Recent Advances in the Synthesis of Sulfonamides Intermediates

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Abstract

Sulfonamides are one of the most important synthons in drug synthesis, which can increase the water solubility of drugs and regulate their metabolism *in vivo*. According to statistics, nearly 30% of sulfur-containing drugs on the market contain sulfonamide groups, including omeprazole, hydrochlorothiazide, and other best-selling drugs. Synthesis of sulfonamide is therefore a very important part of new drug development and active pharmaceutical ingredient manufacturing. In this review, we will focus on the recent 5-year advances in the field of synthetic research and structural modification of sulfonamide-containing drugs and their intermediates. The synthesis strategies, including S–N construction, C–N cross-coupling, N–H functionalization, and C–H sulfonamidation, are discussed, hoping to provide new ideas for the researchers to prepare sulfonamides in a green and efficient way.

Keywords
- sulfonamides
- S–N bond formation
- C–N cross-coupling
- N–H functionalization
- C–H amination

Introduction

Sulfonamide is one of the most representative small-molecule drug modification groups. In drug discovery, the sulfonamide group has significant electron-withdrawing properties, hydrolysis stability, polarity, hydrogen bonding ability, and good resistance to reduction and oxidation. It has the effects of increasing hydrophilicity and changing the site of action in drug design. Many commercial therapeutic drugs contain a sulfonamide group (►**Fig. 1**).[1,2] At present, sulfonamides have been listed as one of the priority structural motifs in the pharmaceutical industry. In 2019, sulfonamides accounted for 25% of all sulfur-containing drugs approved by the Food and Drug Administration (FDA), and their application in medicinal chemistry has been extended to antibiotics and treatable diseases such as cancer, central nervous system diseases, diabetes, and dementia.[3]

With good physical and chemical properties and metabolic stability, sulfonamide compounds have been pushed to the forefront of modern bioactive molecular design. Their synthesis and modification methods have attracted the interest of many researchers. The construction method of sulfonamide structure has become one of the research hotspots in the field of drug synthesis. In this review, we intend to analyze and evaluate the synthetic methods for sulfonamides in recent years, as well as briefly introduce the latest progress in their synthesis and modification from the perspective of green and practical chemistry. According to the existing reports, the synthesis schemes for sulfonamides can be easily divided into four categories through analysis of synthesis and modification methods for sulfonamides: S–N

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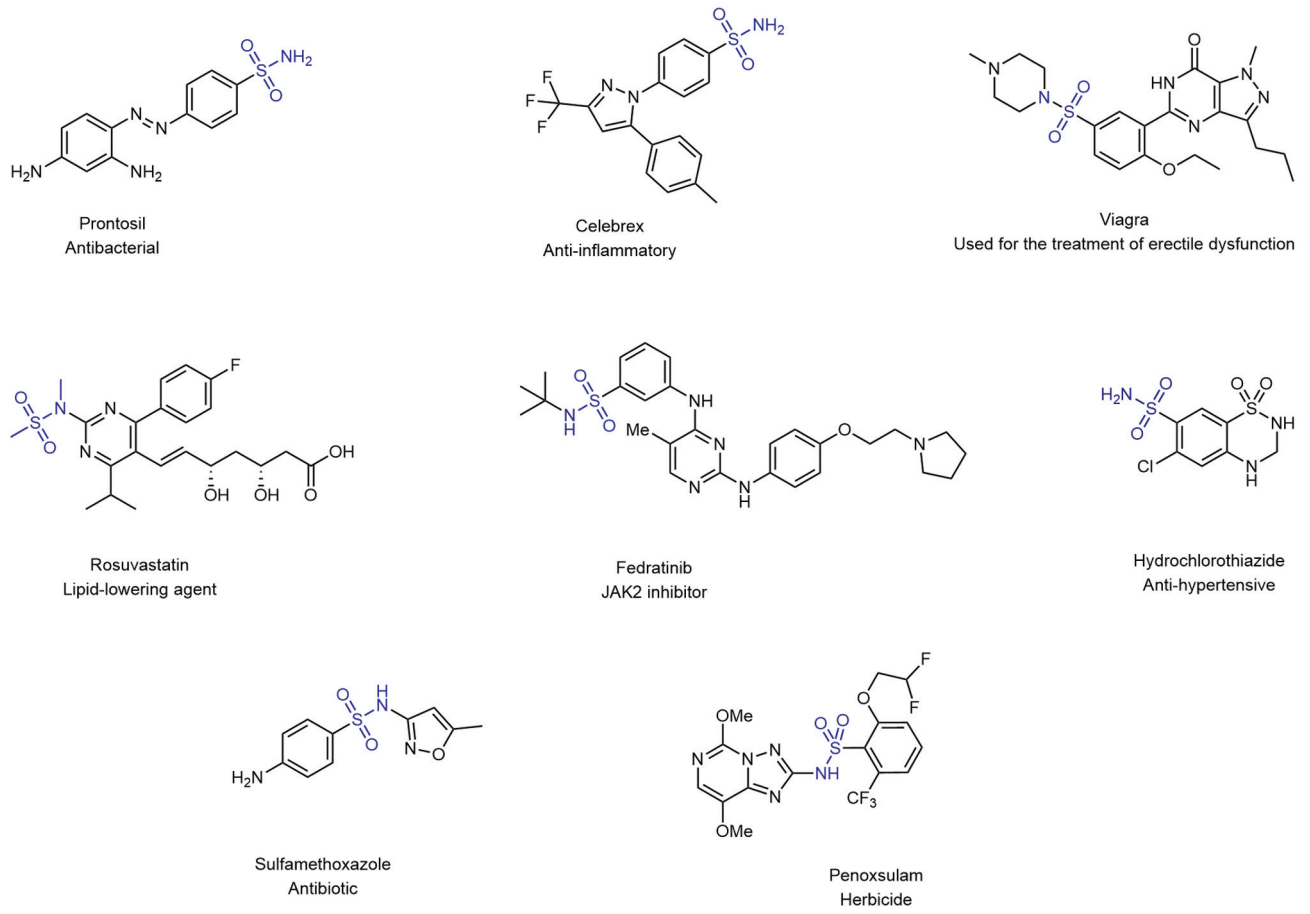

Fig. 1 Representative sulfonamide drugs.

bond construction, C–N bond cross-coupling, N–H bond functionalization, and C–H bond amination (►**Fig. 2**). This article will discuss the new technologies following the above construction methods.

Construction of S–N Bond

In the chemical structure of sulfonamides, the S–N bond is the most easily formed chemical structure. Usually, sulfonamides can be prepared in high yields by amidation reaction with sulfonyl chloride or sulfonic acid. This method ranks among the most classic sulfonamide synthesis processes. At present, most simple sulfonamide drug intermediates are synthesized by this method.

Although the methods usually provide high yields and low prices, they still suffer from many problems from an environmental protection perspective. The active groups such as intermediate sulfonic acid and sulfonyl chloride need to be synthesized by chlorosulfonic acid, concentrated sulfuric acid, and other chemicals. These reagents are highly acidic and polluting, making them unsuitable for unstable intermediates. The sulfonation reaction is a dangerous process, so this method is mainly used for simple aryl sulfonamide drug intermediates.

In view of the above problems, recent studies have found a new strategy for the construction of sulfonamides by catalytic oxidation, which usually occurs through a free radical or ionic mechanism under the interaction of S reagent, N reagent, and oxidant. Sulfinic acid and its salts, sulfur, and sulphonates are usually used as the S reagents. Aliphatic amines and aromatic amines are usually used as the N reagents. In the oxidizing construction of S–N bonds, the oxidants can facilitate the oxidation of S reagents, enabling the resulting active species to react with N reagents and form S–N coupling products. In the process, mild oxidants such as hypervalent iodine compounds and copper salts are often selected, so that the starting compounds are not over-oxidized. As a simple, effective, and environmentally friendly sulfonamide synthesis method, it is widely used in organic chemistry and pharmaceutical chemistry. The most critical factor is the choice of S reagent, N reagent, and oxidant.

S-reagents from Thiols or Disulfides for S–N Construction

The catalytic oxidative sulfonylation of thiols has attracted much attention due to the availability of raw materials, low cost, and high efficiency. Zhu et al reported a method for synthesizing sulfonamides via oxidative S–N coupling between aryl thiols and amines under mild, metal-free conditions using an I_2O_5-mediated reaction (►**Fig. 3**).[4] This method avoids the use of metals and peroxides and affords a variety of sulfonamides in moderate to good yields.

