides were demonstrated not to be substrates in this conversion (Scheme 3).[26]



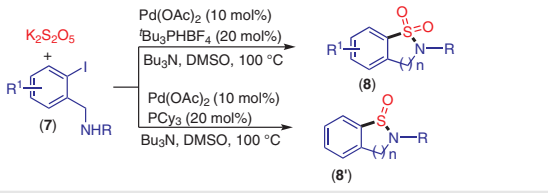
Scheme 3 Synthesis of sulfonamides using aryl halides

In 2019, the Ramon group demonstrated a copper-catalyzed synthesis of sulfonamides **6** from triaryl bismuthines **5**, sodium metabisulfite, and nitro compounds as the amino source in a deep eutectic solvent. It was found that substrates containing neutral, electron-withdrawing, and electron-donating substituents all gave products in moderate to good yields. The reaction was successful for the aliphatic nitrocyclohexane, although a lower yield of the desired product was obtained (Scheme 4).[27]



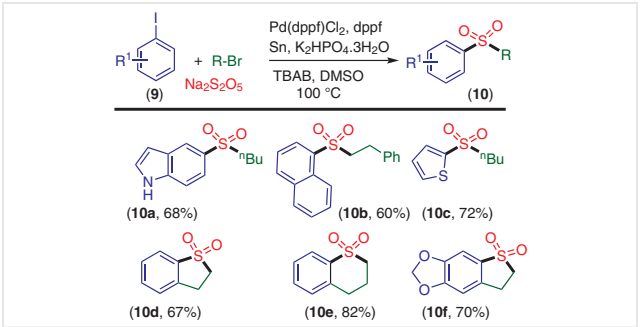
Scheme 4 Synthesis of phenyl *N*-aryl sulfonamide derivatives using nitrobenzene

Manabe et al. in 2017, demonstrated an elegant method for the synthesis of sulfonamides **8** and sulfinamides **8′** from heteroarenes **7** bearing an amino group and $K_2S_2O_5$ as the SO_2 surrogate. In this protocol, the selectivity is governed by the nature of the ligand and the equivalents of the base used. The protocol covers a wide range of cyclic amines with good functional group tolerance. From the mechanistic investigations, the group confirmed the generation of sulfonamides, which are converted into sulfonamides in the presence of ≤1.0 equiv of the base. In the process, sulfinamides are produced through an unprecedented insertion of sulfur monoxide, and products were obtained via oxidation using an iodide/DMSO combination. The presence of iodide and DMSO is vital for the successful conversion of sulfinamides into sulfonamides (Scheme 5).[28]



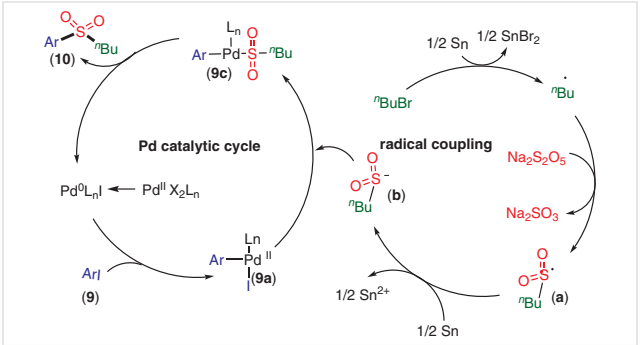
Scheme 5 Synthesis of cyclic sulfonamides

Recently, Jiang and co-workers reported a similar multicomponent approach for the reductive coupling of sodium metabisulfite ($Na_2S_2O_5$), 4-iodotoluene (**9**), and *n*-butyl bromide in the presence of a Pd-catalyst and potassium hydrogen phosphate. Important features of this protocol are the broad substrate scope, tolerance of various functional groups, simple and cheap coupling partner, and high yields of the products (Scheme 6).[29]



Scheme 6 Synthesis of sulfonyl derivatives using alkyl bromides as the coupling partner

From the control experiments performed, a suitable mechanism was proposed. Initially, the *n*-butyl radical is generated via a single-electron transfer between alkyl halide and tin, which reacts with sodium metabisulfite to give sulfonyl intermediate (**a**). The intermediate (**a**) undergoes reduction with tin, giving sulfonyl anion intermediate (**b**). Intermediate (**b**) then reacts with intermediate **9a** (generated via the oxidative addition of Pd(0) and aryl halide) to give intermediate **9c**. Reductive elimination of intermediate **9c** provides the sulfonylated product **10** (Scheme 7).



Scheme 7 Proposed mechanism for the formation of aryl alkyl sulfones

Since methyl sulfones are privileged scaffolds in many pharmaceuticals, synthesis of such molecules has attracted considerable attention.[21] For example, Vismodegib® (Figure 1) is a basal-cell carcinoma treatment that was first explored by Roche. Xiidra® (Figure 2) has been applied for dry eye disease as an ophthalmic solution.[30]

An elegant synthesis of β-methylsulfonylated *N*-heterocycles (**12** or **12′**) via $FeCl_3$-catalyzed C(sp^3)–H dehydrogenation and C(sp^2)–H methylsulfonylation of unactivated cyclic amines using sodium metabisulfite and dicumyl peroxide (DCP) has been demonstrated by the Fan group. However, in this method, DCP serves as an oxidant as well

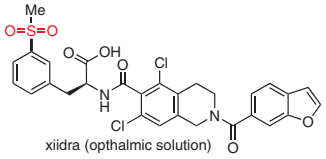
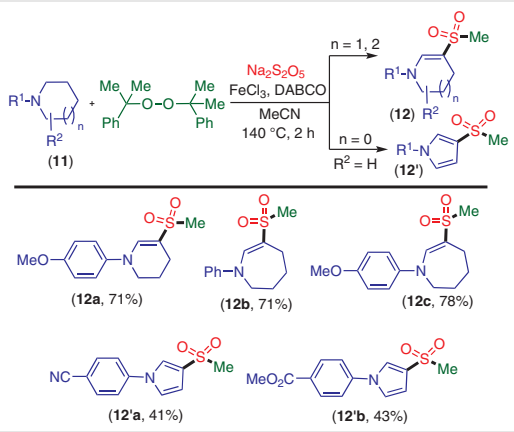


Figure 2 Sulfone-containing drug Xiidra®

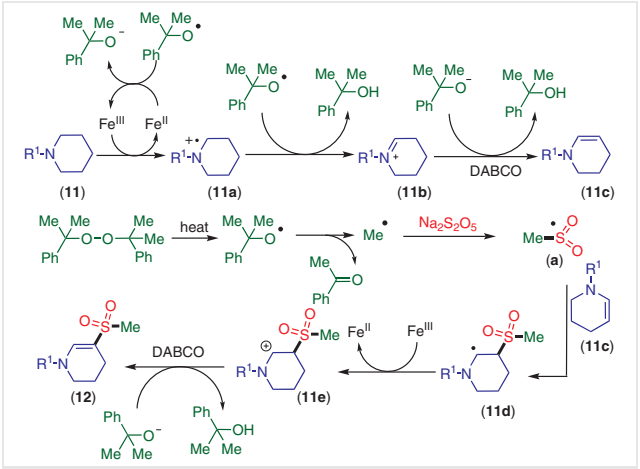
as a methyl radical source to generate a methyl sulfonyl radical. This protocol provided several β-methylsulfonylated tetrahydropyridines, tetrahydroazepines, and pyrroles in one-pot (Scheme 8).[31]



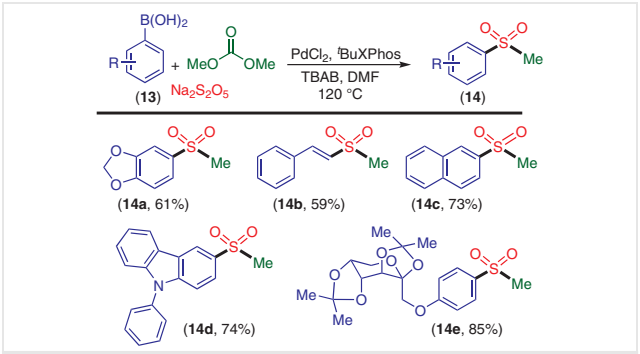
Scheme 8 Synthesis of β-methylsulfonylated *N*-heterocycles

In the proposed mechanism, the methyl radical initially generated from DCP is captured by sulfur dioxide to give a methylsulfonyl radical (**a**) along with the formation of acetone. Meanwhile, compound **11** is oxidized by Fe(III) to deliver a radical cation intermediate **11a**, which undergoes dehydrogenation to produce an iminium intermediate **11b** and $PhC(Me)_2OH$. Subsequently, enamine intermediate **11c** is generated via β-hydrogen abstraction by DABCO or $PhC(Me)_2O^-$. Next, the methylsulfonyl radical intermediate **A** undergoes addition with the enamine intermediate **11c** to provide intermediate **11d**, which, upon Fe(III)-promoted oxidation, gives cationic species **11e**. The final product **12** is obtained upon loss of a proton (Scheme 9).

Similarly, Jiang et al. demonstrated an efficient method for the synthesis of methyl sulfones **14** involving a three-component cross-coupling protocol of boronic acid **13**, sodium metabisulfite, and dimethyl carbonate. Important features of the reaction include a wide range of substrate scope, and good functional group tolerance Among the various ligands tested, it was found that electron-rich and sterically hindered phosphine ligands are more suitable for the desired conversion (Scheme 10).[32]

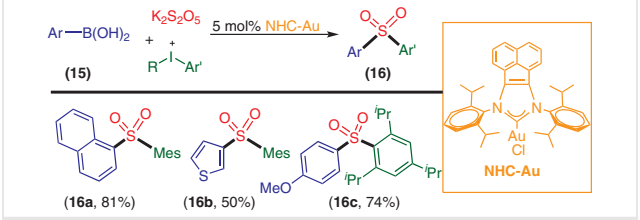


Scheme 9 Proposed mechanism for the formation of aryl alkyl sulfones



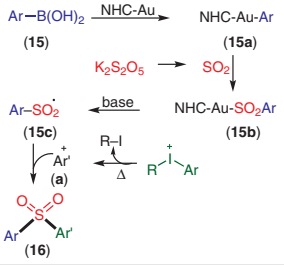
Scheme 10 Synthesis of sulfonyl derivatives using dimethyl carbonate as the methylating agent

Synthesis of *o*-substituted diaryl sulfones **16** via a multicomponent reaction of arylboronic acid **15**, potassium metabisulfite, and diaryliodonium salt was demonstrated by Tu et al. in 2019 using an acenaphthoimidazolylidene gold complex as the catalyst (Scheme 11).[33] The sterically hindered aryl groups in diaryliodonium salts are preferentially transformed over less bulky ones during the process, which might be due to the better stability of the bulky Ar^+ formed from diaryliodonium salt. A wide variety of diaryl sulfones could be obtained using various arylboronic acids and aryldiazonium salts.



