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The same oxygenation-state introduction of hypervalent sulfur under transition-metal-free conditions

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Sulfonyl compounds have attracted considerable interest due to their extensive applications in drug discovery. Access to the assembly of SO₂-containing compounds via the oxygenation oxidative-state introduction of hypervalent sulfur has come to the fore in recent years. This review discusses the application of the same oxygenation-state introduction of hypervalent sulfur strategy under transition-metal-free conditions, and presents it in light of different atoms being linked to the sulfonyl group, including sulfones, sulfonamides, sulfonyl fluorides and thiosulfonates.

1 Introduction

Sulfonyl compounds, having a long and rich history, most notably sulfones and sulfonamides,¹ have received great attention as demonstrated by their extensive applications in medical,² agricultural³ and materials science.⁴ Therefore, the construction of sulfone-containing compounds could be of considerable significance. Sulfonyl compounds are traditionally delivered via the oxidation of sulfides or the combination of sulfinates with aryl or alkyl electrophiles.⁵ Strategies for the

synthesis of sulfonamides rely on the nucleophilic coupling of a pre-installed sulfonyl precursor, that is, sulfonyl chloride used most frequently, and appropriate amine sources.⁶ However, the substrates are usually derived from the odorous and unfriendly thiols, and the reactions need to be performed under harsh conditions, resulting in a low functional group tolerance and thus hampering their advancement in industrial applications. In order to distinguish the change of inorganic sulfur to organic sulfide, the concept of oxygenation-state was used (Scheme 1a). The same oxygenation-state means that the number of oxygen atoms attached to the sulfur atom remains unchanged in the reaction (Scheme 1b). Recently, the same oxygenation-state introduction of hypervalent sulfur conquered these obstacles, and allowed step- and oxidation-economical synthesis of SO₂-containing compounds.⁷ DABSO was developed by Santos *et al.* in 1988, and was first applied by Willis

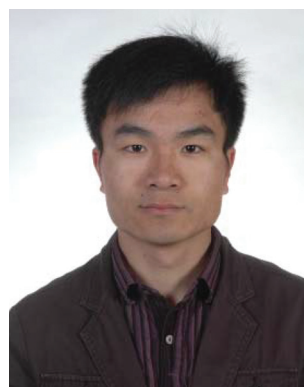
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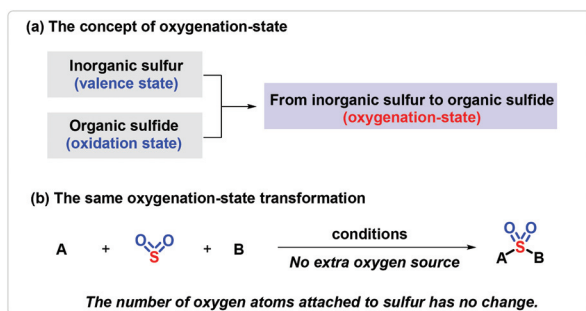
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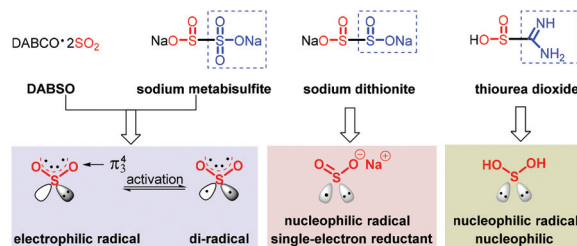
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Scheme 1 The concept of oxygenation-state.

and co-workers as a hypervalent sulfur surrogate.⁸ Subsequently, inorganic hypervalent sulfur sources like sodium/potassium metabisulfite could also be used as SO_2 surrogates and achieve the same oxygenation-state introduction of hypervalent sulfur.⁹ During this process, the method of transition-metal catalysis could effectively connect sulfur dioxide with the coupling partners on both sides,^{5j,9c} yet bringing about a series of cumbersome problems, such as expensive metal catalysts, inconvenient operation and potential β -H elimination. Accordingly, simple, efficient and transition-metal-free methods are well developed and present an upward tendency, as exemplified in the assembly of sulfones and sulfonamides, with a few examples providing sulfonyl fluorides and thiosulfonates. The process originates typically from a radical precursor, followed by trapping with a masked hypervalent sulfur source to produce the sulfonyl radical or sulfinate salt, which eventually couple with other partners to provide the desired products. The different properties of hypervalent sulfur sources lead to great differences in the same oxygenation-state introduction of hypervalent sulfur reactions. DABSO [$\text{DABCO} \cdot (\text{SO}_2)_2$] and $\text{Na}_2\text{S}_2\text{O}_5$ easily release SO_2 with an π^3_4 structure. Triplet SO_2 , possessing a lone pair, shows elec-



Scheme 2 Various hypervalent sulfur sources.

trophilicity. Singlet SO_2 , which is excited to the active state with one electron transferring to the empty orbit, displays a di-radical feature. The homolytic cleavage of $\text{Na}_2\text{S}_2\text{O}_4$ furnishes double sulfur dioxide radical anions, which show bilaterally nucleophilic radical and single-electron reductant features. Thiourea dioxide can generate a sulfur dioxide anion, which can easily form a sulfur dioxide radical anion under basic conditions and shows nucleophilic radical features (Scheme 2). Due to the different properties of hypervalent sulfur sources, the reactions of the same oxygenation-state introduction of hypervalent sulfur are rich and colorful.