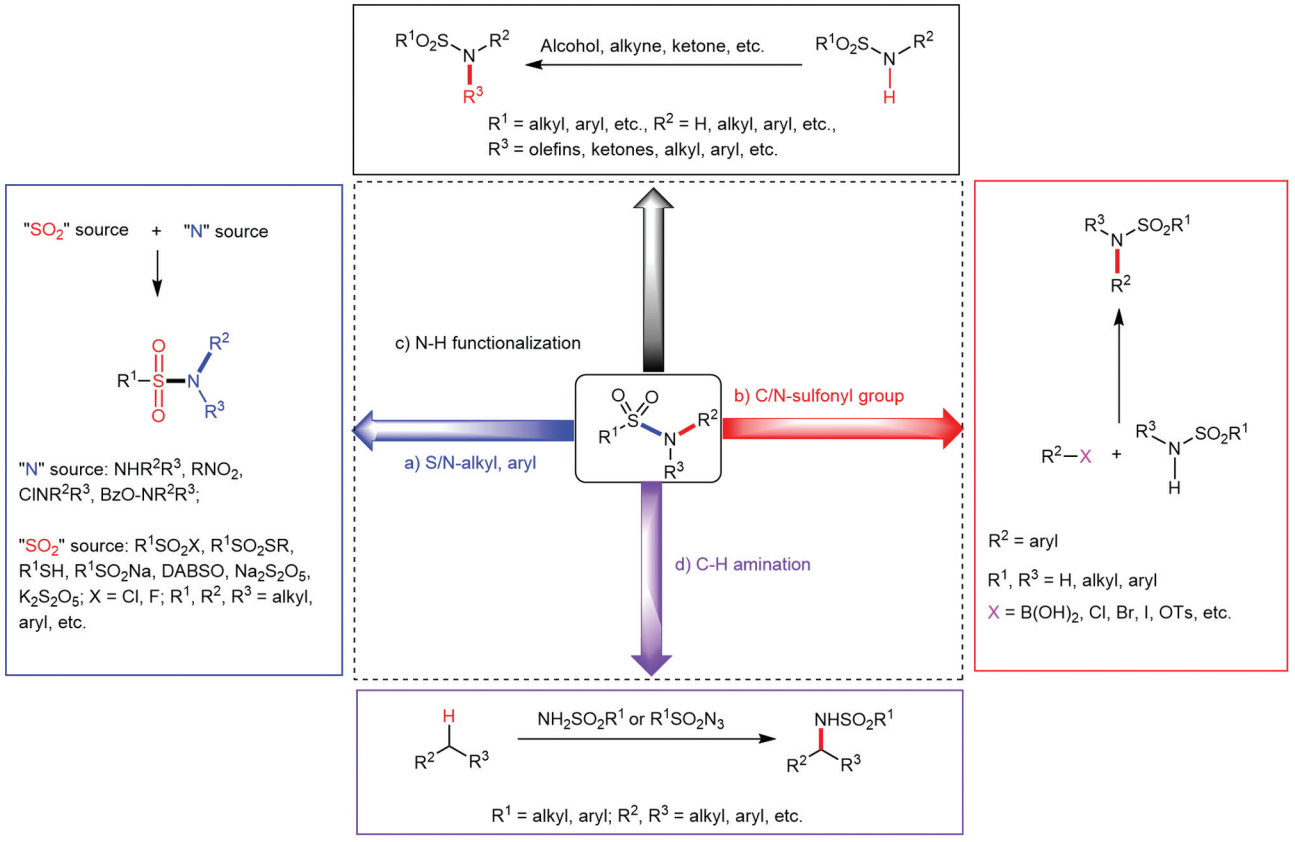

Fig. 2 Synthesis and derivatization of sulfonamides.

In 2018, Tota's group reported the conversion of thiols to sulfonimidates and sulfonamides in methanol. For thiols containing substituted alkoxy groups, conversion to sulfonamides occurs in the presence of lower ammonia concentrations, but extended reaction times are required (►**Fig. 3**).[5] The product distribution in the reaction highly depends on the electronic structure of the aryl group. This method applies to thiols containing polysubstituted aromatics, electron-rich heterocycles, and alkyl groups, with good yields. A drawback of this process is the poor tolerance of amines and thiols to strong oxidants.

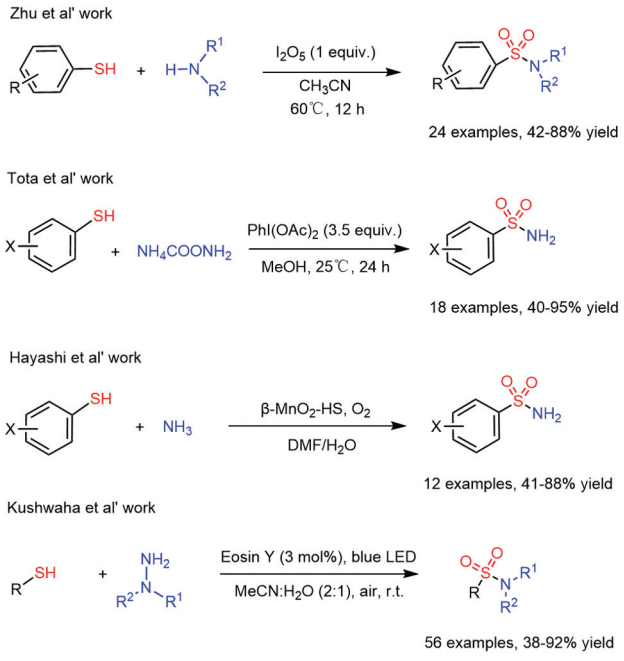

Fig. 3 Construction of sulfonamides from thiols and amines.

Recently, Hayashi et al found that (β-MnO_2-HS) nanoparticles with high specific surface area can be used as an effective and reusable bifunctional solid catalyst for the oxidative sulfonylation of thiols (►**Fig. 3**).[6] By utilizing molecular oxygen and ammonia as oxygen and nitrogen sources, both aromatic and heteroaromatic thiols can be oxidized in a single step to produce primary sulfonamide compounds without additives. Recently, Kushwaha et al introduced an eco-friendly, metal-free photoredox-catalyzed method for synthesizing sulfonamides using eosin Y and thiols with phenylhydrazines in MeCN:H_2O (►**Fig. 3**).[7] This approach offers a broad substrate scope, excellent functional group compatibility, and efficient production of pharmaceutical analogues under mild conditions.

As a green and efficient synthesis method, electrochemistry can solve the problems of transition metals, toxic solvents, excessive oxidants, and cumbersome purification processes in the production of pharmaceutical products. Laudadio et al reported an electrochemical method for the oxidative coupling of thiols and amines to obtain sulfonamides (►**Fig. 4**),[8] enabling S–N bond formation and

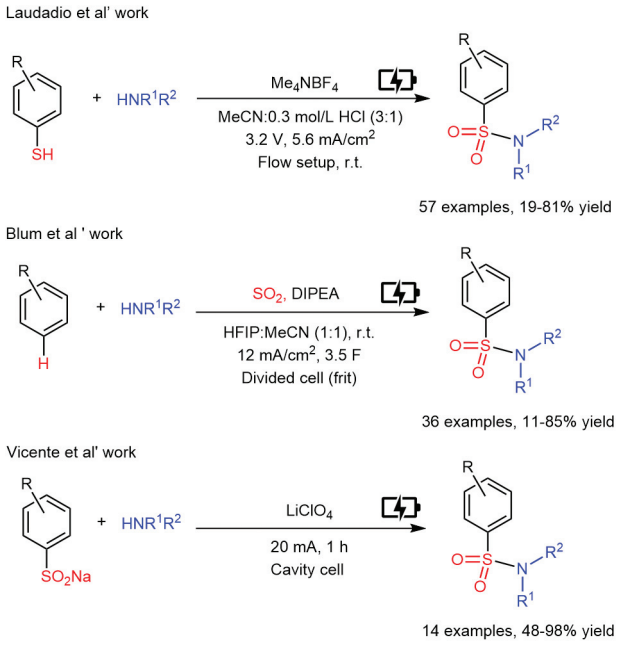

Fig. 4 Electrochemical synthesis of sulfonamides.

subsequent sulfur atom oxidation at room temperature, thus avoiding transition metal catalysis and hazardous reagents. Due to the malodorous properties of thiol compounds, Blum et al recently proposed the first method for electrochemical synthesis of sulfonamides by dehydrogenation (►**Fig. 4**),[9] when using the inherent reactivity of (heterocyclic) aromatic hydrocarbons, sulfonamides can be selectively synthesized by polymerization of sulfamate intermediates with SO_2 and amines in the presence of boron-doped diamond electrode and HFIP–MeCN mixed solvent. Because this method avoids harsh conditions and can be scaled up for continuous systems, it is more conductive to industrial adoption. In addition, Vicente et al realized the electrochemical synthesis of sulfonamides from sodium arylsulfinates by using graphite powder rough electrode and $LiClO_4$ as an electrolyte in a cavity cell (►**Fig. 4**).[10] This method is especially suitable for rapid and efficient synthesis of complex sulfonamides.