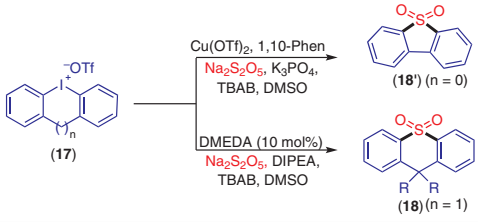
Scheme 11 Synthesis of diaryl sulfones using boronic acid and diaryliodonium salts

According to the proposed mechanism, initial transmetalation of NHC-Au(I) with arylboronic acid **15** provides NHC-Au-Ar species **15a**. This is then followed by the insertion of SO_2 to provide a sulfonyl Au(I) complex **15b**. The NHC-AuSO_2-Ar (**15b**), furnishes an aryl sulfonyl radical intermediate **15c** in the presence of base. The combination of intermediate **15c** with the more stable bulky Ar^+ species (**a**), generated from diaryliodonium salt, affords the sterically hindered diaryl sulfone **16** (Scheme 12).



Scheme 12 Proposed mechanism for the formation of diaryl sulfones

By utilizing the same SO_2 insertion strategy, the Jiang group reported a method for the synthesis of diarylannulated sulfones **18** and **18′** using $Na_2S_2O_5$ as SO_2 surrogate. The diarylannulated sulfones were synthesized via SO_2/I exchange of iodonium (III) salts **17**. By this protocol, a new type of OLED material was synthesized on gram scale with good functional group tolerance, permitting a broad range of substrate scope (Scheme 13).[34]



Scheme 13 Synthesis of diaryl annulated sulfones

Often, compounds having a furan2(5*H*)-one backbone have high biological activity.[35a] For example, Rofecoxib® (Figure 3) is an anti-inflammatory drug launched by Merck and approved by the US FDA.[35b] Several 4-aryl-3methyl-furan-2(5*H*)-ones are effective in controlling fungal diseases in plants of agronomic importance.[36] In this context, Wu et al. in 2019 demonstrated a method in which 4-sulfonylated furan-2(5*H*)-ones **20** are formed by a three-component reaction of 2,3-allenoic acids **19**, sulfur dioxide, and aryldiazonium tetrafluoroborates in the presence of a copper catalyst. The method utilizes both DABSO and $Na_2S_2O_5$ as the SO_2 source. Mild reaction conditions, as well as tolerance of various functional groups, such as nitro groups and esters, as well as broad substrate scope are the important features of the protocol. However, steric effects in the aryl diazonium salt greatly affect the outcome, giving a downward trend in the yield of the product (Scheme 14).[37]

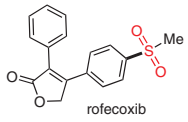
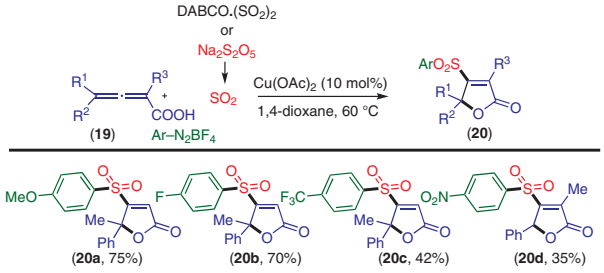
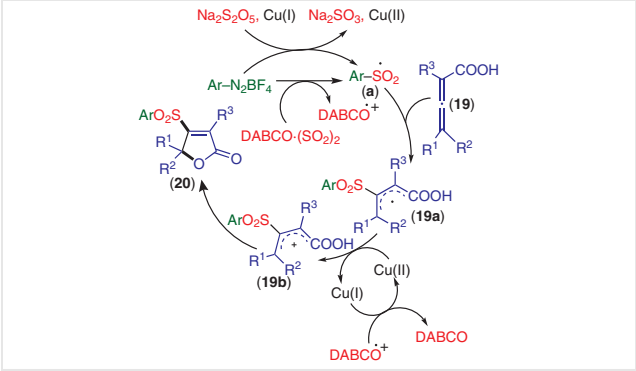


Figure 3 Rofecoxib® an anti-inflammatory drug



Scheme 14 Synthesis of 4-sulfonylated furan-2(5*H*)-ones

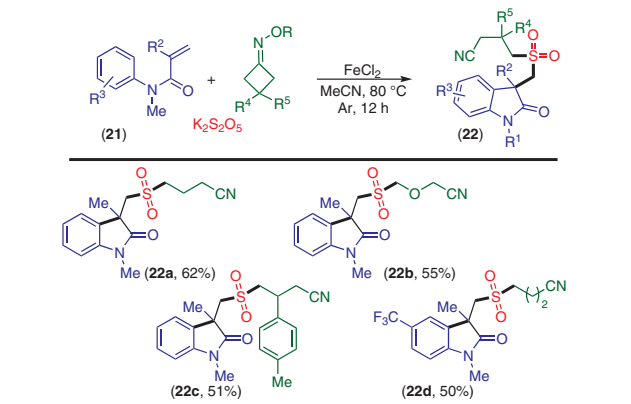
Based on literature precedent, the proposed mechanism involves the generation of an aryl radical via single-electron transfer of an aryl diazonium tetrafluoroborate with Cu(I). This radical then reacts with SO_2 obtained from $Na_2S_2O_5$, affording an aryl sulfonyl radical intermediate (**a**). The C-central position of 2,3-allenoic acid **19** is then attacked by the aryl sulfonyl radical (**a**) to give intermediate **19a**, which is transformed into intermediate **19b**, assisted by the copper(II) catalyst. Subsequently, the intermediate **19b** undergoes intramolecular nucleophilic attack by the carboxylate anion in the presence of a base, leading to 4-sulfonylated furan-2(5*H*)-one (**20**) (Scheme 15).



Scheme 15 Proposed mechanism for the formation of 4-sulfonylated furan-2(5*H*)-ones

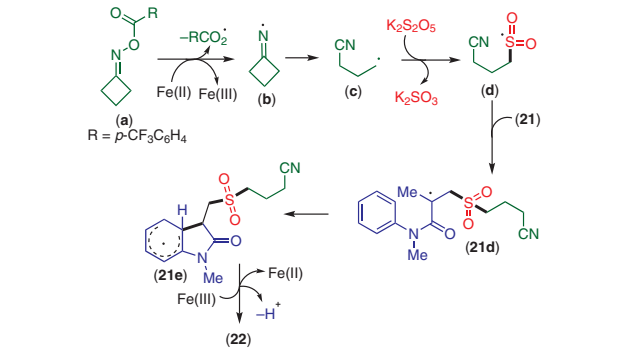
Alkyl nitriles are present in various natural products and pharmaceuticals.[38] Moreover, cyanoalkyl groups can be readily converted into other useful functional groups such as esters, amides, carboxyls, and tetrazoles.[39] Similarly, oxindoles are privileged scaffolds in many drugs and biologically active compounds.[40] Liu's group demonstrated an

iron-catalyzed protocol for the synthesis of cyanoalkyl sulfonylated oxindoles **22** from activated olefins **21** and cyclic keto oximes via C–C single-bond insertion of sulfur dioxide. The method does not require any additional base or oxidant, which is one of the main advantages of the protocol (Scheme 16).[41]



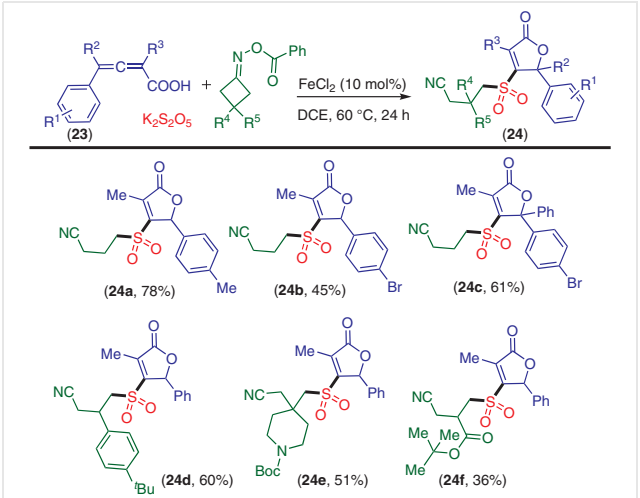
Scheme 16 Synthesis of 3-cyanoalkyl sulfonylated oxindoles

Based on literature precedent and on experimental results, a mechanism for the iron-catalyzed radical cyanoalkylsulfonylation/arylation of active olefins was proposed (Scheme 17). Initially, the oxime ester (**a**) undergoes SET reduction by Fe(II) to give an iminyl radical intermediate (**b**), which forms intermediate (**c**) via cleavage of the C–C bond. Subsequently, the intermediate (**c**) is captured by the SO_2 generated from $K_2S_2O_5$, to provide another intermediate (**d**). Next, the radical intermediate (**d**) attacks the C–C bond of acrylamide (**21**) to provide intermediate **21d**, which undergoes intramolecular cyclization to give intermediate **21e**. Finally, SET oxidation of intermediate **21e** by Fe(III) followed by 4-(trifluoromethyl)benzoate ion assisted deprotonation gives the final product **22** and regenerates Fe(II) for the next catalytic cycle.



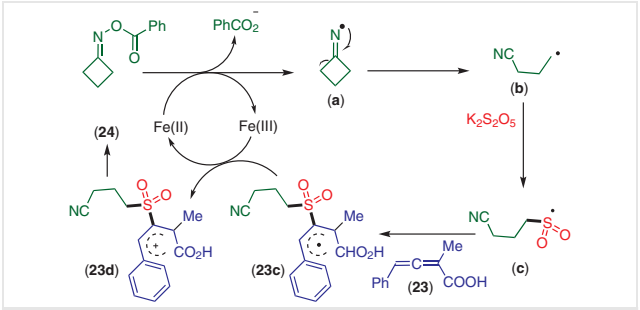
Scheme 17 Proposed mechanism for the formation of 3-cyanoalkyl-sulfonylated oxindoles

In 2021 Yu et al. demonstrated an iron-catalyzed SO_2 insertion between 2,3-allenoic acids **23** and cyclobutanone oxime esters using $K_2S_2O_5$ as the SO_2 surrogate (Scheme 18).[42] During the reaction, ring-opening of the cyclobutanone oxime ester produces a cyanoalkyl radical, which is followed by a radical tandem cyclization providing cyanoalkylsulfonylated butenolides **24**.



Scheme 18 Cyanoalkylsulfonylation of 2,3-allenoic acids

The suggested mechanism involves the reduction of the cycloketone oxime ester by Fe(II) via SET, leading to the formation of an iminyl radical (**a**) through N–O bond cleavage. Subsequently, the C–C bond cleavage of intermediate (**a**) gives an alkyl radical species (**b**), which, in combination with sulfur dioxide from $K_2S_2O_5$, provides a sulfonyl radical intermediate (**c**). This is then followed by the addition to allenoic acid **23** to form intermediate **23c**. The intermediate **23c** undergoes oxidation in the presence of the Fe(III) catalyst to provide allylic cation **23d**. Finally, the cyclized product **24** is obtained via intramolecular nucleophilic attack (Scheme 19).