2 Sulfones

Sulfones, formed by the combination of a sulfonyl and hydrocarbon group, play a prominent role in organic chemistry and drug discovery. Sulfones are commonly prepared by the oxidation of sulfides under the condition of a strong oxidant, 3-chloroperoxybenzoic acid (*m*CPBA) or hydrogen peroxide *etc.*, and the starting material sulfides need to be achieved from the smelly thiols. A multicomponent cross-coupling strategy, based upon the same oxygenation-state introduction of hypervalent sulfur, has attracted much interest, owing to the flexible



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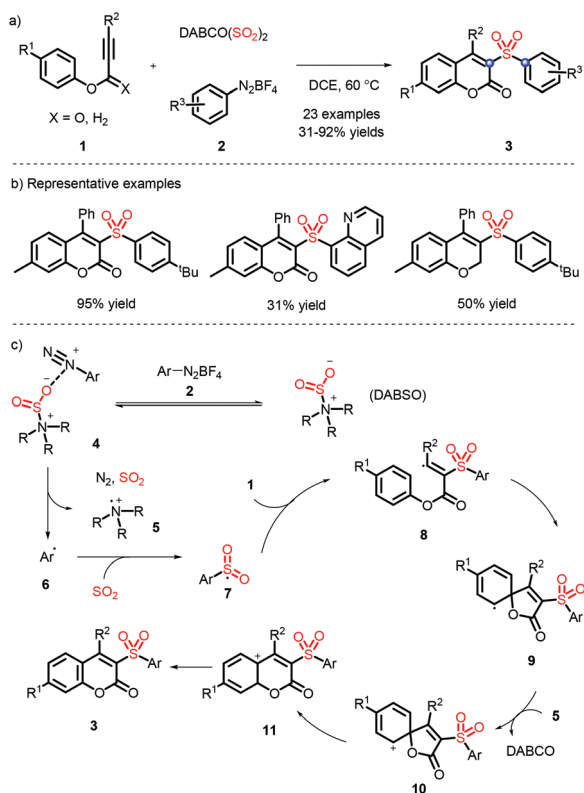
tuning of the substituents and step economy.⁹ According to the difference in the carbon moieties, which connect on both sides of the sulfonyl group, the modular assembly of sulfones can be classified into the following four categories: C(sp²)-C(sp²), C(sp²)-C(sp³), C(sp)-C(sp³) and C(sp³)-C(sp³).

2.1 C(sp²)-C(sp²)

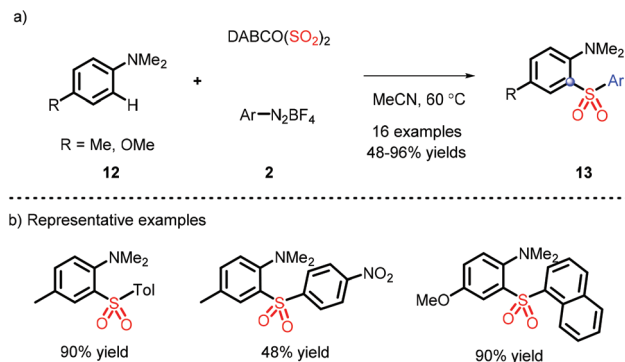
In 2016, a metal-free strategy was disclosed by Wu and co-workers, liberating a series of 3-sulfonated coumarins *via* the sulfonyl radicals from aryldiazonium tetrafluoroborate and DABSO (Scheme 3a).¹⁰ Meanwhile, a plausible reaction mechanism was proposed (Scheme 3c) and indicated that diazonium 2 firstly removes N₂ with the assistance of DABSO, followed by trapping of *in situ* formed sulfur dioxide to obtain the vital species 7, which undergoes the radical addition, spirocyclization and ester migration. Eventually, the intermediate H accesses the corresponding 3-substituted sulfones by further aromatization.

Subsequently, Wu's group achieved the *ortho* C(sp²)-H sulfonylation using anilines by virtue of the sulfonyl radical intermediates (Scheme 4).¹¹ Although the process is performed under catalyst-free conditions to afford the functional products in moderate to good yields, the aniline substrates exhibit a limited scope and only methyl and methoxy groups are installed on the *para*-position.

The substrates that couple with the sulfonyl radical are not only restricted to electron-donating compounds; electron



Scheme 3 Synthesis of 3-sulfonated coumarins.



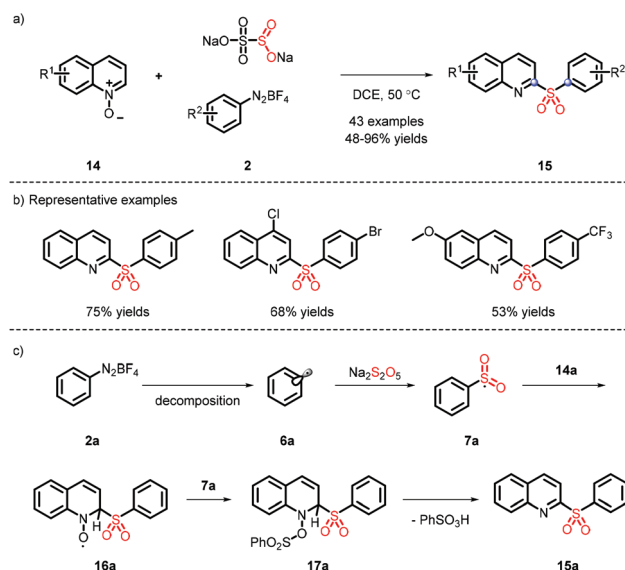
Scheme 4 Sulfonylation of anilines via the sulfonyl radical intermediates.

deficient substrates can also proceed well. In 2019, Xia *et al.* reported the synthesis of 2-sulfonyl-quinolines under metal- and oxidant-free conditions (Scheme 5a), which showed a wide substrate scope¹² (Scheme 5b). It is different from the previous system, which was catalyzed by CuOTf.¹³ The intermediate 7a not only reacts with 14a, but also implements efficiently deoxygenation in combination with 16a (Scheme 5c).