Thiosulfonate is a stable and nontoxic metal sulfite substitute because of its easy catalytic aerobic dimerization reaction and good reactivity with various amines. Shyam's group reported a method for synthesizing sulfonamides via direct coupling of thiosulfonates with amines in the presence of Cs_2CO_3 and *N*-bromosuccinimide or under copper-catalyzed conditions (►**Fig. 5**).[11,12] Among them, the thiosulfonate is cracked by the nucleophile to form a sulfite anion, which then reacts with the amine group to obtain the required sulfonamide. Because the reaction has characteristics such as simple reaction mode and high yields, it can be used as an effective synthesis strategy.

Sulfosalts as the Sulfur Source

Sulfur dioxide insertion is considered to be an effective strategy for the synthesis of sulfonyl-containing compounds. For example, sulfur dioxide substitutes, such as $K_2S_2O_5$ and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) have been used as starting materials to introduce sulfonyl groups into small molecules to obtain various functional sulfonamides. Compared with traditional sulfide oxidation, this method is highly compatible with different functional groups present in the compound molecules, providing an effective way for the conversion of sulfonamide compounds.

Sulfur-Containing Organic Salts as the Sulfur Source

Sulfites have been widely used as an S reagent for oxidative S–N coupling due to their easy oxidation to S-centered sulfonyl radicals. Compared with sulfonyl chloride, they have characteristics such as moisture resistance and easy synthesis. Alvarez et al have reported a method for obtaining aryl sulfonamides through C–H sulfonation of thianthrenium salts (►**Fig. 6**).[13] Utilizing inexpensive and readily available sodium hydroxymethylsulfinate (Rongalite) as a coupling agent, aryl hydroxymethyl sulfones (intermediate **A**) were generated under the catalysis of $Pd(dppf)Cl_2$, which then lost formaldehyde to form aryl sulfites in the presence of alkali. Finally, sulfonamides **B** were obtained by oxidative amination with morpholine. To further prove the practicability of this method, the authors have also realized the postfunctionalization of some complex active drugs through experiments and found that when the solubility of raw materials in the solvent isopropanol is low, the conversion rate decreases. However, the conversion rate can be improved by using polar aprotic acetonitrile as a co-solvent.

Sodium arylsulfinate is an effective aryl reagent with advantages such as stability and ease of operation. Eid et al first revealed a sustainable method for one-step synthesis of sulfonamides using sodium arylsulfinate as a sulfur source (►**Fig. 7**).[14] The key step of the reaction is the nucleophilic attack of the sulfur atom by the nitro group of the substrate, forming the S–N bond before the N–O bond is reduced by sodium bisulfite, leading to the formation of sulfate ions and

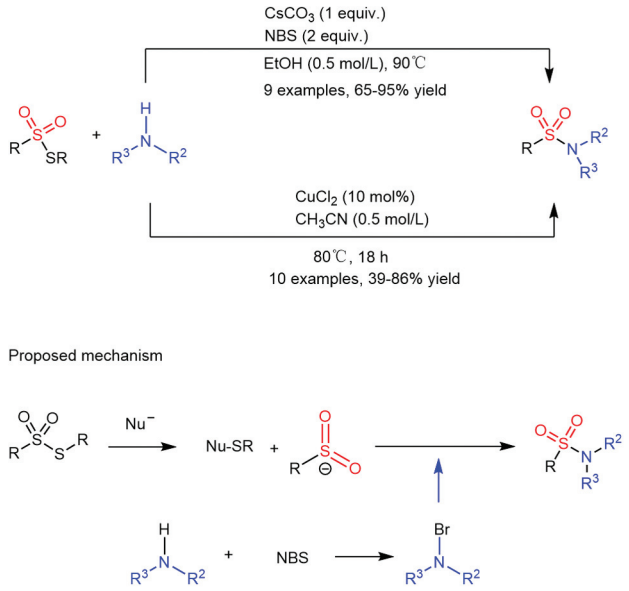

Fig. 5 Synthesis of sulfonamides via thiosulfonates.

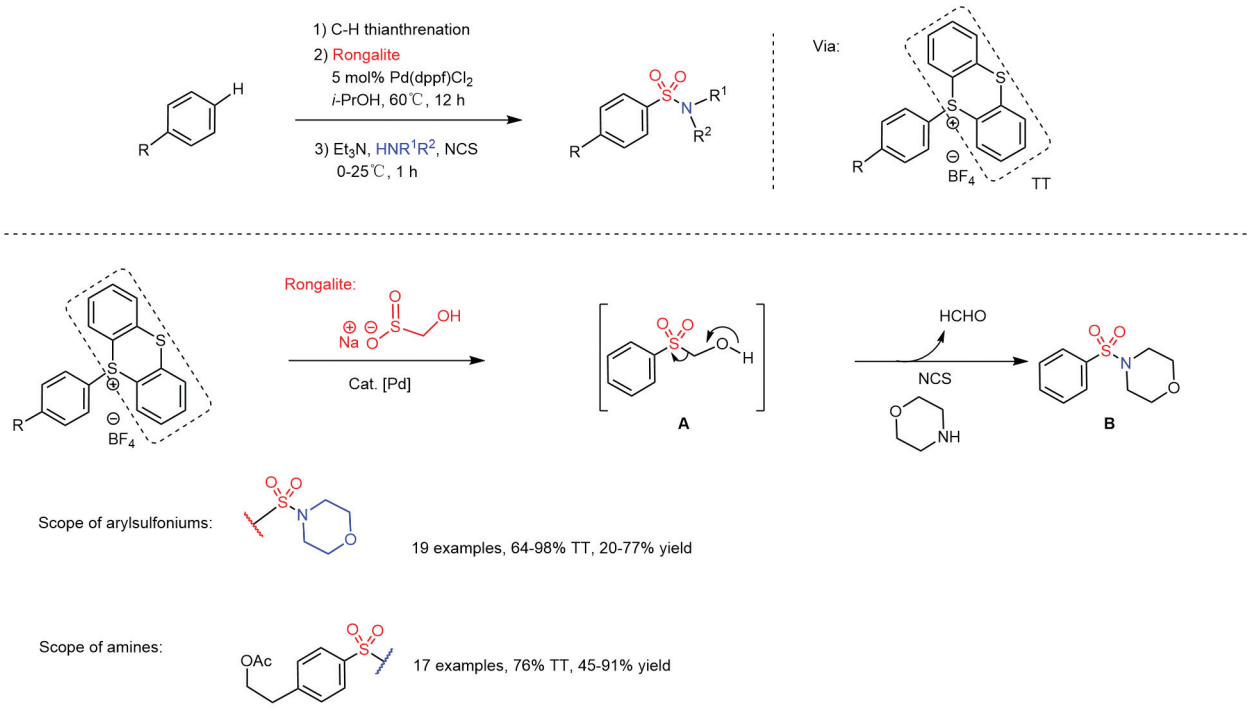

Fig. 6 Thianthrenium salts for palladium-catalyzed coupling with rongalite toward synthesis of sulfonamides.

sulfonamide groups. As a result, electron-deficient nitroarenes are more reactive than their electron-rich counterparts.

Additionally, Li et al reported a method for synthesizing *N*-arylsulfonamides through the reaction of sodium arylsulfinate with nitroaromatics, utilizing an iron-based metal-organic framework MIL-101 (Fe) as the catalyst and water as a solvent, offering benefits such as recyclable catalytic system, high chemical selectivity, and high yields (►**Fig. 7**).[15]

Yang et al reported a one-step direct reduction coupling reaction of nitroarenes and sodium arylsulfinates using an inexpensive Pd/C catalyst (►**Fig. 7**).[16] In this process, sodium arylsulfinate acts as both a sulfur source and a reducing agent. This method, without the need for additional reducing agents or ligands, features low catalyst loading, good functional group tolerance, and high efficiency, providing a straightforward synthesis strategy for producing *N*-arylsulfonamide. Gatarz et al have devised an innovative method for the synthesis of (hetero)aryl sulfonamides via the reductive coupling of nitro-heteroarenes with aryl sulfinates, utilizing sodium bisulfite, optionally in the presence of $SnCl_2$, in DMSO (►**Fig. 7**).[17] Enhanced by ultrasound to optimize reaction homogeneity, this method presents a valuable alternative to conventional sulfonamide synthesis, particularly advantageous for the production of heteroaryl derivatives. The research further elucidates the transformation mechanism by identifying nitrosoarene intermediates.