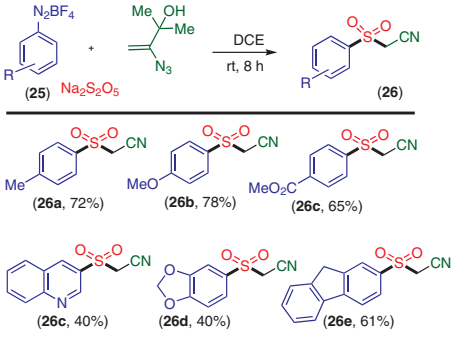


Scheme 19 Proposed mechanism for the cyanoalkylsulfonylation of 2,3-allenoic acids

2.2 Transition-Metal-Free SO_2 Insertion

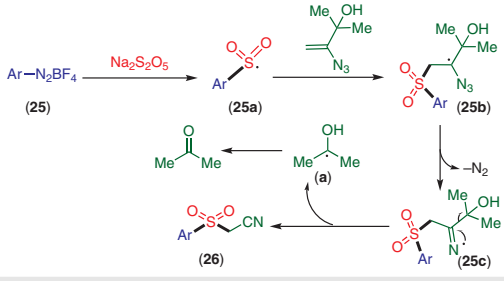
Although transition-metal-catalyzed SO_2 insertion has gained considerable attention, the development of efficient and practical protocols for the direct introduction of sulfonyl group in the absence of a transition-metal catalyst is an attractive approach. The introduction of a sulfonyl group under transition-metal-free conditions is a challenging task.[43]

A metal-free multi-component strategy was disclosed by Wu et al. for the synthesis of nitrile-containing sulfones **26** using aryldiazonium tetrafluoroborates **25**, and 3-azido-2-methylbut-3-en-2-ol with sodium metabisulfite as the sulfur dioxide surrogate (Scheme 20).[44]



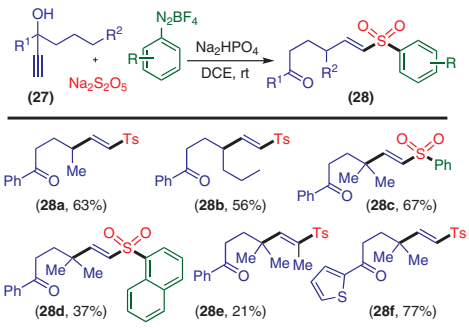
Scheme 20 Synthesis of nitrile-containing sulfones

A plausible mechanism for this sulfonylation process is described in Scheme 21. Initially, aryl sulfonyl radical **25a** is generated in situ by the reaction of aryldiazonium tetrafluoroborate **25** and sodium metabisulfite. Further, the addition of aryl sulfonyl radical **25a** to 3-azido-2-methylbut-3-en-2-ol gives the radical intermediate **25b**, which subsequently releases N_2, generating a nitrogen-centered radical **25c**. The radical intermediate **25c** provides arylsulfonylacetonitrile **26** via C–C bond cleavage, along with a ketyl radical (**a**), which, upon loss of a proton, forms acetone as the sole by-product.



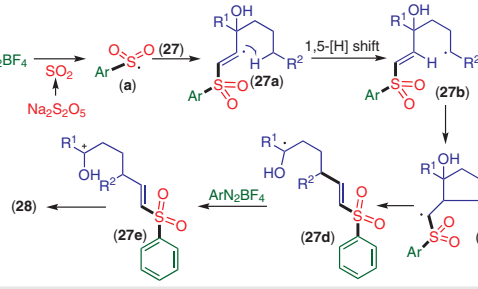
Scheme 21 Proposed mechanism for the formation of nitrile-containing sulfones

Vinyl sulfones are found in many natural products and pharmaceuticals.[45] The reactivity of α,β-unsaturated sulfones leads to various organic transformations via nucleophilic addition, radical addition, and cycloaddition. A metal-free, three-component reaction protocol involving propargyl alcohol **27**, sodium metabisulfite, and aryldiazonium tetrafluoroborates was demonstrated by Wu et al. in 2020 (Scheme 22).[46] The reaction proceeds efficiently at room temperature in the absence of catalyst, providing *E*-vinyl sulfones **28** in moderate to good yields. The approach involves a vinyl radical-induced 1,5-hydrogen atom transfer and functional group migration, resulting in sequential cleavage of inert C–H and C–C bonds, respectively. Aryldiazonium tetrafluoroborates bearing electron-donating or electron-withdrawing groups on the aromatic ring worked smoothly in this transformation, providing the desired products **28** in moderate to good yields. Besides this, a wide variety of propargyl alcohols was also successful (Scheme 22).



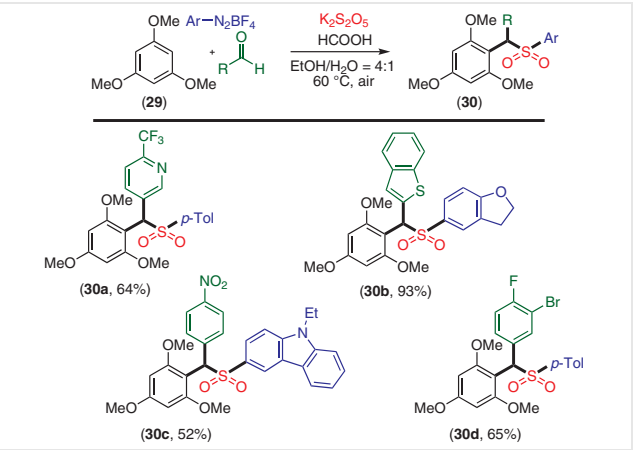
Scheme 22 Synthesis of vinyl sulfones

In the proposed mechanism, an aryl sulfonyl radical intermediate (**a**) is generated from the aryl diazonium salt and $Na_2S_2O_5$. Radical addition of intermediate (**a**) to alkyne **27** provides intermediate **27a**, which, upon 1,5-[H] shift, gives intermediate **27b**. The intermediate **27b** undergoes radical cyclization followed by SET and deprotonation to give product **28** (Scheme 23).



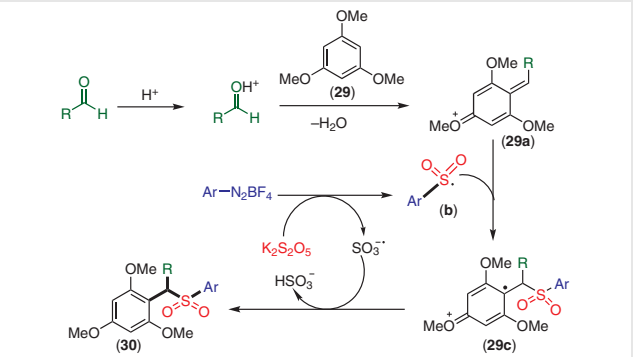
Scheme 23 A tentative mechanism for the formation of vinyl sulfones

Recently, an elegant method for the synthesis of aryl sulfones was reported by Wu et al. The method offers a range of (arylsulfonyl)methylbenzenes **30** via a multicomponent reaction of electron-rich arenes **29**, potassium metabisulfite, aromatic aldehydes, and aryldiazonium tetrafluoroborates in the presence of formic acid (Scheme 24).[47] The reaction proceeds very well under mild reaction conditions with broad substrate scope tolerating various functional groups.



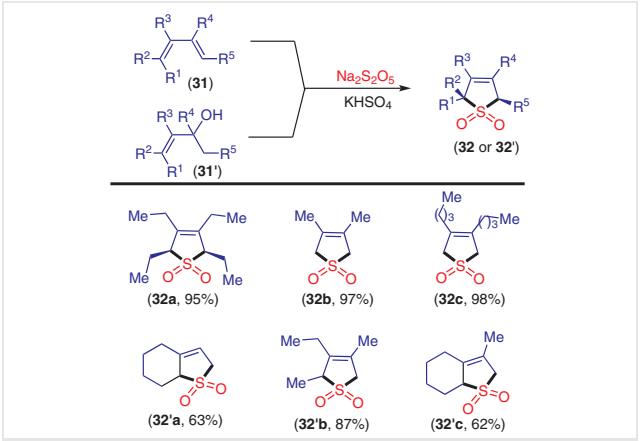
Scheme 24 Synthesis of aryl sulfones using aromatic aldehydes and aryl diazonium salts

According to the proposed mechanism, condensation of 1,3,5-trimethoxybenzene (**29**) with an aldehyde in the presence of formic acid generates cationic intermediate **29a**. Aryldiazonium tetrafluoroborate reacts with potassium metabisulfite, leading to an arylsulfonyl radical intermediate (**b**) that attacks intermediate **29a** to provide a radical cation **29c**. Subsequently, deprotonation via SET affords product **30** (Scheme 25).



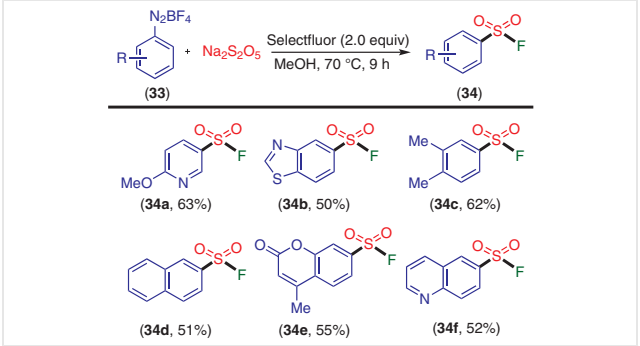
Scheme 25 A plausible mechanism for the formation of aryl sulfones

Five-membered sulfur heterocycles have a major presence in medicinal chemistry and materials sciences.[48] In this regard, Larionov et al. in 2018 reported an efficient method for the synthesis of 3-sulfolenes **32** or **32′** from 1,3-dienes **31** or allylic alcohols **31′** with sodium metabisulfite as the SO_2 surrogate. Most of the sulfolenes were obtained in good to excellent yields when carried out in HFIP or with $KHSO_4$ in methanol. Broad substrate scope, good product yield, gram-scale synthesis, and metal-free conditions are some noteworthy features of this protocol (Scheme 26).[49]



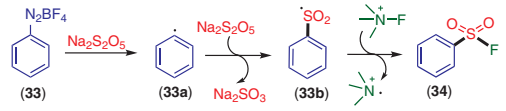
Scheme 26 Synthesis of 3-sulfolenes using 1,3-dienes

Sulfonyl fluorides have gained importance and attracted attention due to their unique reactivity and stability. In addition, sulfonyl fluorides are also used in place of sulfonyl chloride for the synthesis of sulfonylated compounds.[50] Inspired by this, Lu and co-workers established a method for the formation of aryl sulfonyl fluorides **34** from arene diazonium salts **33** using sodium metabisulfite as the SO_2 source (Scheme 27).[51] Aryl diazonium salts possessing electron-donating, as well as electron-withdrawing substituents, performed well in this transformation. Furthermore, several heteroaromatic diazo compounds reacted smoothly under identical reaction conditions to give the corresponding sulfonyl fluorides. Using this protocol, a copper-free Sandmeyer fluorosulfonylation was established.