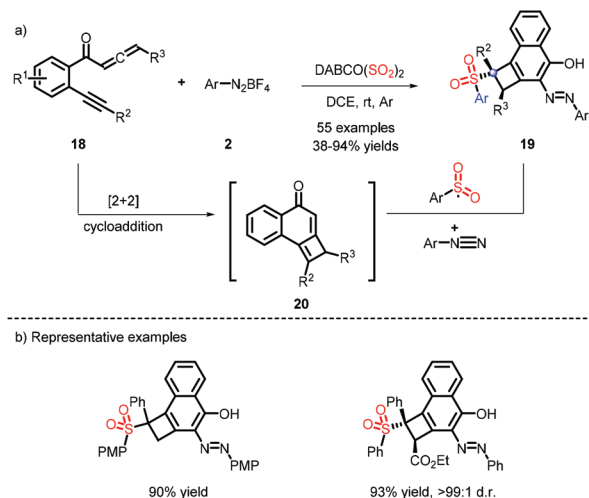
2.2 C(sp²)-C(sp³)

Tu and co-workers reported an unexpected discovery for the synthesis of cyclobuta[*a*]naphthalen-4-ols, which were efficiently decorated with sulfone and azo functionalities.¹⁴ As depicted in Scheme 6, the species 20 was formed by a cascade [2 + 2] cycloaddition, and was then captured by a sulfonyl radical and diazonium to obtain the target compounds. Accordingly, the substrate 2 plays a dual role to construct C-S and C-N bonds.

When the sulfonyl radical is intercepted by an aryl olefin, followed by the attack of a nucleophilic radical, the bifunction-



Scheme 5 Synthesis of 2-sulfonated isoquinolines.

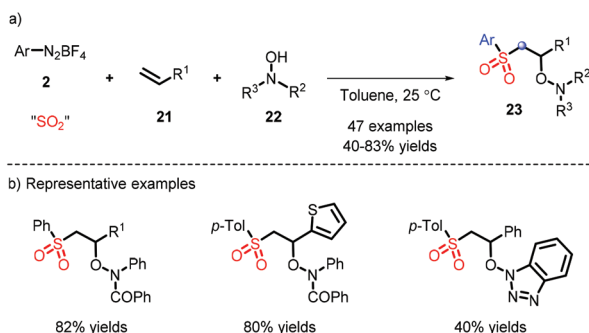


Scheme 6 Synthesis of cyclobuta[a]naphthalen-4-ols from species 20.

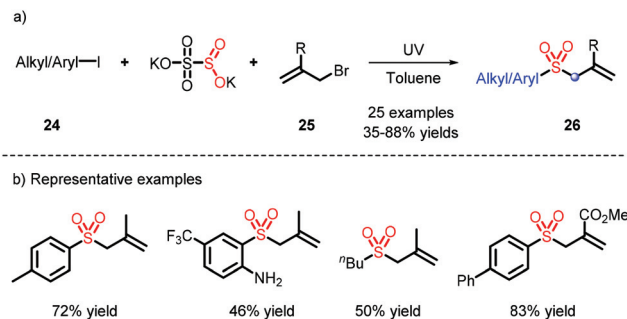
nalization of the alkene is achieved. Based upon this protocol, Wu *et al.* developed a four-component reaction for oxysulfonylation by taking advantage of different sulfur dioxide sources, DABSO and K₂S₂O₅, which are both effective in this process (Scheme 7).¹⁵

Diazonium is continually used as a radical precursor, yet faces unavoidable issues, such as instability and limited scope. In 2019, Wu and co-workers employed aryl or alkyl iodides, K₂S₂O₅ and 25 under ultraviolet irradiation to obtain the corresponding radicals, and thus realized the construction of allylic sulfones (Scheme 8).¹⁶ It is worth mentioning that toluene, as a non-polar solvent, can also participate in the introduction of SO₂.