Similarly, Poeira's group[18] has developed a sulfonylation method using hypervalent iodine reagents, with sodium arylsulfinate as a sulfur source (►**Fig. 8**). This method employs the polarity reversal and atomic transfer properties of benzoimidazole derivatives to combine sulfonyl groups with aliphatic or aromatic amines. As an environmentally friendly approach, it provides sulfonamides with moderate to excellent yields on a gram-scale. Lam et al have established an innovative copper-catalyzed S–N coupling method for synthesizing sulfonamides from sodium arylsulfinates and aryl amines (►**Fig. 8**).[19] This approach utilizes stable solid

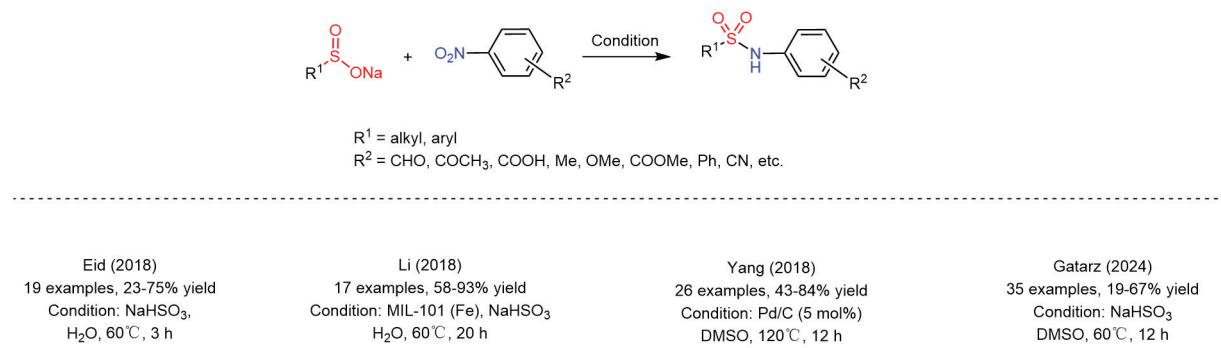

Fig. 7 Synthesis of *n*-arylsulfonamides from nitroarenes and sodium sulfinate.

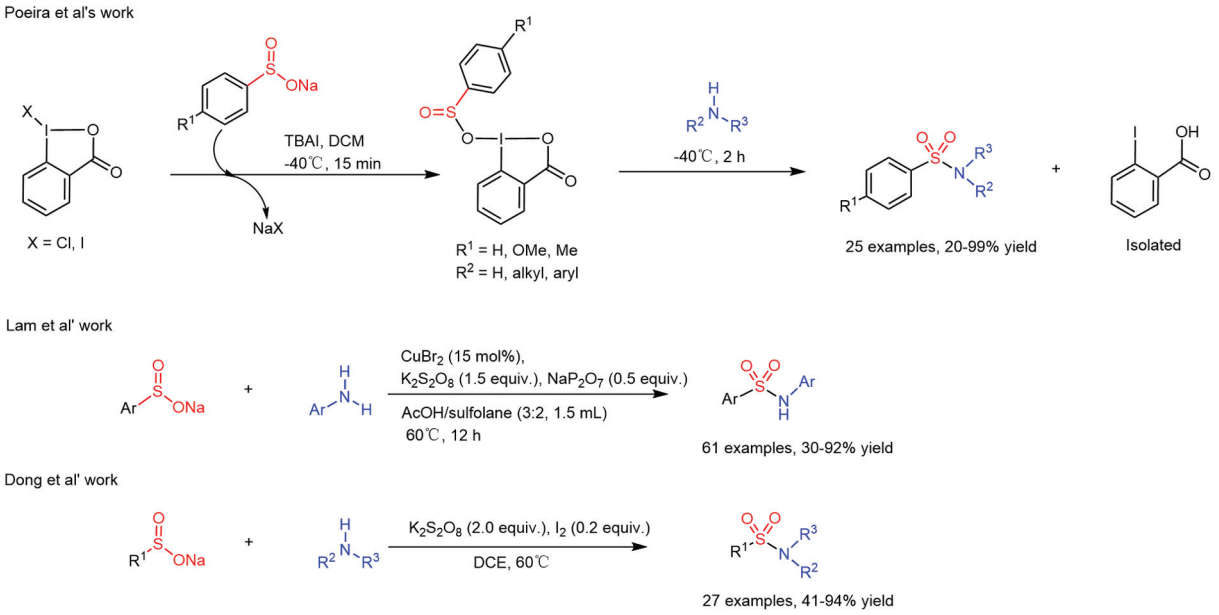

Fig. 8 Synthesis of sulfonamides from sodium sulfinates and amines.

chemicals in sulfolane or environmentally friendly solvents with acetic acid, effectively accommodating a range of functional groups commonly found in pharmaceuticals. The reaction mechanism involves radical coupling between sulfonyl and anilinium radicals facilitated by $K_2S_2O_8$ and a copper catalyst. Recently, Dong's group has developed an innovative method for the selective synthesis of sulfenamides using I_2 as a catalyst (►**Fig. 8**).[20] This approach offers mild reaction conditions, a wide substrate scope, and high efficiency, making it highly suitable for drug discovery and scalable synthesis.

Sulfur-Containing Inorganic Salts as the Sulfur Source

The insertion of sulfur dioxide by combining stable and safe sodium pyrosulfite or potassium pyrosulfite with nitroaromatics offers a rapid method to obtain sulfonamides. Jiang's group first introduced a metal-free, three-component reaction method for the construction of primary sulfonamides using arenediazonium tetrafluoroborates, sodium pyrosulfite ($Na_2S_2O_5$), and sodium azide (►**Fig. 9**).[21] This method was used to synthesize the nonsteroidal anti-inflammatory drug celecoxib and the antipsychotic drug sulpiride, demonstrating the practicability of this three-component coupling approach. However, further study is needed to avoid the use of hazardous sodium azide.

Mechanistic studies revealed that an aryl radical intermediate is generated through a single electron transfer between the arenediazonium salt and triphenylphosphine. This intermediate reacts with $Na_2S_2O_5$ to form a sulfonyl radical, releasing Na_2SO_3. The sulfonyl radical then couples with a conjugated phosphine imine radical intermediate, followed by hydrolysis to yield the sulfonamide compound.

According to the report by Marset et al, $Na_2S_2O_5$, nitro compounds and nontoxic triaryl bismuth were used to obtain sulfonamide compounds under copper-catalyzed reaction conditions, using a deep eutectic solvent (DES) as a green reaction solvent (►**Fig. 10**).[22] In this process, triaryl bismuth reacts with 3 equiv. of $Na_2S_2O_5$, demonstrating high atom economy. The bismuth salt produced by the reaction can be easily removed by water precipitation, and the generation of toxic organic by-products can be avoided. Therefore, it can be used as a green and effective method for the synthesis of sulfonamides.

Recently, Wu's group reported a copper-catalyzed three-component reaction of arylboronic acids, nitroarenes, and potassium pyrosulfite ($K_2S_2O_5$), to obtain sulfonamides (►**Fig. 10**).[23] Among them, the interaction between arylsulfinates, as intermediates, and nitroarenes, is a key step in the reaction, which has good tolerance to functional groups such as hydroxyl, cyano, amino, and carbonyl groups, and is extended to the synthesis of currently marketed drugs (flutamide) in good yield. In the same year, Chen et al reported a method for the synthesis of sulfonamides by continuous C–S and S–N coupling reactions of nitroaromatics, (hetero)arylboronic acids, and $K_2S_2O_5$ under metal-free catalytic conditions (►**Fig. 10**).[24] The scheme is compatible with a range of electron-rich and electron-deficient boric acids, though it is not suitable for nitroaromatics containing hydroxyl and formyl groups. The expected sulfonamide compounds can be isolated in good yield by amplifying more complex bioactive molecules into gram-scale preparation, validating the practicability of this heavy metal-free synthesis method.