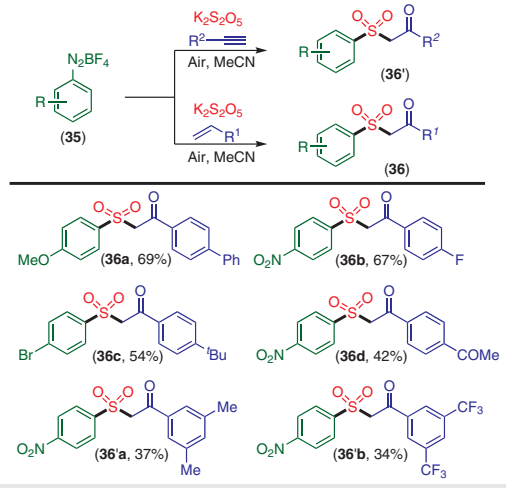
Scheme 27 Synthesis of aryl sulfonyl fluorides

According to the proposed mechanism, the aryl diazonium salt undergoes SET to give an aryl radical **33a** that then captures SO_2 from the sodium metabisulfite to give the aryl sulfonyl radical intermediate **33b**. The radical intermediate **33b** then reacts with the fluoride radical obtained from Selectfluor®, affording the desired product **34**. In this protocol, sodium metabisulfite serves the dual role of reductant and SO_2 source, enabling this copper-free Sandmeyer-type fluorosulfonylation (Scheme 28).



Scheme 28 Proposed mechanism for the formation of aryl sulfonyl fluorides

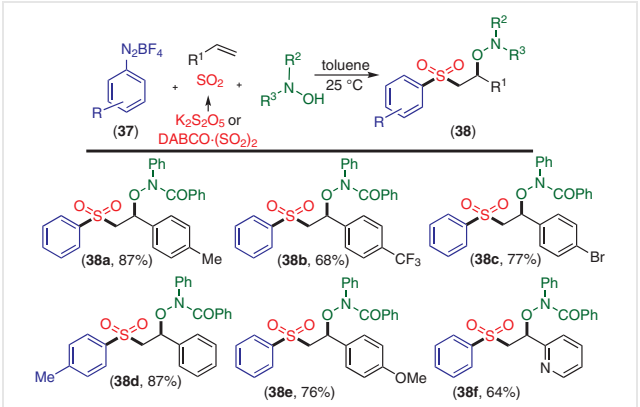
Radical difunctionalization of alkenes and alkynes is an interesting approach to introduce two functional groups simultaneously.[52] Singh et al. in 2020 reported an efficient method for the synthesis of β-ketosulfones **36** and **36′** via a multicomponent reaction of alkenes or alkynes, aryldiazonium salts **35**, and SO_2 derived from $K_2S_2O_5$ under transition-metal-free conditions. The strategy is equally successful for phenyl acetylenes and styrenes bearing electron-withdrawing as well as electron-donating groups (Scheme 29).[53]



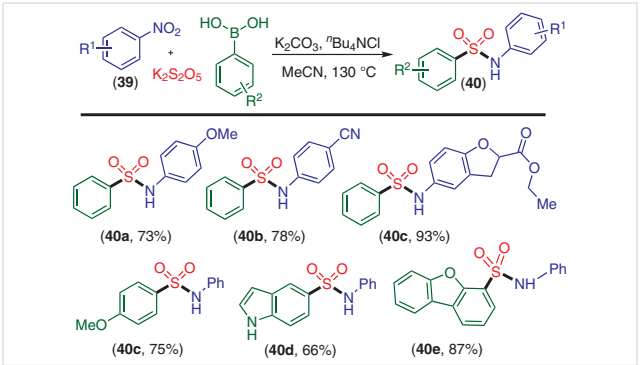
Scheme 29 Synthesis of β-ketosulfones

Similarly, Wu et al. reported a four-component reaction of aryldiazonium salts **37**, sulfur dioxide, alkenes, and hydroxylamine. The methodology utilized both DABCO·$(SO_2)_2$ and $K_2S_2O_5$ as the SO_2 surrogate, which underwent a smooth reaction both with aryl diazonium salts and styrenes (Scheme 30).[54]

Sulfonamide synthesis via a metal-free approach is challenging for synthetic chemists. In this regard, Wu et al. in 2021 developed a multicomponent reaction involving nitroarenes **39**, arylboronic acids, and potassium metabisulfite, leading to the formation of sulfonamides **40**. A noteworthy feature of this protocol is that it is transition-metal-free, and exhibits broad functional group tolerance. A range of sulfonamides bearing different reactive functional groups was obtained in good to excellent yields (Scheme 31).[55]



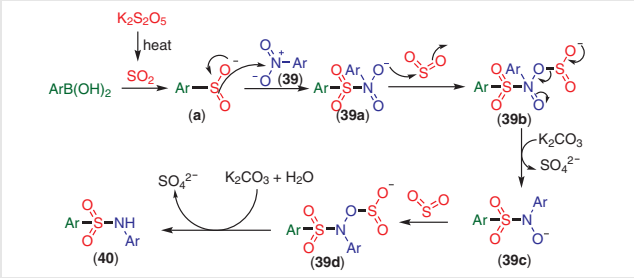
Scheme 30 *Vicinal* difunctionalization of alkenes via SO_2 insertion



Scheme 31 Metal-free synthesis of sulfonamides

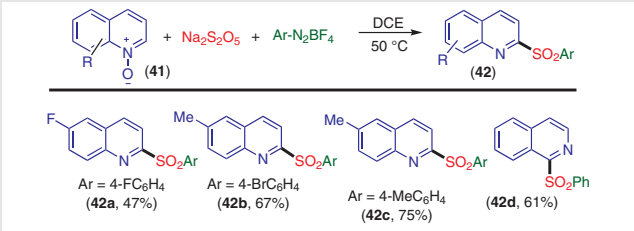
The mechanism shown in Scheme 32 involves decomposition of $K_2S_2O_5$, resulting in formation of SO_2, which undergoes nucleophilic addition with the arylboronic acid to form benzenesulfinate (**a**). Subsequently, nucleophilic addition of (**a**) to nitroarene **39** generates intermediate **39a**, which couples with another molecule of SO_2 to provide intermediate **39b**. In the presence of K_2CO_3, intermediate **39b** eliminates SO_4^{2-} to give intermediate **39c**. Subsequently, addition of SO_2 followed by elimination of SO_4^{2-} provides the desired sulfonamide **40** via the intermediacy of **39d**.

Quinolines are an important class of heterocycles with diverse biological and pharmacological properties.[56] In this context, quinoline *N*-oxides are valuable starting materials for different transformations to provide functionalized quinolines. Recently, Xia and co-workers developed a metal-free, three-component reaction of quinoline *N*-oxides **41**, sodium metabisulfite, and aryldiazonium tetrafluoroborates via a radical process to give 2-sulfonyl quinolones/



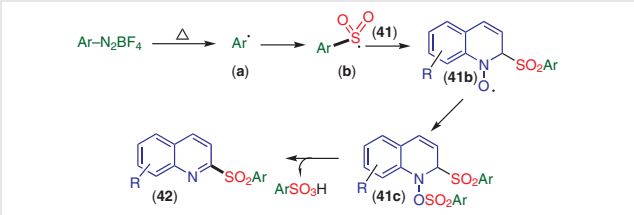
Scheme 32 Proposed mechanism for the formation of sulfonamides

isoquinolines **42** (Scheme 33).[57] In this approach, aryldiazonium tetrafluoroborates bearing *p*-substituents were more efficient than those bearing *m*- and *o*-substituents. This might be due to steric effects. On the other hand, aryldiazonium tetrafluoroborates bearing electron-donating groups reacted better than those bearing electron-withdrawing groups. Besides this, a variety of quinoline *N*-oxides and isoquinoline *N*-oxides worked well in this methodology.



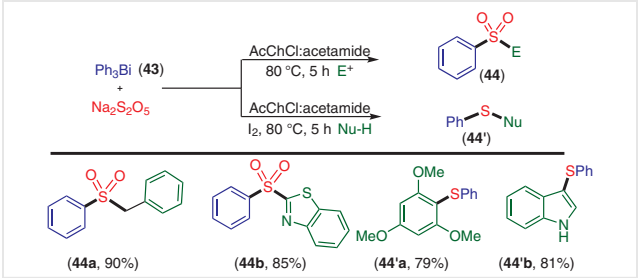
Scheme 33 Metal-free synthesis of 2-sulfonyl quinolones/isoquinolines

In the proposed mechanism (Scheme 34), the aryldiazonium tetrafluoroborate undergoes thermal decomposition to give an aryl radical (**a**) that combines with SO_2 obtained from sodium metabisulfite to provide an aryl sulfonyl radical (**b**). Then addition of (**b**) to quinoline *N*-oxide **41** via a Minisci-like radical transformation generates an *O*-radical intermediate **41b** that captures another aryl sulfonyl radical to give intermediate **41c**. Finally, elimination of aryl sulfonic acid from intermediate **41c** affords the corresponding 2-sulfonyl quinolines **42**.



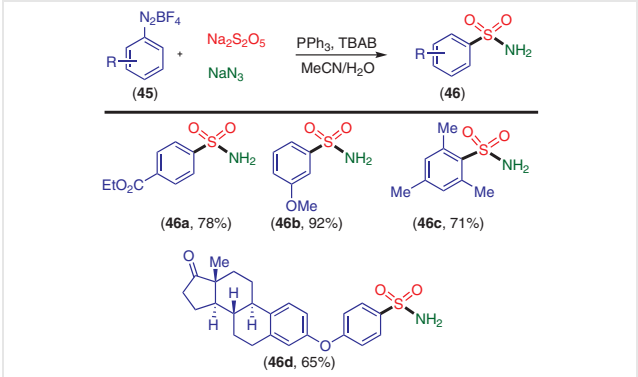
Scheme 34 Proposed mechanism for the formation of 2-sulfonyl quinolones

In 2020, Ramon et al. developed a catalyst-free methodology for the multicomponent synthesis of sulfones, disulfides, and sulfides using non-toxic triarylbismuthines (Ar_3Bi) (**43**) and sodium metabisulfite in a deep eutectic solvent (DES) (Scheme 35).[58] The use of DES helped to solubilize all reagents, thereby, enhancing their reactivity. A variety of electrophiles and nucleophiles in the synthesis of sulfones and sulfide worked well.