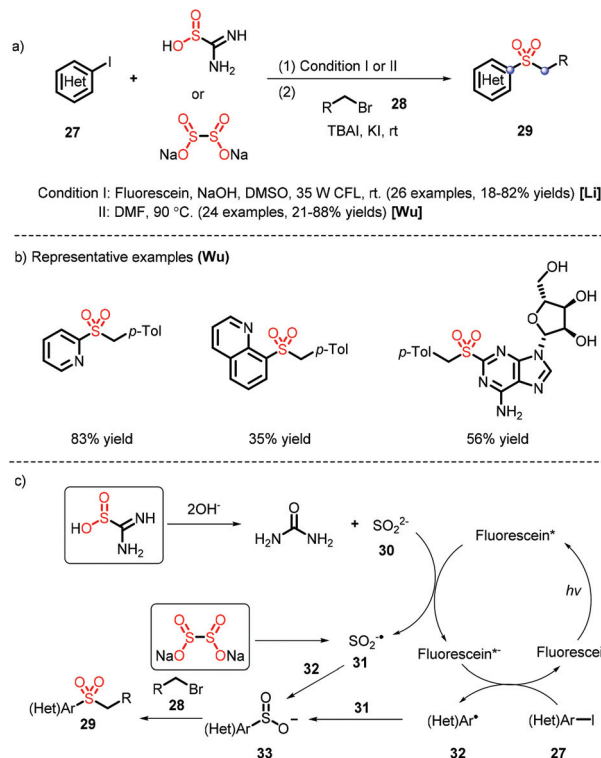
A diverse range of heteroaryl sulfones were furnished from different sulfur dioxide surrogates (thiourea¹⁷ and sodium dithionite¹⁸) under metal-free conditions, which was reported by Li's and Wu's groups (Scheme 9). The difference in their systems lies in the reaction mechanism (Scheme 9c): thiourea dioxide is subjected to hydrolysis and oxidation to provide the sulfur dioxide anion 31, which is coupled with the heteroaryl radical 32 and electrophile 28 to prepare heteroaryl alkyl sulfones; the species 31 is formed *via* the homolysis of sodium dithionite, without needing to be oxidized by virtue of a photo-



Scheme 7 Difunctionalization of alkene with the insertion of SO₂.



Scheme 8 Proto-induced synthesis of allylic sulfones.



Scheme 9 Synthesis of heteroaryl alkyl sulfones.

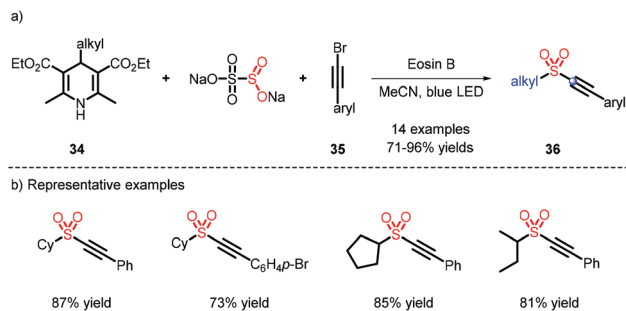
catalyst. Meanwhile, the sulfur dioxide radical anion B serves as a reductant and promotes the generation of sulfinate intermediate 33.

2.3 C(sp)-C(sp³)

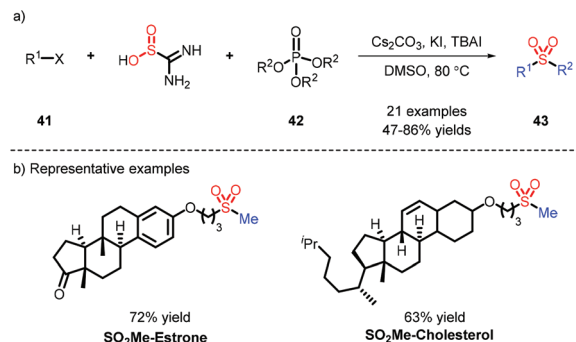
In 2020, a metal-free strategy for alkynyl sulfone construction was developed by Wu *et al.* 4-Alkyl Hantzsch esters were used as alkyl radical sources *via* the activation of Eosin B (Scheme 10).¹⁹ The reaction afforded a chain of C(sp)-C(sp³) sulfones in good and excellent yields, and a few examples of the alkyl scope were also furnished.

2.4 C(sp³)-C(sp³)

Due to only a small amount of alkyl substrates being obtained in the previous work (Scheme 8), potassium alkyltrifluorobo-



Scheme 10 Synthesis of alkynyl sulfones from 4-alkyl Hantzsch esters.



Scheme 12 Synthesis of alkyl-alkyl sulfones via phosphate esters.

rates, serving as abundant alkyl partners, were applied by Wu's group for the construction of alkyl sulfones, and showed good alkyl compatibility (Scheme 11a).²⁰ Cyclopropyl, which is prone to undergoing an open-ring reaction, could be tolerated in this transformation. When alkyl iodine was involved in the process, it needed a reductant to form an alkyl radical, followed by interception of DABSO, and addition to an electron-withdrawing alkene to afford alkyl-alkyl sulfones (Scheme 11b).²¹

In light of the transformation from inorganic sulfur to organic sulfurs by our group, the assembly of alkyl-alkyl sulfones was efficiently accomplished, which employed an available phosphate ester as an alkyl source leading to favorable results (Scheme 12).²² This strategy was also deployed in late-stage modification, as exemplified by coupling estrone or cholesterol with a SO₂Me fragment.

3 Sulfonamides

Sulfonamide, as an indispensable motif, showcases excellent properties and exists extensively in the pharmaceutical and agrochemical industries. Traditionally, sulfonamides are prepared through oxidation of the corresponding thiols with chlorine gas with the assistance of aqueous hydrochloric acid,

and the subsequent amination of sulfonyl chloride. Analogous to the synthesis of sulfones, the introduction of sulfur dioxide is also extensively deployed in the assembly of sulfonamide. However, the study of these compounds converges mainly on carbon substitution, including aryl or alkyl diazonium, aryl halides and aryl boronic acids.