In addition, using $K_2S_2O_5$ as a substitute for SO_2, Manabe's group first reported a method for selective synthesis of cyclosulfonamides and sulfinamides with amino-containing halogenated aromatic hydrocarbons under palladium catalysis (►**Fig. 11**).[25] The alkali concentration is crucial for the selective synthesis. Through mechanism research, amino-containing halogenated aromatic hydrocarbons are first

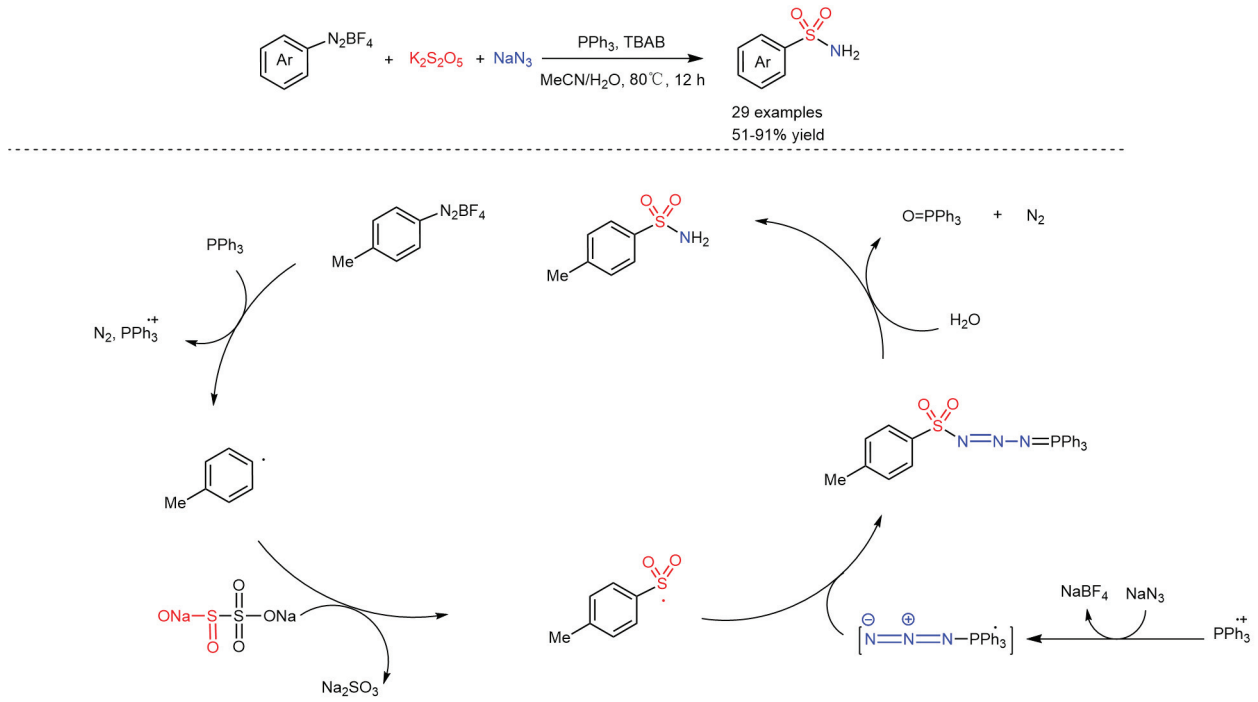

Fig. 9 Construction of primary sulfonamides through arenediazonium, $Na_2S_2O_5$, and NaN_3.

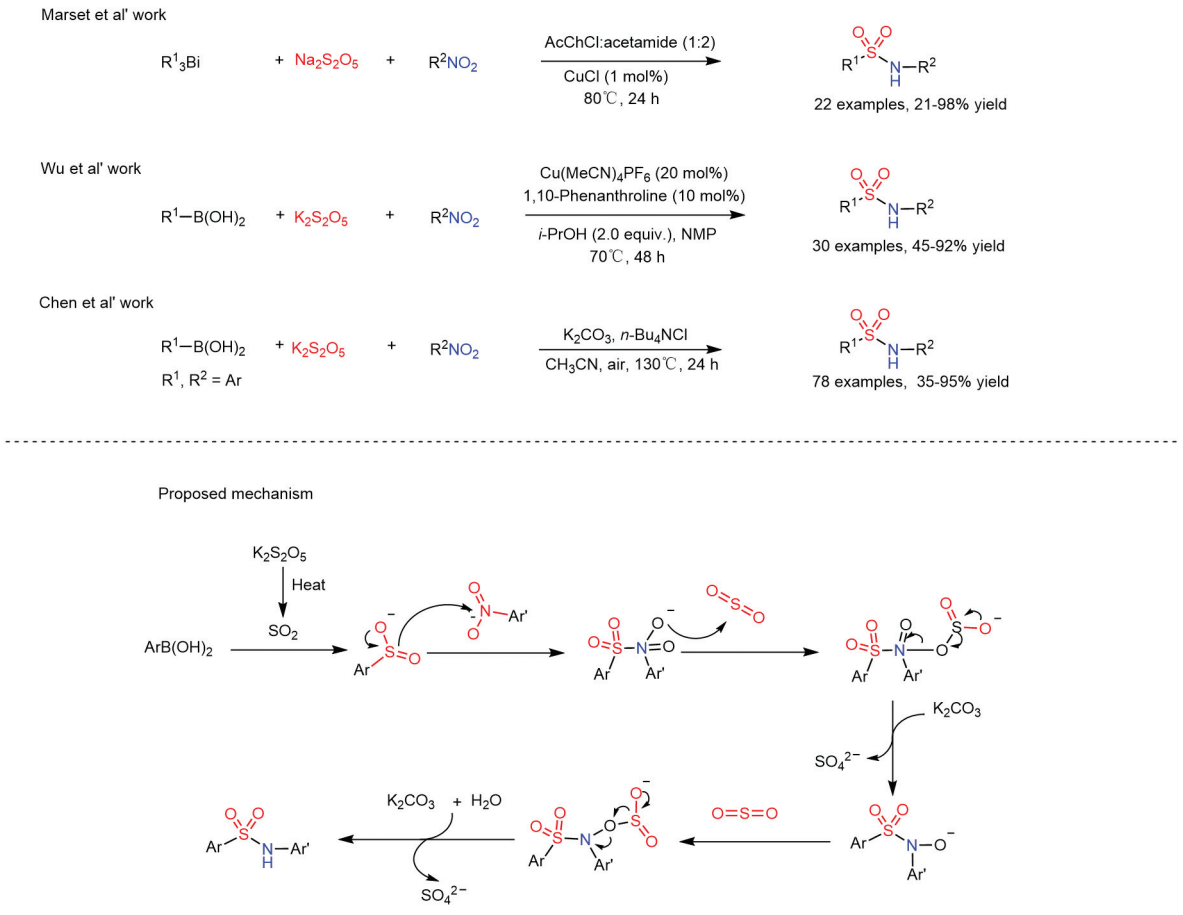

Fig. 10 Sequential C–S and S–N coupling approach to sulfonamides.

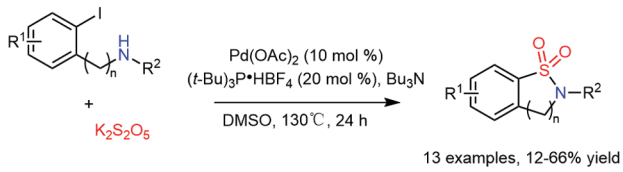

Fig. 11 Pd-Catalyzed selective synthesis of cyclic sulfonamides using $K_2S_2O_5$.

inserted into sulfur monoxide to form sulfinamides, and then oxidized to sulfonamides under the action of iodine ions and dimethyl sulfoxide. Among them, iodide as an oxidant and dimethyl sulfoxide as an oxygen source play important roles in the formation of sulfonamides. However, the reaction mechanism of sulfonamide formation needs to be further explored.

Recently, Mkrtchyan and Iaroshenko achieved a three-component coupling reaction of $K_2S_2O_5$, primary or secondary amines with aryl bromides or aromatic carboxylic acids via a mechanochemical method under palladium-catalyzed conditions (►**Fig. 12**).[26] This novel green synthesis strategy enables the production of sulfonamides with diverse structures and broad functional group tolerance. It is worth mentioning that this method can be prepared on a gram scale with a yield of 69 to 80%.

DABSO as Sulfur Source

DABSO is a stable, air-resistant reagent that safely facilitates the introduction of sulfonyl groups into molecules, making it an ideal sulfur source for the construction of sulfonamides.

Du et al reported a highly selective oxidative coupling reaction of DABSO with hydrazine and amines under copper-catalyzed conditions, achieving sulfonamide compounds in good yields (►**Fig. 13**).[27] The reaction can be carried out under mild reaction conditions without other additives. However, there is a need to use excessive amines and hydrazine nucleophiles. Chen et al developed a Cu(II)-catalyzed one-step synthesis of sulfonamides by replacing hydrazine with boric acid, utilizing (hetero)arylboronic acids, amines, and DABSO (►**Fig. 13**).[28] This reaction is compatible with aryl, heteroaryl, and alkenylboronic acids, as well as cyclic and acyclic secondary amines and primary amines, and has a wide range of functional group tolerance. The author verified the good reactivity of the method through a variety of complex drugs and active drug molecules. Notably, these complex drug molecules yield the expected sulfonamide compounds under standard reaction conditions, though the related reaction mechanism remains under investigation. In previous studies, electron-deficient amines exhibited poor reactivity. Recently, Zhang et al developed a method leveraging synergetic photoredox and copper catalysis for the synthesis of sulfonamides from various aryl radical precursors, amines, and a sulfur dioxide source under ambient conditions (►**Fig. 13**).[29] This one-step process effectively accommodates both electron-rich and electron-deficient amines. Oxygen in the air plays a critical role, facilitating the catalytic cycles. The method shows excellent functional group compatibility and broad substrate applicability, successfully enabling the synthesis of sulfanitran and an *N*-aryl sulpiride derivative.