Scheme 35 Synthesis of sulfones and sulfides in deep eutectic solvents

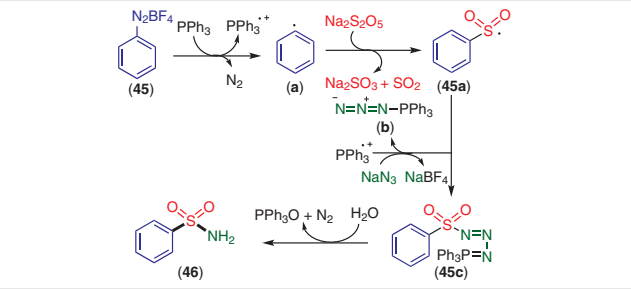
In 2018, Jiang et al. demonstrated a metal-free synthesis of sulfonamides **46** via a three-component reaction involving sodium metabisulfite, sodium azide, and aryl diazonium salts **45** (Scheme 36).[59]



Scheme 36 Synthesis of primary sulfonamides

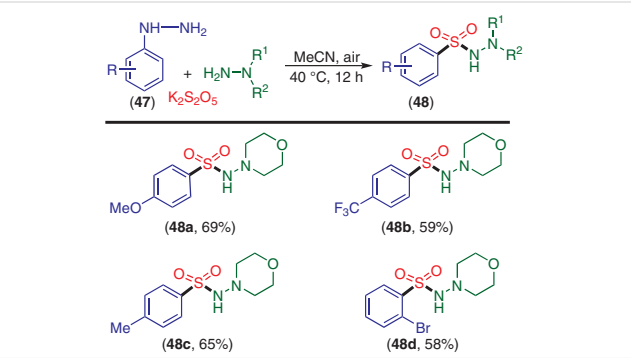
The mechanism for the formation of the product **46** is depicted in Scheme 37. The process involves the generation of an aryl radical intermediate (**a**) via SET between the aryl diazonium salt and triphenylphosphine. Then the SO_2 combines with the aryl radical intermediate (**a**) to give an aryl sulfonyl intermediate **45a**, which reacts with the phosphine imine radical (**b**) and sodium azide to provide intermediate **45c**. Subsequent hydrolysis of intermediate **45c** affords the product **46** along with the by-product triphenylphosphine oxide.

Previously, the Pan group in 2013 demonstrated a catalyst-free method for the synthesis of sulfonylhydrazides **48** from phenylhydrazines **47** as the aryl source and potassium metabisulfite as the SO_2 source. Metal-free, additive-free conditions, readily available starting materials, and low



Scheme 37 Proposed mechanism for the formation of primary sulfonamides

reaction temperatures are the merits of this protocol, in which phenylhydrazines bearing both electron-withdrawing and electron-donating groups were well tolerated (Scheme 38).[60]

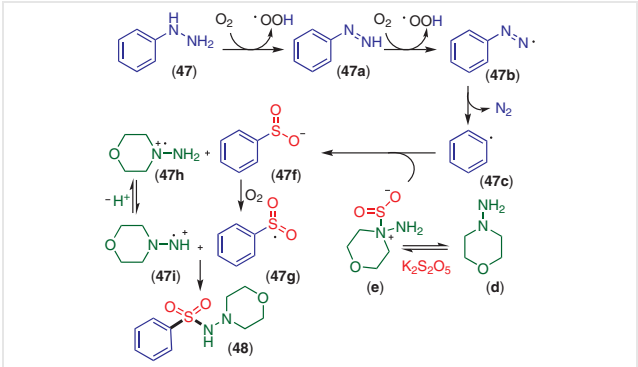


Scheme 38 Synthesis of primary sulfonylhydrazides

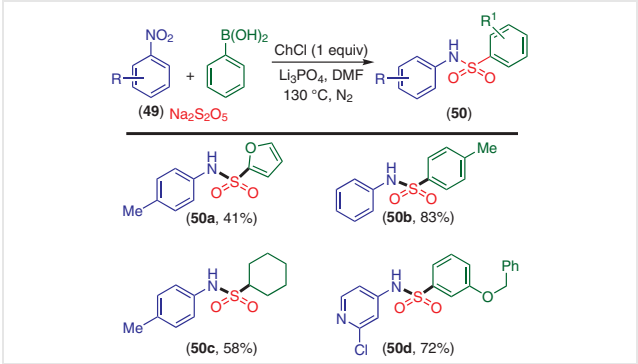
In the suggested mechanism, in the presence of O_2, phenylhydrazines **47** undergoes two-step deprotonation to give an aryl radical intermediate **47c** via the intermediacy of **47a** and **47b**. Then the intermediate **47c** combines with the sulfonyl anionic intermediate (**e**) (obtained from the reaction of cyclic amine (**d**) and $K_2S_2O_5$) to generate an anionic intermediate **47f** along with a radical cation **47h** via SET. Oxidation of intermediate **47f** affords the aryl sulfone radical **47g**, and deprotonation of the intermediate **47h** provides intermediate **47i**. Finally, radical coupling of intermediate **47g** and **47i** affords the desired product **48** (Scheme 39).

In 2018 Jiang et al. developed an efficient method for the synthesis of sulfonamides **50** from readily available nitrobenzenes **49**, boronic acids, and $Na_2S_2O_5$ as the SO_2 surrogate. In this protocol sodium metabisulfite ($Na_2S_2O_5$) serves the role of both activator as well as reductant during sulfonamidation (Scheme 40).[61]

In the proposed reaction, nitrobenzene (**49**) reacts with sodium metabisulfite to give intermediate **49a**, which is converted into nitrosyl intermediate **49b** with the release of Na_2SO_3 and SO_3 (Scheme 41). Simultaneously, sodium metabisulfite acts as an anionic counterpart to activate the C–B

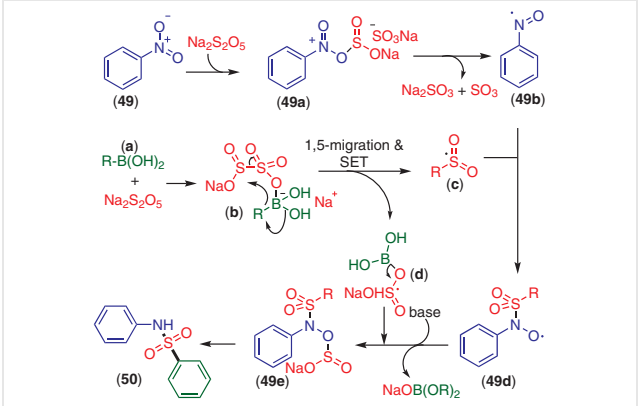


Scheme 39 Proposed mechanism for the formation of sufonylhydrazides



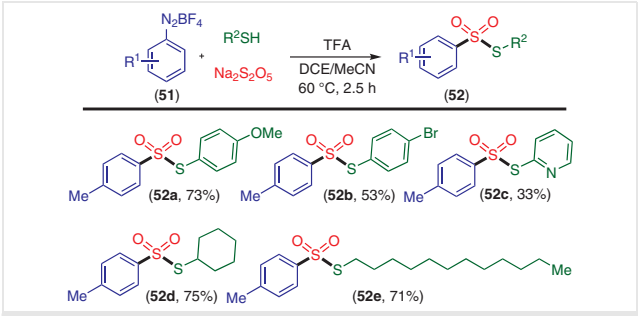
Scheme 40 Synthesis of sulfonamides using nitrobenzenes, boronic acids, and $Na_2S_2O_5$

bond of boronic acid (**a**) to afford an SO_2 conjugate intermediate (**b**). The sulfonyl radical intermediate (**c**) is generated from (**b**) via 1,5-migration and SET. Subsequently, intermediate **49b** and (**c**) combine to give the nitroso radical intermediate **49d** followed by hydrolysis to afford the desired product **50**.



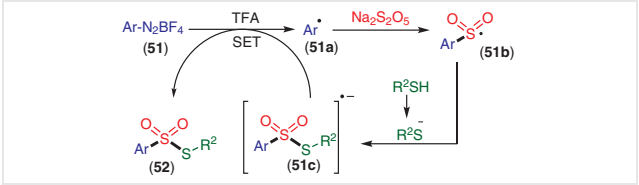
Scheme 41 Proposed mechanism for the formation of *N*-aryl sulfonamides

In 2020, the Shun-Jun Ji group reported an efficient TFA-promoted, transition-metal-free, multicomponent reaction of aryldiazonium salts **51** with sodium metabisulfite ($Na_2S_2O_5$) and thiols to construct thiosulfonates **52** (Scheme 42).[62] The reaction proceeds smoothly with a broad tolerance of functional groups present in the aromatic rings of both the aryldiazonium salts as well as in thiols. Moreover, heteroaromatic and aliphatic thiols are also well tolerated to afford the desired thiosulfonates.



Scheme 42 Synthesis of thiosulfonates

Based on the proposed mechanism (Scheme 43) TFA reacts with diazonium salt **51** to generate the corresponding aryl radical **51a**. This aryl radical **51a** then reacts with $Na_2S_2O_5$ to give an arylsulfonyl radical intermediate **51b** that combines with the sulfur anion to give radical anion intermediate **51c**. The radical anion **51c** undergoes SET to give the thiosulfonate **52**.

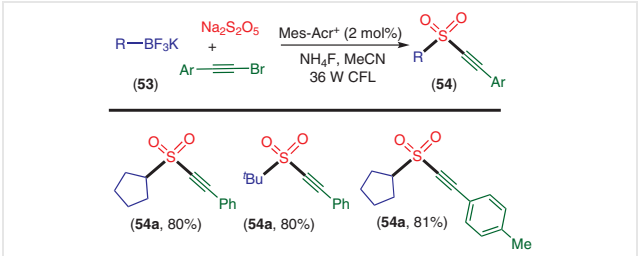


Scheme 43 Proposed mechanism for the formation of thiosulfonates

2.3 Visible-Light-Mediated SO_2 Insertion

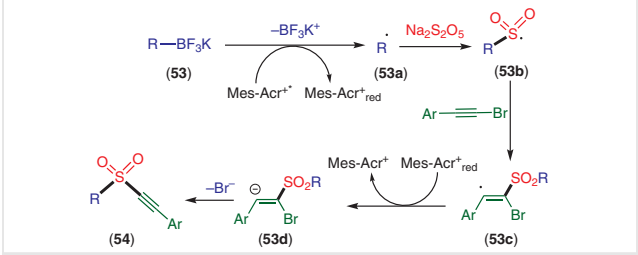
Recently, visible-light-mediated functionalizations have emerged as significant methodologies in contemporary organic chemistry.[63,64] However, most organic compounds do not absorb visible light efficiently, which limits the application of light-mediated organic synthesis. To overcome this, either a transition-metal complex (complexes of Rh, Ir, Ru) or organic dyes such as eosin Y or rose Bengal are used as sensitizers for the required photochemical transformation.[65,66] As mentioned above, various methods used for SO_2 insertion require high temperatures and harsh reaction conditions; hence, there is a need for developing methods for SO_2 insertion under milder reaction conditions. In this context, SO_2 insertion reaction mediated by visible light either in the presence of transition-metal complexes or organic dyes as photoredox catalysts has gained a place in organic synthesis.[67,68]

In 2020 Wu et al. reported a photocatalytic synthesis of alkylalkynyl sulfones **54** through the insertion of sulfur dioxide between potassium alkyltrifluoroborates **53** and alkynyl bromides using sodium metabisulfite ($Na_2S_2O_5$) as the SO_2 source (Scheme 44).[69] This photoinduced reaction proceeded well at room temperature, had broad substrate scope, and gave the products in moderate to good yields.