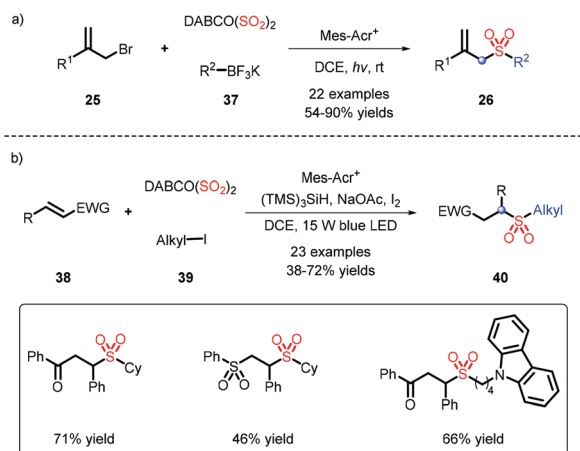
3.1 Aryl or alkyl diazonium

The metal-free synthesis of *N*-aminosulfonamides was reported by Wu and co-workers, who employed aryldiazonium and hydrazines in combination with DABSO under mild conditions to afford favorable yields (Scheme 13a).²³ Moreover, a probable process is demonstrated in Scheme 13b, wherein the substituted nitrogen of the hydrazine attacked SO₂, rather than the “free” nitrogen, and subsequently the species **E** was formed, where the radical tended to be installed in an unsubstituted nitrogen. Regrettably, the system was only suitable for hydrazine compounds. On the basis of this mechanism, the same group elaborated the substrate placement of an alkene moiety and implemented the construction of multiple bonds (comprising C–C, C–S and S–N). It is interesting that a one-pot synthesis could be effectively performed from anilines (Scheme 13c).²⁴

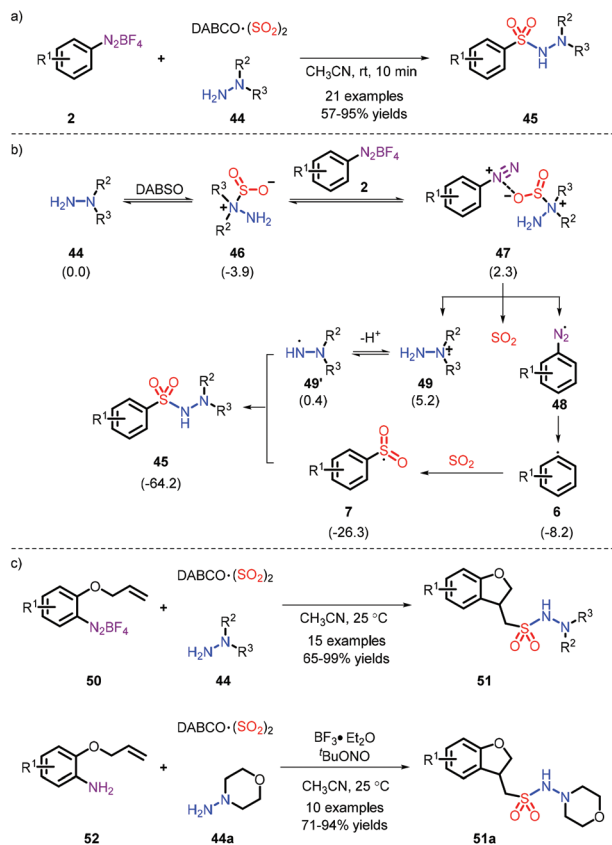
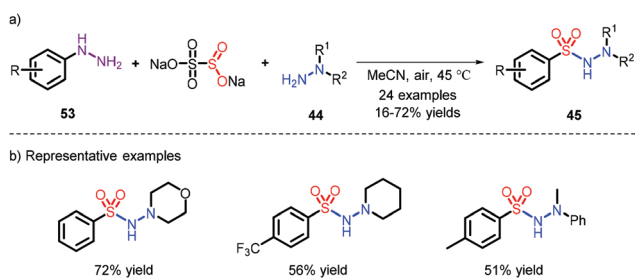
In addition, aryl hydrazine also acts as a precursor of diazonium. The reaction provides a range of *N*-aminosulfonamides with moderate yields in the presence of air, and was developed by Han and co-workers (Scheme 14).²⁵

Compared to aryl fragment, the synthesis of alkyl sulfonamides is less covered, owing to the fact that diazoniums bearing an alkyl moiety, possessing the risk of explosion, are not easily accessible. Accordingly, Tsai and co-workers developed a method *via in situ* generation of diazo compounds to realize the preparation of alkyl sulfonamides (Scheme 15).²⁶

In 2018, the first metal-free example was established toward the synthesis of free sulfonamides *via* Na₂S₂O₅ as the sulfur dioxide source and sodium azide as the nitrogen source by our group (Scheme 16).²⁷ The strategy was also extended to prepare the sulfonamide-containing drugs Celecoxib and Sulpiride at a later stage. In this process, the role of PPh₃ was important (Scheme 16c): the aryl radical **6b** is firstly formed through the action of PPh₃ *via* a SET pathway. Subsequently,



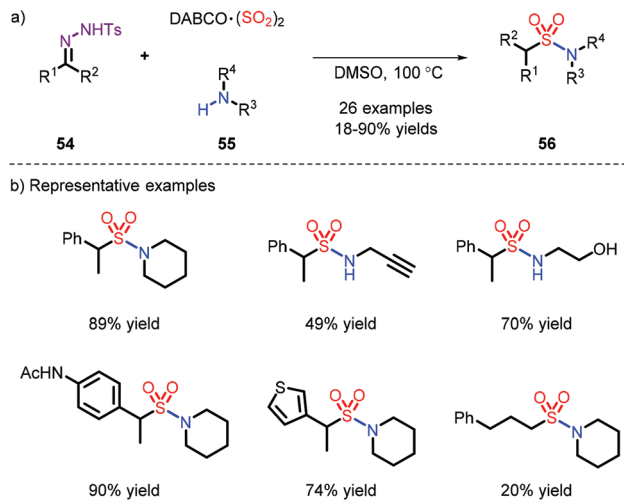
Scheme 11 Photoredox-catalyzed reaction to construct alkyl sulfones.