Additionally, Willis' group pioneered a nickel (II)-catalyzed (hetero)arylboronic acid sulfonation reaction under neutral redox conditions (►**Fig. 14**).[30] By using commercially available and air-stable phenanthroline ligands $NiBr_2$•(Glyme) and DABSO, boric acid can be effectively converted into corresponding sulfinates, which can be further converted into active pharmaceutical molecules containing sulfonyl groups such as sulfonamides. Notably, the reaction achieves good yields of sulfonamides from both electron-rich and electron-deficient aryl and heteroarylboronic acids and can be scaled up to a gram-scale with just 2.5 mol% catalyst dosage.

Similarly, sulfite served as a key intermediate in the transformation process. Tu's group developed a bimetallic-catalyzed sulfonamide reaction of DABSO with *O*-benzoylhydroxylamine without ligand participation. In this method, aryl iodides or arylboronic acids were used as aryl sources, and low-loading $Pd(OAc)_2$ and $CuBr_2$ were used as catalysts. Under mild reaction conditions, sulfonamide compounds were obtained in good yield by one-pot reaction

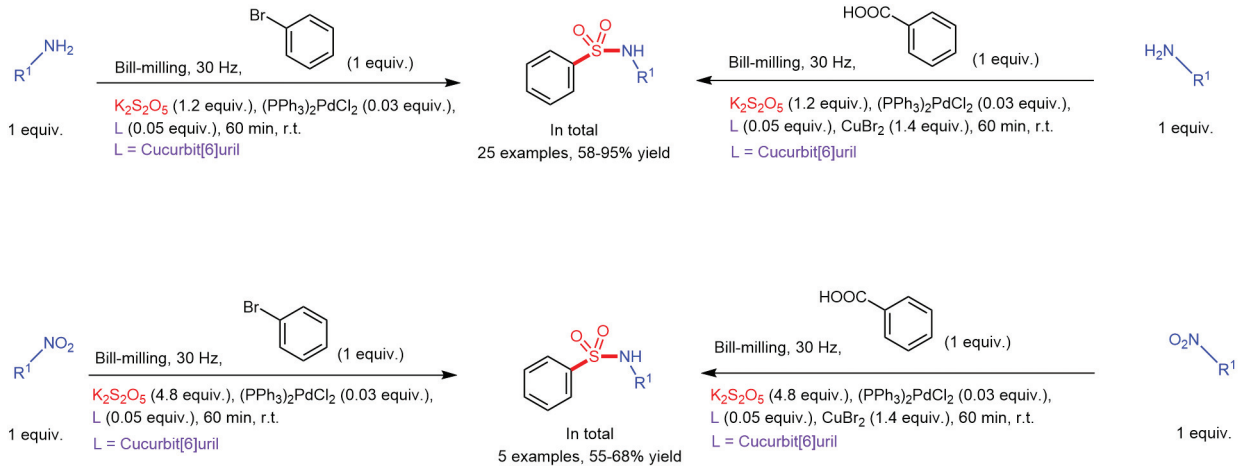

Fig. 12 Mechanochemical synthesis of aromatic sulfonamides.

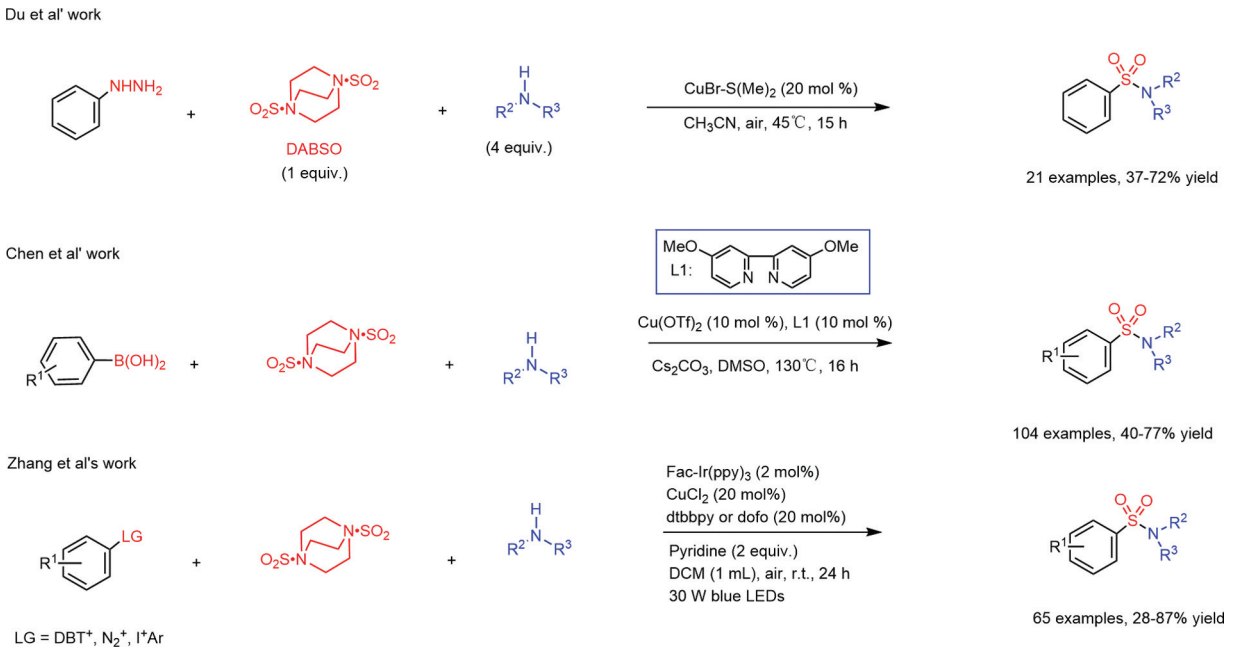

Fig. 13 Copper-catalyzed three-component synthesis of sulfonamides.

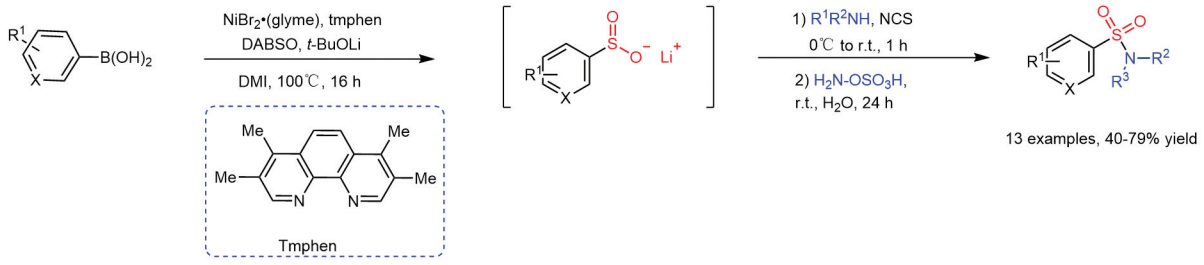

Fig. 14 Nickel-catalyzed preparation of sulfonamides from aryl and heteroaryl boronic acids.

(►**Fig. 15**).[31,32] The reaction performs better with substrates having electron-donating groups but shows reduced efficacy with sterically hindered substrates.

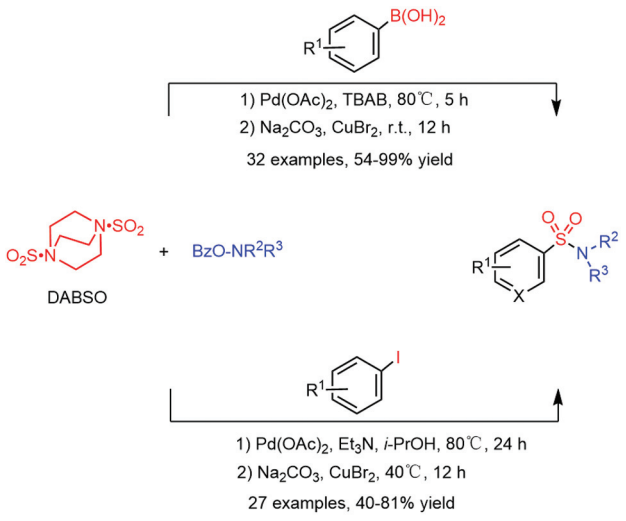

Fig. 15 Aminosulfonylation of DABSO with *O*-benzoyl hydroxylamines. DABSO, 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide).

In the absence of a catalyst, Wu's group reported an effective way to prepare sulfonamides by a one-pot two-step continuous reaction with DABSO as a sulfur source (►**Fig. 16**).[33] The three-component reaction of aryldiazotetrafluoroborate, DABSO, and an amine in the presence of *N*-hydroxybenzotriazole yields sulfonamide compounds in good amounts. Among them, the tertiary amine radical cation produced by the reaction of aryldiazotetrafluoroborate with DABSO extracts the H atom from the nucleophilic substrate to produce a free-radical intermediate, which is then captured by the sulfonyl group, to form a sulfonated product. In addition, the research group reported the aminosulfonylation of aryldiazotetrafluoroborate and DABSO, with chloramine as an electrophilic amine source under copper-catalyzed conditions (►**Fig. 16**).[34] As a simple and effective method, the coupling reaction shows a wide range of substrates. In addition, the author also described the mechanism that may involve free-radical processes and transition metal catalysis.