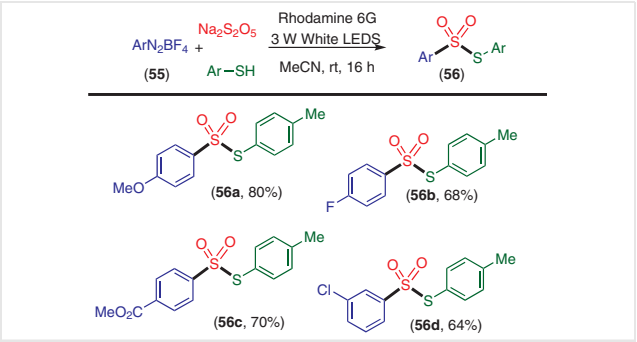
Scheme 44 Visible-light-mediated synthesis of alkylalkynyl sulfones

According to the proposed mechanism (Scheme 45) an alkyl radical **53a** is generated from potassium alkyltrifluoroborate **53** by the influence of the photocatalyst under visible-light irradiation. Subsequently, the sulfur dioxide generated from $Na_2S_2O_5$ couples with radical **53a** to provide alkylsulfonyl radical **53b** that then attacks the C–C triple bond of the alkynyl bromide to provide vinyl radical intermediate **53c**. Next, SET converts vinyl radical **53c** into vinyl anion **53d**. Finally, elimination of bromide gives rise to alkylalkynyl sulfone **54**.



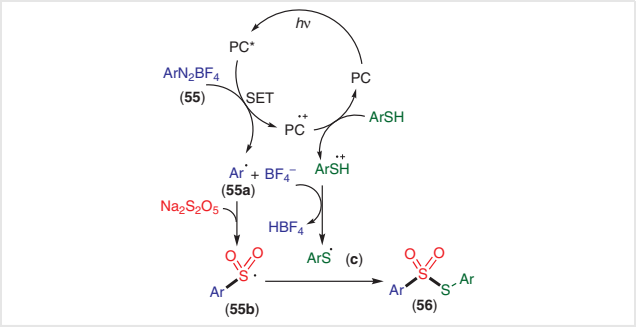
Scheme 45 Proposed mechanism for the formation of alkylalkynyl sulfones

Thiosulfonates are useful building blocks in organic synthesis owing to their unusual reactivity and stability.[70] A visible-light-promoted synthesis of thiosulfonates **56** was reported by He et al. using thiols, aryldiazonium salts **55**, and sodium metabisulfite under metal-free conditions (Scheme 46).[71] This mild, three-component reaction utilizes rhodamine 6G as the photocatalyst to provide unsymmetrical thiosulfonates.



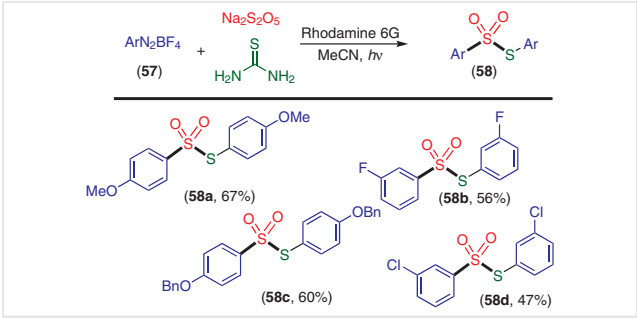
Scheme 46 Visible-light-mediated synthesis of thiosulfonates

Following the proposed mechanism (Scheme 47), rhodamine 6G (PC) is first excited to an excited species PC* under visible-light irradiation. Then, aryl radical **55a** is generated from the aryldiazonium salt **55** via SET with the release of N_2 and BF_4^-. Subsequently, the interaction of aryl radical **55a** with $Na_2S_2O_5$ generates arylsulfonyl radical **55b** and Na_2SO_3. The PC radical cation obtained from the SET process oxidizes the thiol to produce a thiyl radical cation, which is deprotonated by BF_4^- to produce a thiyl radical (**c**). Finally, coupling of arylsulfonyl radical **55b** with the thiyl radical (**c**) gave the product **56**; whereas homocoupling provided the disulfide.



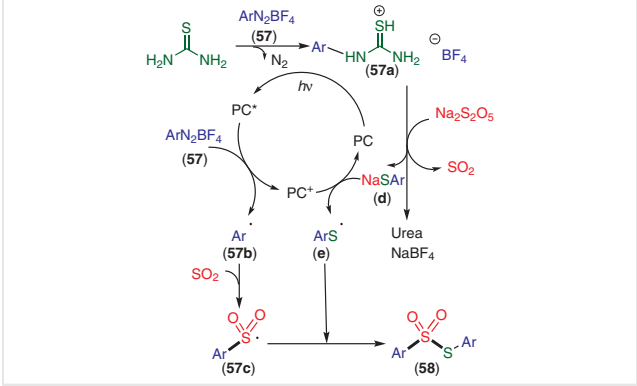
Scheme 47 Proposed mechanism for the formation of thiosulfonates

Subsequently, Wu and co-workers reported a photoinduced three-component reaction of aryldiazonium tetrafluoroborates **57**, sodium metabisulfite, and thiourea, leading to *S*-aryl thiosulfonates **58** (Scheme 48).[72] A variety of aryldiazonium tetrafluoroborates worked well in this transformation. This method was unsuccessful for *S*-alkyl thiosulfonate preparation because of stability issues with the alkyl diazonium tetrafluoroborates. Moreover, the reaction was unsuccessful for 2-substituted aryldiazonium tetrafluoroborates. This might be due to the steric hindrance.



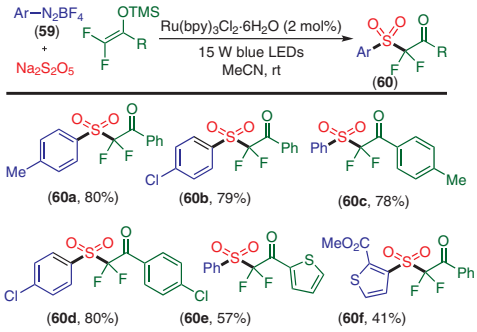
Scheme 48 Visible-light-mediated synthesis of *S*-aryl thiosulfonates

According to the suggested mechanism (Scheme 49), initial reaction between thiourea and aryldiazonium tetrafluoroborate **57** generates a salt intermediate **57a**, which reacts with $Na_2S_2O_5$ to give sodium thiophenolate (**d**), and urea with the release of SO_2. In the presence of visible light, the photocatalyst is exited and produces aryl radical **57b** from another molecule of aryldiazonium tetrafluoroborate **57** via SET. Aryl radical **57b** then reacts with SO_2, generated from sodium metabisulfite, giving aryl sulfonyl radical intermediate **57c**. Subsequently, thiophenolate anion (**d**) affords an aryl sulfur radical (**e**), regenerating the ground-state photocatalyst. Finally, the combination of arylsulfonyl radical **57c** with the aryl sulfur radical (**e**) affords *S*-aryl thiosulfonate **58**.



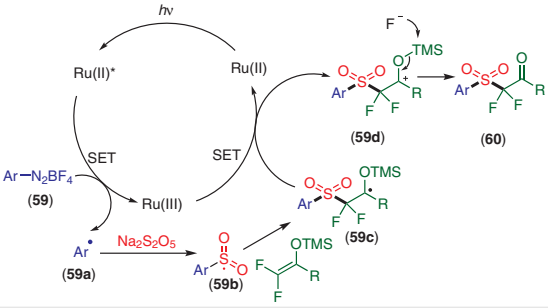
Scheme 49 Proposed mechanism for the synthesis of *S*-aryl thiosulfonates

A Ru(II) photoredox-catalyzed synthesis of α,α-difluoro-β-ketosulfones **60** was reported by Wu et al. in 2020 (Scheme 50).[73] The reaction involves a three-component coupling of aryldiazonium tetrafluoroborates **59** with sodium metabisulfite and 2,2-difluoroenol silyl ethers under mild conditions. In this conversion, the difluoromethyl group and sulfone moiety can be introduced in a single step.



Scheme 50 Visible-light-mediated synthesis of α,α-difluoro-β-keto-sulfones

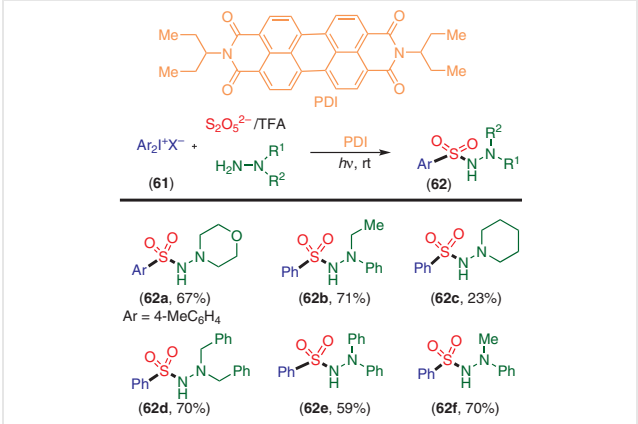
Based on the suggested mechanism as depicted in Scheme 51, initially, aryl radical **59a** is generated from the aryldiazonium tetrafluoroborate **59** via SET. Intermediate **59a** then reacts with SO_2, giving rise to arylsulfonyl radical **59b**. Intermediate **59b** subsequently attacks the double bond of the difluoroenoxysilane to provide a carbon-centered radical intermediate **59c** followed by SET with the oxidized photocatalyst, to yield carbocationic intermediate **59d**. Finally, the product **60** is formed through a fluoride-mediated desilylation.