Scheme 13 Synthesis of *N*-aminosulfonamides via aryl diazonium.Scheme 14 Synthesis of *N*-aminosulfonamides via aryl hydrazines.

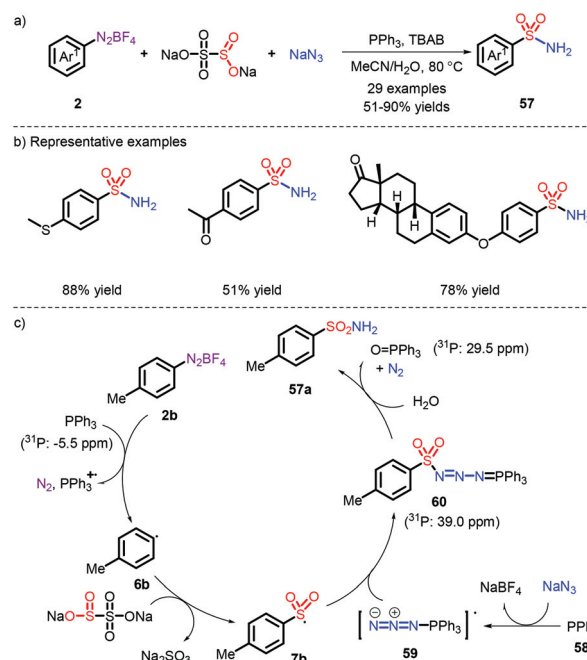
the species **62** reacts with sodium azide, followed by combination of an aryl sulfonyl radical. Eventually, the obtained intermediate **64** (as proved by ³¹P NMR) is exposed to water and removes a N₂ and O=PPh₃, thereby releasing the corresponding products. However, the employment of explosive NaN₃ makes the current strategy risky.

3.2 Aryl halide and its derivative

On account of the unstable nature of aryl diazonium salts as radical precursors, a series of different substrates were employed,^{16,28} most frequently aryl bromides, iodides and iodoniums. Accordingly, in order to capture the momentum, Wu *et al.* used low-cost and available aryl bromides to achieve this reaction under metal-free conditions, which provided



Scheme 15 Synthesis of alkyl sulfonamides via the hydrazones.

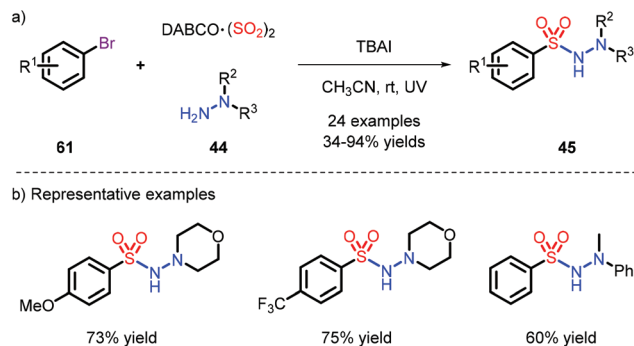


Scheme 16 Synthesis of free sulfonamides via sodium azide.

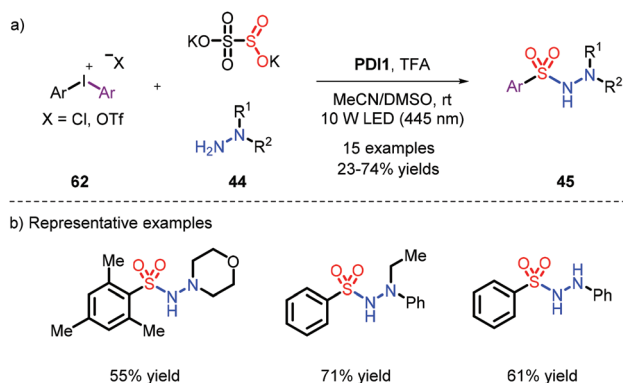
N-aminosulfonamides with 34% to 94% yields under the condition of UV (Scheme 17).^{28b} Pleasingly, when the bromides were replaced with chlorines, the reaction could also effectively proceed.

Since the use of high-energy ultraviolet irradiation leads to a very limited substrate scope, Manolikakes's group outlined a novel synthetic pathway by employing aryl-iodoniums as radical precursors with visible light to furnish the products (Scheme 18).^{28d} It was a pity that aniline was not tolerated in their system.

An additive-free reaction toward trifluoro-methylation and aminosulfonylation of alkynes was disclosed by Wu *et al.* Their



Scheme 17 Synthesis of *N*-aminosulfonamides via aryl bromide substrates.

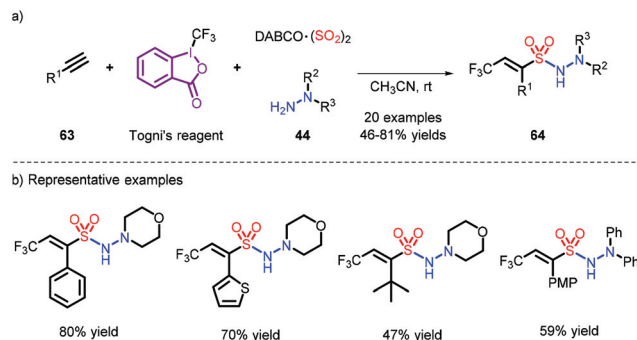


Scheme 18 Synthesis of *N*-aminosulfonamides via diaryliodonium salts with hydrazines.