Sulfonyl Fluorides

Nowadays, green chemistry encourages the design of process routes that can reduce or eliminate the use and production of

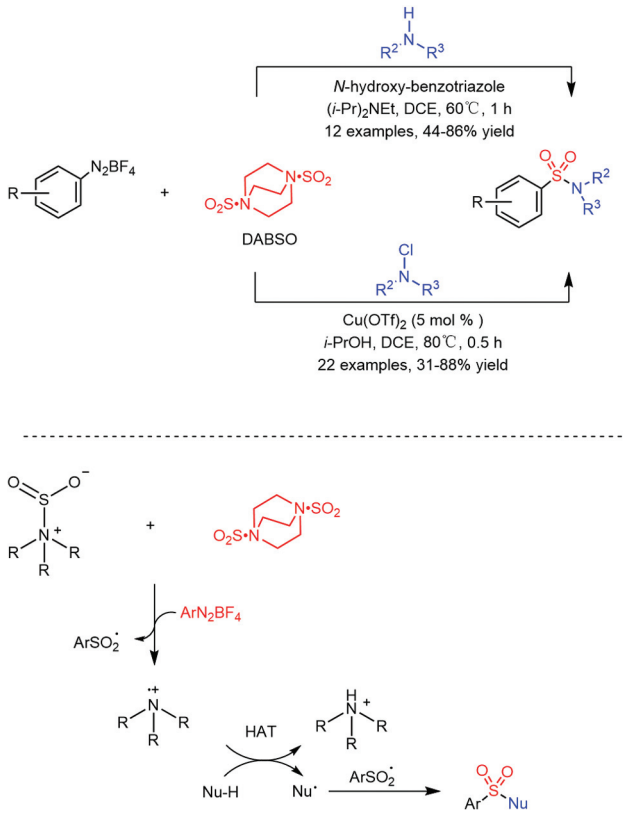

Fig. 16 Aminosulfonylation of aryldiazonium tetrafluoroborates with DABSO. DABSO, 1,4-diazabicyclo [2.2.2] octane bis (sulfur dioxide).

harmful substances. Sulfonyl fluorides are considered an attractive alternative to sulfonyl chlorides due to their excellent stability and adjustable reactivity. Sharpless coined the term "sulfur (VI) fluoride exchange (SuFEx) chemistry" to emphasize the unique reactivity associated with the S (VI)–F bond, and the corresponding sulfonyl fluorides have received increasing attention in drug discovery and other aspects.[35] For example, Willis' group reported a method for preparing sulfonamides from alkenyl sulfonyl fluorides.[36]

Ball's group utilized calcium trifluoride [$Ca(NTf_2)_2$] as Lewis acid to activate less active sulfonyl fluoride in *tert*-amyl alcohol, followed by nucleophilic addition with amines to produce various aryl, alkyl, and heteroaryl sulfonamides (►**Fig. 17**).[37] This may be transformed by the interaction between divalent cations and triflimide anion. Moreover, they also reported a method for efficiently obtaining sulfonamides by activating sulfonyl fluorides at room temperature with calcium triflimide and DABCO.[38] Compared with previous work, this method can obtain comparable or improved yields at lower reaction temperatures while significantly increasing the reaction rate.

Although the above scheme is also effective for the activation of less active sulfonyl fluoride, completion of the reaction requires the participation of stoichiometric calcium activators. Li's group developed a broad-spectrum synthesis method for the synthesis of sulfonamides from sulfonyl fluorides (►**Fig. 17**).[39] High yields of sulfonamide

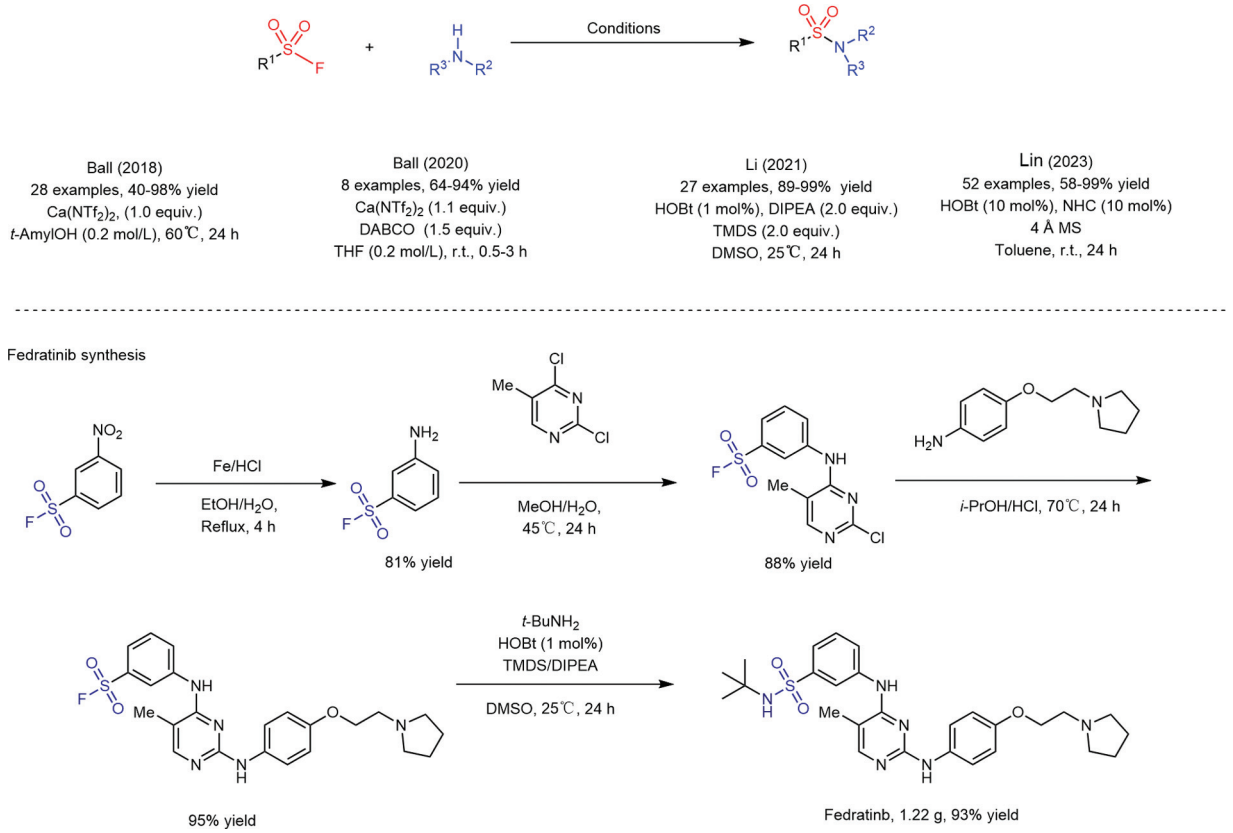

Fig. 17 Amidation of sulfonyl fluorides with amine.

compounds are achieved under the combined catalysis of 1-hydroxybenzotriazole (HOBt) and silicon additives, making this protocol particularly effective for substrates with large steric hindrance. It has been successfully applied in the synthesis of the orphan drug fedratinib for the treatment of bone marrow fibrosis in gram-scale preparation, which was approved by the U.S. FDA recently.[40] The original synthesis route for fedratinib involved early-stage amidation of sulfonyl chloride with *tert*-butylamine, followed by two nucleophilic aromatic substitutions. In contrast, Li's group utilized readily available 3-nitrobenzenesulfonyl fluoride as the starting material. Through a sequence of reduction and nucleophilic aromatic substitutions, they generated a key intermediate, sulfonyl fluoride. This intermediate was then amidated to produce the desired product, fedratinib, achieving a yield of 93% and a final product weight of 1.22 g (►**Fig. 17**). The use of sulfonyl fluoride enables late-stage functionalization and diversification at the sulfonamide terminal, facilitating the development of fedratinib analogues for further biological screening.

Recently, Lin et al have developed an organocatalytic SuFEx reaction employing *N*-heterocyclic carbene (NHC) to effectively mediate the transformation of sulfonyl fluorides with amines (►**Fig. 17**).[41] NHCs function as carbon-centered Brønsted bases, facilitating substrate activation through hydrogen bonding. This approach provides mild reaction conditions, broad substrate compatibility, high yields, and scalability, establishing a robust platform for synthesizing a diverse array of valuable sulfonamide compounds.