Scheme 51 Proposed mechanism for the formation of α,α-difluoro-β-ketosulfones

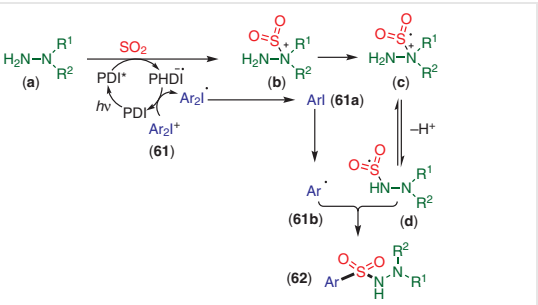
In 2017, Manolikakes et al. established a method for the formation of sulfonamides **62** by reacting diaryldiazonium salts **61**, $Na_2S_2O_5$, and hydrazines under visible-light photoredox catalysis. In this reaction, a combination of sodium metabisulfite and acid TFA is used as the SO_2 surrogate and perylene (PDI) as the photoredox catalyst. Both aromatic as well as aliphatic hydrazines worked well under identical reaction conditions (Scheme 52).[74]

In the proposed mechanism, formation of a stable hydrazine-sulfur dioxide adduct (**b**) is suggested. Meanwhile PDI* is produced by irradiation of photoredox catalyst PDI. The radical quenching of PDI* with the hydrazine-sulfur dioxide complex (**b**) forms a radical cation (**c**), which undergoes deprotonation to give a sulfonyl radical intermediate (**d**). Simultaneously, aryl radical **61b**, generated from the



Scheme 52 Synthesis of sulfonamide using PDI as photoredox catalyst

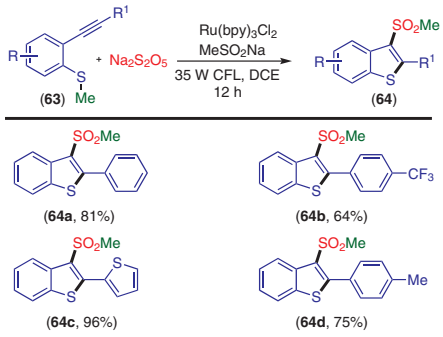
aryl diazonium salt **61** via an electron transfer from PDI radical anion, couples with the sulfonyl radical intermediate (**d**) to provide the final product **62** (Scheme 53).



Scheme 53 Proposed mechanism for the formation of sulfonamides

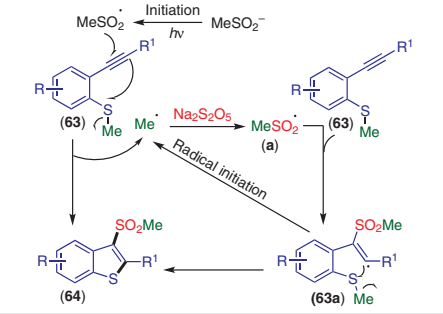
In 2019, Wu et al. demonstrated an efficient method for the synthesis of 3-(methylsulfonyl)benzo[*b*]thiophenes **64** by reacting methyl(2-alkynyl phenyl)sulfonates **63** with sodium metabisulfite as the SO_2 source in the presence of a Ru complex as the photoredox catalyst and sodium methyl sulfinate as the initiator for the reaction. Low catalyst loading, room temperature reaction and broad substrate scope are important features of the reaction. The protocol was successfully applied using methyl(2-alkynyl phenyl)sulfonates **63**, bearing electron-donating and electron-withdrawing groups (Scheme 54).[75]

In the proposed mechanism, the excited state of the photocatalyst oxidizes methylsulfinate to a methylsulfonyl radical (**a**) as an initiator via SET. The triple bond of methyl(2-alkynyl phenyl)sulfonate (**63**) is attacked by the methylsulfonyl radical (**a**), providing the cyclized product **64** with the release of a methyl radical. The released methyl radical is subsequently captured by sulfur dioxide, to give the methylsulfonyl radical (**a**). After this, the methylsulfonyl radical (**a**) reacts with methyl(2-alkynyl phenyl)sulfonate (**63**) to give product **64**, with regeneration of the methyl radical. In this process, the methyl radical relay combined



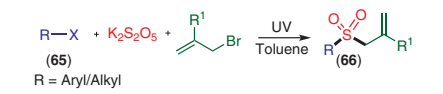
Scheme 54 Synthesis of 3-(methylsulfonyl)benzo[*b*]thiophenes

with the insertion of sulfur dioxide provides a useful route towards methylsulfonyl containing compounds (Scheme 55).



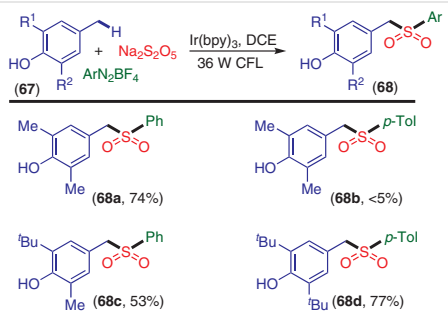
Scheme 55 Proposed mechanism for the formation of 3-(methylsulfonyl)benzo[*b*]thiophenes

Wu et al. reported a UV-irradiation mediated synthesis of allylic sulfones **66** by reacting aryl/alkyl halides **65**, potassium metabisulfite, and allylic bromides. The desired transformation was successful without any metal or photoredox catalyst. A broad reaction scope covering alkyl and aryl halides was demonstrated, and various sensitive functional groups such as amino and ester groups were well tolerated (Scheme 56).[76]



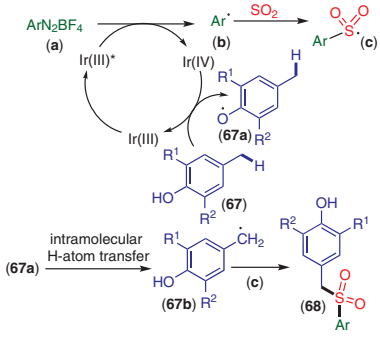
Scheme 56 Visible-light-mediated synthesis of aryl/alkyl sulfonamides

Following the recent trends in C(sp^3)–H functionalization for sulfonylation, the Wu group demonstrated a visible-light-mediated sulfonylation of 2,4,6-trimethylphenol (**67**) using sodium metabisulfite ($Na_2S_2O_5$) as the SO_2 surrogate. Although the result is interesting, the substrate scope was limited and only 4-methyl phenols with a methyl or *tert*-butyl group attached to the *ortho*-position are suitable for this transformation. The reactions failed to provide the desired products when 4-methylphenols with other groups attached to the *ortho*-position were used. However, benzylic C(sp^3)–H bond functionalization was achieved under mild conditions and visible-light irradiation by using this protocol (Scheme 57).[77]



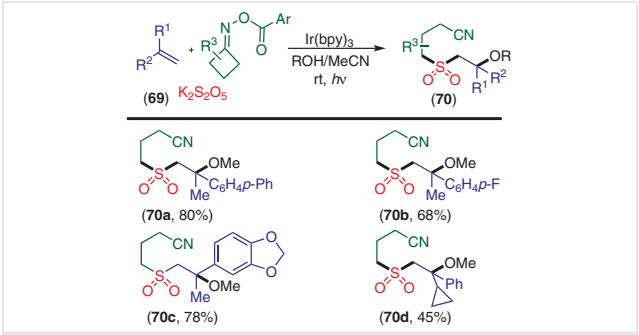
Scheme 57 Visible-light-mediated benzylic C(sp^3)–H sulfonylation of 2,4,6-trialkylphenols

According to the proposed mechanism, an aryl radical (**b**) is generated from the aryl diazonium salt (**a**) by the excited Ir(bpy)$_3$, which combines with the sulfonyl radical to provide an arylsulfonyl radical intermediate (**c**). Meanwhile, phenol **67** undergoes oxidation via a SET to give intermediate **67a**, followed by intermolecular hydrogen atom abstraction to give the benzylic radical intermediate **67b**. Finally, combination of intermediate **67b** and (**c**) affords the desired product **68** (Scheme 58).



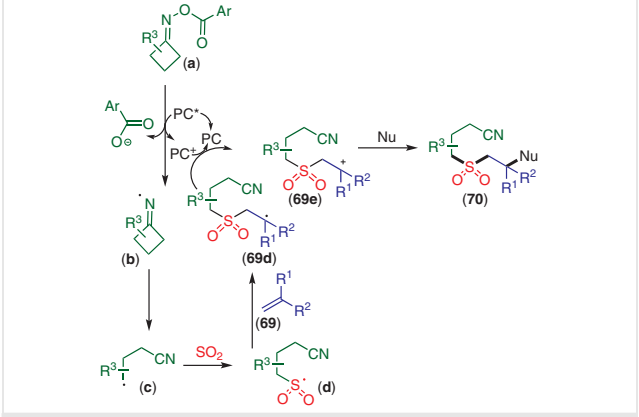
Scheme 58 Proposed mechanism for benzylic C(sp^3)–H sulfonylation of 2,4,6-trialkylphenols

Alkylnitriles are privileged scaffolds in various natural products and pharmaceuticals and can be readily converted into other useful functional groups, including esters, amides, carboxyls, and tetrazoles. In this context, in 2019, the Wu group demonstrated a method for sulfonylation of alkenes **69** using *o*-acyl oximes in the presence of Ir(bpy)$_3$ as the photoredox catalyst under visible-light irradiation. A wide range of substrates worked well with good functional group tolerance (Scheme 59).[78]



Scheme 59 Visible-light-mediated sulfonylation of *o*-acyl oximes

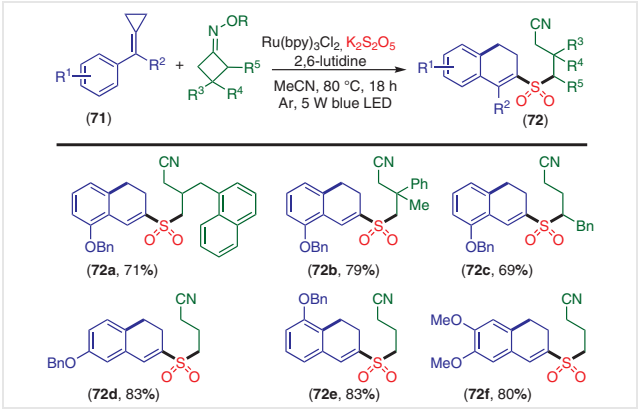
Mechanistically, it was suggested that, in the presence of a photocatalyst and visible light, N–O bond cleavage of *O*-acyloxime (**a**) provides an iminyl radical intermediate (**b**), which undergoes ring opening via C–C bond cleavage to give a carbon-centered radical (**c**). The latter carbon radical is captured by SO_2, providing a sulfonyl radical (**d**), which, on reaction with alkene **69**, provides another carbon-centered radical **69d**. Subsequently a cationic intermediate **69e** is generated from **69d** via SET, and is attacked by the nucleophilic MeOH in the presence of a base to give the desired product **70** (Scheme 60).