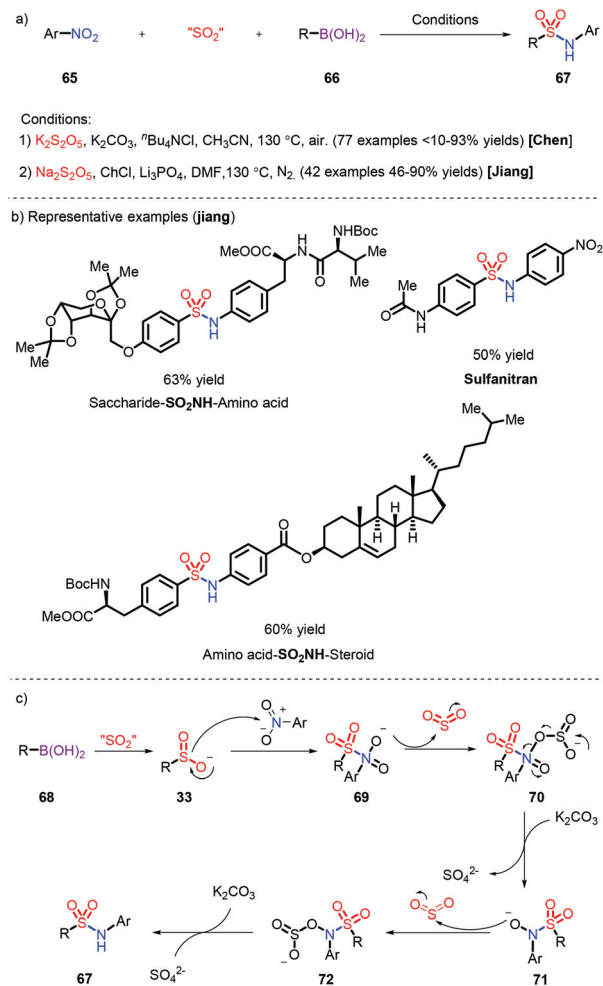
reaction employs Togni's reagent with DABSO and hydrazines (Scheme 19).²⁹ The trifluoromethyl radical is generated by induction of hydrazine, which removes a hydrogen radical, and provides access to the *N*-aminosulfonamides *via* coupling with a sulfonyl radical. However, the use of stoichiometric amounts of Togni's reagent makes the current reaction costly.

3.3 Aryl boronic acid

The introduction of sulfur dioxide is generally restricted to the assembly of *N*-aminosulfonamides. There are a dearth of examples of the preparation of sulfonamides, which need transition-metal catalysts such as Pd³⁰ and Au.³¹ Nitroarenes, as readily available and low-cost nitrogen sources, have been successfully employed for the synthesis of sulfonamides in combination with aryl boronic acid, which was reported by Chen³² and us³³ respectively (Scheme 20a). The reaction displays a wide substrate scope and was extended to the linking of different biomolecules and pharmaceuticals *via* the SO₂NH fragment by us (Scheme 20b). A plausible mechanism was proposed: K₂S₂O₅ was used to release SO₂, which not only integrated with aryl boronic acid to form the sulfinate 33, but also facilitated the deoxygenation of 72 and 74 species (Scheme 20c).



Scheme 19 Vicinal difunctionalization of alkynes through trifluoromethylation and aminosulfonylation.



Scheme 20 Synthesis of sulfonamides from nitroarenes.

4 Sulfonyl fluorides

SuFEx (sulfur fluoride exchange), the new embodiment of click chemistry, was first disclosed by Sharpless *et al.*,³⁴ presenting powerful flexibility for modular linkage of different nucleophilic compounds. Intriguingly, a strategy where sulfonyl fluoride

serves as a chemical biology probe has been applied to identify amino acid residues.³⁵ The synthesis of sulfonyl fluorides is typically implemented *via* fluoride-chloride exchange, which is deemed to be the most practical method. However, the substrates, sulfonyl chlorides, face unavoidable issues as they are liable to undergo hydrolysis and redox side reactions. A strategy for steering clear of the highly active molecules can be accomplished *via* the *in situ* formed sulfinate by a Pd catalyst and electrophilic fluoride sources (Selectfluor *etc.*).³⁶ Although great progress has been demonstrated, the use of a toxic metal catalyst limits this strategy to small-scale applications.

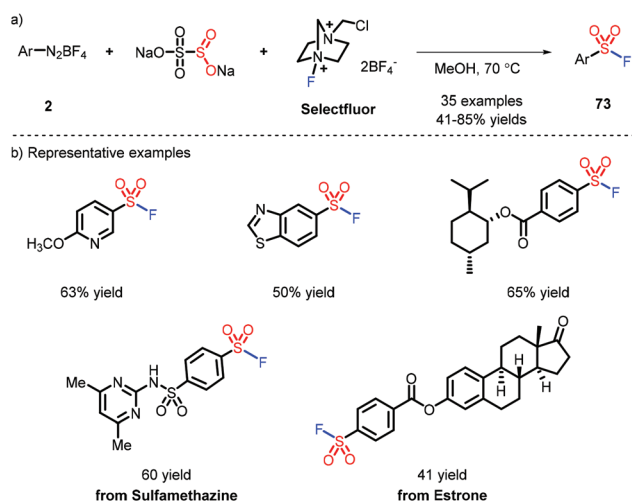
Weng and co-workers developed a metal-free method to access the sulfonyl fluorides *via* aryl diazoniums (Scheme 21).³⁷ The reaction needs MeOH as a solvent and heating to obtain the corresponding products, indicating the favorable stability of sulfonyl fluoride.

5 Thiosulfonates

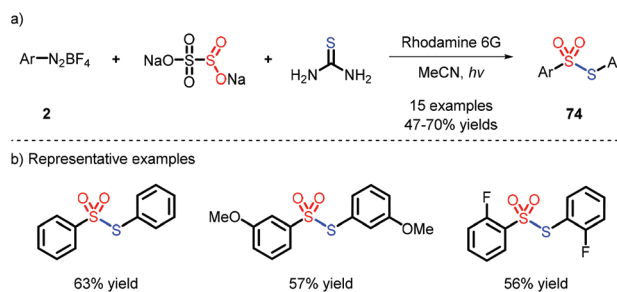
In contrast to sulfones and sulfonamides, sulfur-linked sulfonyl compounds thiosulfonates, which display biological activities such as anti-viral and anti-bacterial, are less studied.³⁸ Moreover, thiosulfonate derivatives, as prominent building blocks, have been diffusely used in organic synthesis owing to their desirable stability and reactivity.³⁹ Conventionally, the thiosulfonates are prepared *via* the oxidation of the corresponding disulfides or thiols and the reduction of sulfonyl chlorides. When an aryl or alkyl fragment is located in the thiosulfonyl skeleton, the compounds displayed symmetry and asymmetry. In general, the construction of unsymmetrical thiosulfonates was relatively difficult due to the chemoselectivity issue.

5.1 Symmetrical thiosulfonates

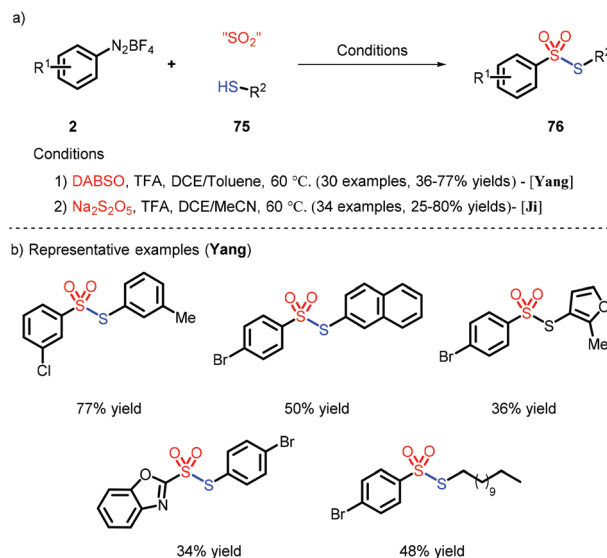
In 2019, Wu and co-workers reported an unexpected reaction which afforded a library of symmetrical thiosulfonates using



Scheme 21 Synthesis of sulfonyl fluorides from Selectfluor.



Scheme 22 Synthesis of symmetrical thiosulfonates from thiourea.



Scheme 23 Synthesis of unsymmetrical thiosulfonates from thiols.

thiourea as the sulfur source *via* a photoinduced strategy (Scheme 22),⁴⁰ yet with the original purpose to obtain *N*-carbamothioylargonsulfonamide. Nevertheless, the process was not suitable for the connection of different aryl groups.

5.2 Unsymmetrical thiosulfonates

Very recently, the preparation of unsymmetrical thiosulfonates was achieved by combination of different SO₂ surrogates and thiols as sulfur sources, as described by Yang⁴¹ and Ji⁴² (Scheme 23). The role of TFA, noteworthy, was to react with 2 and promote the generation of the aryl radical.

6 Conclusions

The sulfonyl-containing compounds are not only emerging widely in the pharmaceutical, agricultural and material fields, but are also utilized frequently in organic synthesis, implementing the modular assembly of natural products and bio-active molecules. Accordingly, the same oxygenation-state introduction of hypervalent sulfur has been an active research area for accessing SO₂-containing molecules, due to the

untrammeled varying of the substituents, avoiding some pre-formed precursors. Compared with transition-metal-catalyzed methods, transition-metal-free strategies are characterized by inexpensive materials, low toxicity and simple operation. The synthesis of SO₂-containing compounds has witnessed much development in the past several years, as exemplified by sulfones, sulfonamides, sulfonyl fluorides and thiosulfonates. Although a chain of efficient protocols have been outlined, cumbersome issues still exist: (1) the aryl radical source relies mainly on the diazonium salts, which are not conducive to storage and exhibit a risk of explosion; (2) harsh reaction conditions, such as high temperature or UV radiation, might be needed to enable the generation of intermediates, resulting in narrow substrate scopes; (3) in most cases, the nitrogen-linked partner was restricted to the hydrazine, thereby obtaining merely the *N*-aminosulfonamide; (4) lower selectivity and efficiency was presented *etc.* Hence, optimized and practical methods *via* the same oxygenation-state introduction of hyper-valent sulfur for the assembly of SO₂-containing compounds are still indispensable. More favorable outcomes, we believe, will be exposed in the future, where new reaction patterns (different from the traditional method *via* the sulfonyl radical or sulfinate) are widely deployed and structurally complicated compounds are expediently furnished.

Conflicts of interest

There are no conflicts to declare.

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