Scheme 60 Proposed mechanism for sulfonylation of *O*-acyl oximes

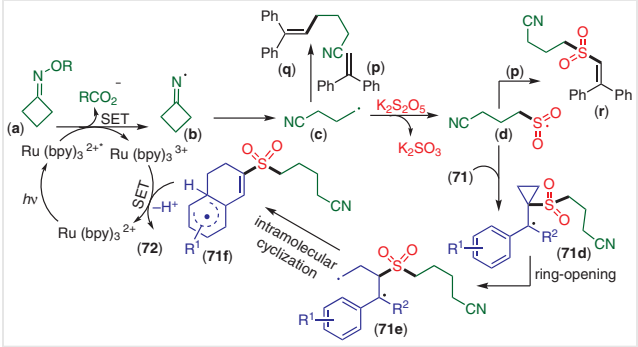
In 2020, Tang and co-workers described a similar protocol in which simultaneous cleavage of two C–C bonds of methylenecyclopropane **71** and cycloketone oxime gave 2-cyanoalkylsulfonylated 3,4-dihydronaphthalenes **72** (Scheme 61).[79]

In the suggested mechanism, cycloketone oxime (**a**) undergoes reduction by the excited state photocatalyst $[Ru(bpy)_3]^{2+*}$ providing an iminyl radical (**b**), which undergoes C–C bond cleavage to give a cyanoalkyl radical (**c**), which is captured by the SO_2 to give a cyanoalkyl sulfonyl radical (**d**). Both the cyanoalkyl intermediate (**c**), and cyanoalkylsulfonyl radical intermediate (**d**) are trapped by 1,1-



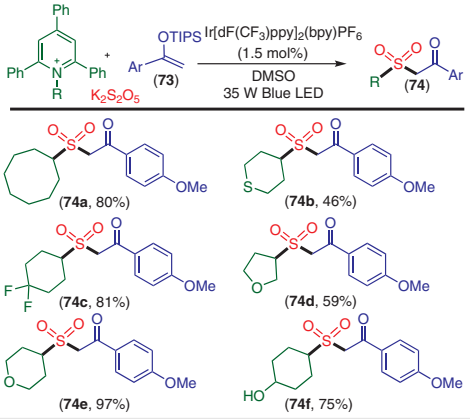
Scheme 61 Visible-light-mediated synthesis of 2-cyanoalkylsulfonylated 3,4-dihydronaphthalenes

diphenylethylene (**p**) to give adducts (**q**) and (**r**), respectively. The cyanoalkylsulfonyl radical (**d**) then adds to the C–C double bond of the methylene cyclopropane **71**, providing intermediate **71d**. The intermediate **71d** undergoes ring-opening via another C–C bond cleavage to provide carbon-centered radical **71e**. After this, intermediate **71f** is generated by an intramolecular cyclization of intermediate **71e**, which undergoes SET from $[Ru(bpy)_3]^{3+}$. Deprotonation of intermediate **71f** in the presence of a base affords product **72** and, finally, $[Ru(bpy)_3]^{3+}$ reverts to the ground state $[Ru(bpy)_3]^{2+}$ (Scheme 62).



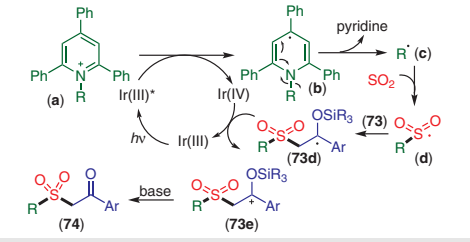
Scheme 62 Mechanism for synthesis of 2-cyanoalkylsulfonylated 3,4-dihydronaphthalenes

Recently, *N*-functionalized pyridinium salts such as Katritzky's salt have been found to be effective alkylating agents under photoredox catalytic process for various transformations.[80] In 2019, Wu and co-workers reported the synthesis of β-keto sulfone **74** using Katritzky's salt as an alkyl radical precursor and potassium metabisulfite as the SO_2 surrogate (Scheme 63).[81] A broad reaction scope, good functional group tolerance including amino, cyano, hydroxy, trifluoromethyl groups and good product yields are the merits of this methodology.



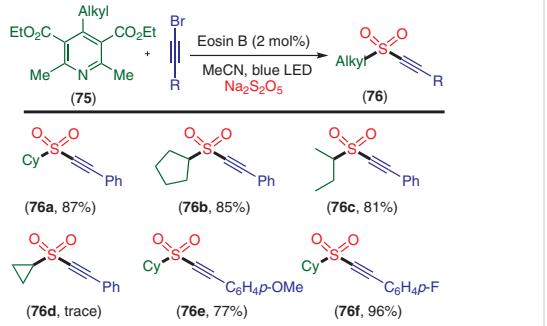
Scheme 63 Visible-light-mediated synthesis of β-keto sulfones

Following the suggested mechanism, a photoredox excited Ir(III) species generates an alkyl radical (**c**) through an intermediate (**b**) from the Katritzky salt (**a**) via SET. Then sulfur dioxide from potassium metabisulfite combines with the alkyl radical intermediate (**c**) to give an alkylsulfonyl radical intermediate (**d**) that is trapped by the silyl enol ether **73**, leading to a carbon radical intermediate **73d**. In the presence of Ir(IV), this carbon radical intermediate is oxidized to a carbocation species **73e** that then undergoes desilylation in the presence of base to afford the corresponding β-keto sulfone **74** (Scheme 64).



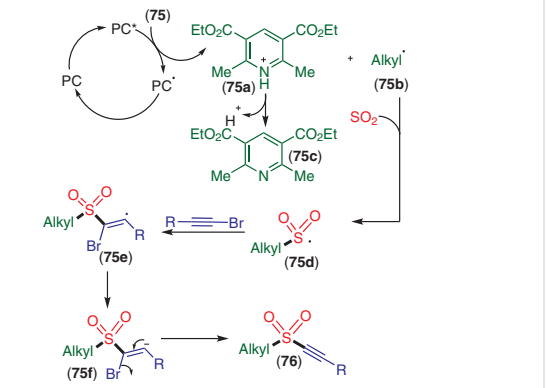
Scheme 64 Mechanism for synthesis of β-keto sulfones

Use of 4-substituted Hantzsch esters as alkyl radical precursors has been demonstrated and these alkyl units could be readily installed into various substrates.[82] The alkyl radical is generated from the 4-alkyl Hantzsch ester under visible-light irradiation in the presence of a photoredox catalyst through SET. Thus, synthesis of alkynyl sulfones **76** involves the reaction of 4-alkyl Hantzsch esters **75**, sodium metabisulfite, and alkynyl bromides under metal-free photoinduced conditions as reported by Wu et al. in 2020 (Scheme 65).[83] This transformation proceeds smoothly under visible-light irradiation at room temperature, giving rise to the corresponding alkyl alkynyl sulfones **76** in moderate to good yields. Besides this, a broad range of substrate scope with good functional group tolerance are other merits of the methodology.



Scheme 65 Visible-light-mediated synthesis of alkyl alkynyl sulfones

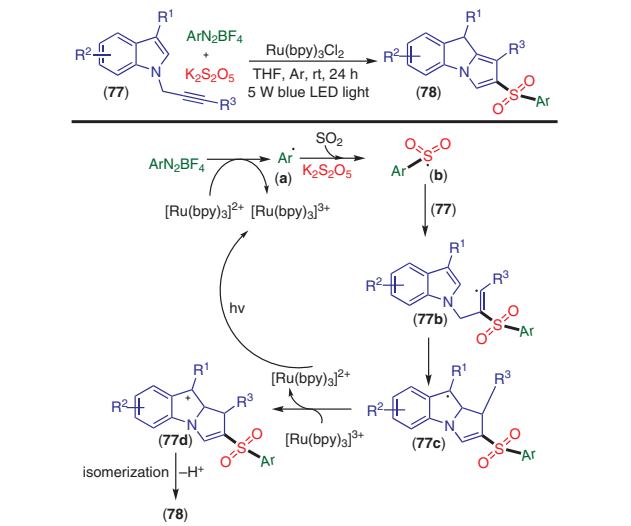
According to the proposed mechanism, alkyl radical **75b** is generated from the 4-alkyl Hantzsch ester **75** in the presence of the photocatalyst under irradiation. The alkyl sulfonyl radical **75d** is formed via trapping of sulfur dioxide by the alkyl radical intermediate **75b**. Subsequently, addition of alkyl sulfonyl radical **75d** to the alkynyl bromide produces vinyl radical intermediate **75e**. With the assistance of excited photocatalyst, vinyl anion **75f** is formed, which affords the corresponding alkylalkynyl sulfone **76** with the release of bromide anion (Scheme 66).



Scheme 66 Mechanism for the synthesis of alkyl alkenyl sulfones

An elegant method for the synthesis of 2-sulfonyl-substituted 9*H*-pyrrolo[1,2-*a*]indoles **78** was reported by Xie et al. in 2019 through reaction of aryldiazonium tetrafluoroborates, potassium metabisulfite, and *N*-propargylindoles **77** under visible-light irradiation (Scheme 67).[84] The proposed mechanism involves the generation of an aryl radical (**a**) from the aryldiazonium tetrafluoroborate by the assistance of $[Ru(bpy)_3]^{2+*}$ via SET. The aryl radical (**a**) then reacts with the potassium metabisulfite and captures SO_2 to afford aryl sulfonyl radical (**b**) that then attacks the triple bond of *N*-propargylindole **77** giving rise to vinyl radical intermediate **77b**. This is followed by intramolecular cyclization and generation of cyclic radical intermediate **77c**. This cyclic radical intermediate undergoes oxidative SET and generates cat-

ionic intermediate **77d**, which undergoes deprotonation and isomerization to afford the desired cyclic product **78** (Scheme 67).



Scheme 67 Mechanism for synthesis of 2-sulfonyl-substituted 9*H*-pyrrolo[1,2-*a*]indoles

3 Conclusion and Outlook

This review focuses on the recent advancement in sulfonylation reactions using inorganic sulfites as the source of the sulfonyl group. Inorganic sulfites are readily available, easy to manipulate and inexpensive. The use of inorganic sulfites as sulfur dioxide surrogates has proven to be a transformative tool, leading to a diverse range of sulfonyl compounds including sulfones and sulfonamides. The sulfonylation protocols have been achieved under transition-metal catalysis or through metal or additive-free conditions. In some cases, a photocatalyst is utilized, which mediates the reaction in the presence of visible light. Using $K_2S_2O_5$ or $Na_2S_2O_5$ as SO_2 sources, many substrates were well tolerated under mild conditions. The reactivities of inorganic sulfites in organic reactions deserves to be explored further. The present review shows that only potassium metabisulfite or sodium metabisulfite have been found to be efficient, but these strategies will surely find application in the synthesis of natural products and pharmaceuticals in the immediate future. Considering the great potential of inorganic sulfites in organic synthesis, it is believed that new methodologies involving insertion of sulfur dioxide using inorganic sulfites will be developed.

Conflict of Interest

The authors declare no conflict of interest.

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