C–N Cross-Coupling

The synthesis of sulfonamides through C–N bond formation is a widely used transformation method in pharmaceutical chemical synthesis. The critical structural motif in these important compounds is *N*-(hetero)aryl sulfonamides. Although the technique of direct cross-coupling of amines with aryl halides has advanced rapidly, the reduced nucleophilicity of sulfonamides compared to alkylamines remains a significant challenge.

Due to the lower nucleophilicity of sulfonamides relative to nucleophilic substrates like alkylamines, achieving metal-catalyzed C–N cross-coupling reactions with sulfonamide is challenging, particularly with (hetero)aryl chlorides or phenol derivatives. Zu et al reported a copper-catalyzed chemoselective Chan–Evans–Lam cross-coupling reaction between unprotected aminobenzenesulfonamides and arylboronic acids to synthesize *N*-arylsulfonamides (►**Fig. 18**).[42] Notably, the *N*-arylation of aminobenzene sulfonamide on either the amino or sulfonamide nitrogen atoms can be tuned by

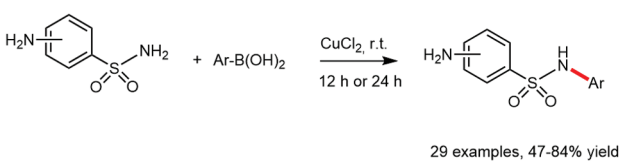

Fig. 18 Chemoselective *N*-arylation of aminobenzene sulfonamides.

varying the reaction conditions, such as the copper catalyst, solvent, and base source, at room temperature and in the presence of air. However, the rate of this reaction is somewhat low and thus needs to be improved.

Palladium-catalyzed C–X (X=C, N, O, S) coupling reactions are classic methods for forming carbon–nitrogen bonds, with the effectiveness hinging on suitable biarylphosphine ligands. Shashank' group developed a library of biarylphosphines, which have been applied as ligands in palladium-catalyzed cross-coupling reactions, such as those involving aryl sulfonamides (►**Fig. 19**).[43] Their various ligand combinations enhance the reductive elimination steps in the palladium-catalyzed formation of aryl sulfonamides, effectively catalyzing reactions of aryl bromides, aryl chlorides, and aryl trifluorides with (alkyl) aryl sulfonamides.

Among tertiary sulfonamides, *N*,*N*-diaryl sulfonamides are challenging to obtain via arylation due to the low nucleophilicity of secondary sulfonamides.[44] Dobereiner's group introduced a simple and efficient Pd/AdBippyPhos catalyst system to achieve *N*-arylation of secondary sulfonamides (►**Fig. 19**).[45] This method demonstrated the catalyst's adaptability to various heterocyclic electrophiles and sulfonamide structures, consistently yielding a range of *N*,*N*-diaryl sulfonamide compounds with pharmaceutical relevance. Compatible heterocycles include substituted pyridines, pyrazines, thiazoles, thiophenes, furans, benzothiazoles, and azaindoles. However, five-membered N-containing heterocycles like pyrroles and pyrazoles remain challenging. Notably, several tertiary sulfonamide products have been successfully isolated on a 0.2–2 mmol scale with yields ranging from good to excellent. Additionally, the above *N*-arylation reactions of primary and secondary sulfonamides have been validated through targeted high-throughput experiments to confirm their practicability and effectiveness.

In metal-catalyzed C–N cross-coupling reactions, nickel is an effective substitute for copper or palladium due to its low price and tendency to participate in oxidative addition. However, the reductive elimination of Ni(II)C–NR_2 as a high-barrier step limits its wide application. MacMillan's laboratory utilized the excited state of a nickel photocatalyst to facilitate the challenging C–N bond reductive elimination step, developing an efficient nickel-catalyzed method for the formation of C–N bonds between primary sulfonamides and aryl electrophiles (►**Fig. 20**).[46] Although this technology provides a broad pathway for the *N*-(hetero)aryl sulfonamide motif, it has poor catalytic performance for (hetero)aryl chlorides and phenol derivatives.

Thus, Mcguire et al reported a nickel-catalyzed C–N cross-coupling reaction of primary (secondary) sulfonamides with (hetero)aryl chlorides (►**Fig. 20**).[47] The reaction employs a "photoless redox" method complementary to the work of MacMillan's group. The design of (L)NiCl (*o*-tol) precatalysts (L=PhPAd-DalPhos and PAd_2-DalPhos) featuring diphosphine auxiliary ligands is noteworthy for enabling nickel-catalyzed C–N cross-coupling. The sulfonamide *N*-arylation reaction is effective for (hetero)aryl chlorides and phenol derivatives and adapts to many (hetero) aryl electrophiles (X=Cl, Br, I, Ots, and $OC(O)NEt_2$).

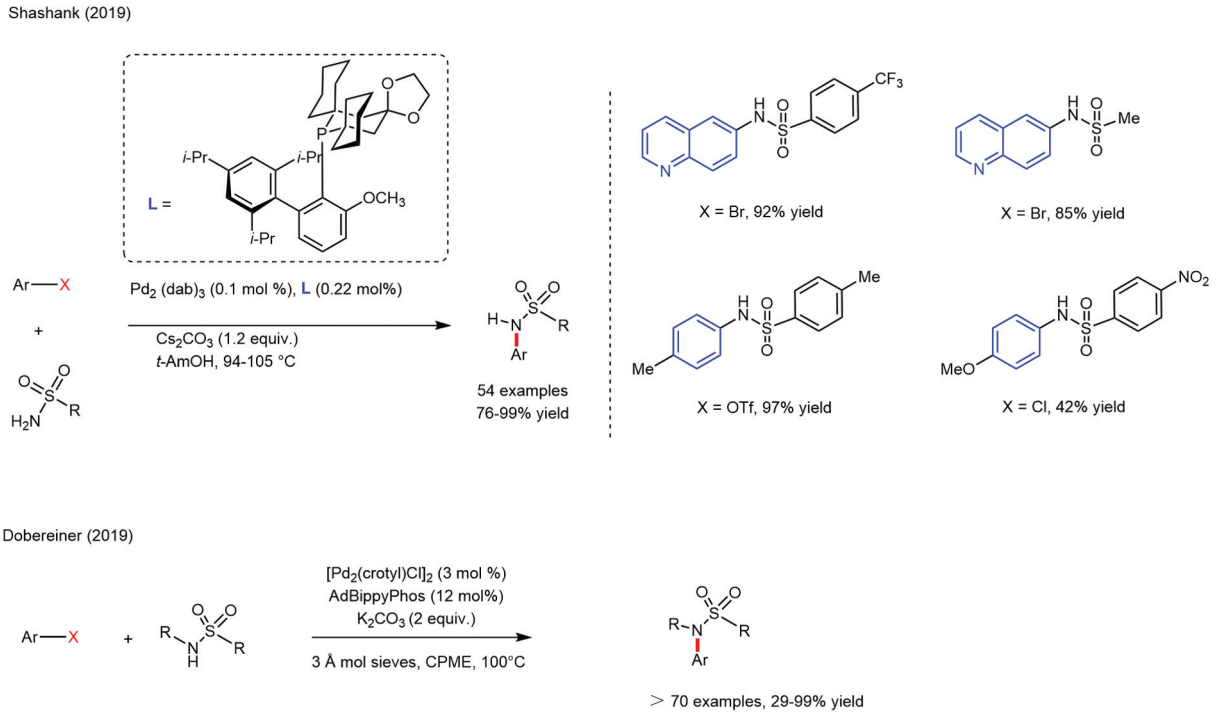

Fig. 19 *N*-Arylation of primary sulfonamides and secondary sulfonamides.

You and Li have introduced a novel C–N cross-coupling reaction utilizing Ni(cod)(DQ) as a single-component catalyst (►**Fig. 20**).[48] This advancement enables the synthesis of *N*,*N*-diarylsulfonamides from *N*-arylsulfonamides and aryl bromides without the need for additional ligands. The method demonstrates broad compatibility with both electron-deficient and electron-rich aryl/heteroaryl bromides. Notably, this approach is distinguished by its simplicity, air stability, rapid reaction times, and suitability for gram-scale synthesis. This study represents the first application of Ni(cod)(DQ) for C–N cross-coupling under these specific conditions.

Recently, Song et al presented a Ni-catalyzed photochemical C–N coupling of (hetero)aryl chlorides with sulfonamides (►**Fig. 20**),[49] employing mild organic amines as the base and removing the need for an external photocatalyst. This method is distinguished by its broad substrate scope and excellent functional group tolerance, enabling selective coupling even in the presence of multiple NH_2 groups. The utility of this protocol is demonstrated through the synthesis and late-stage modification of pharmaceutical compounds, providing a cost-effective and practical solution for electron-rich (hetero)aryl chlorides.

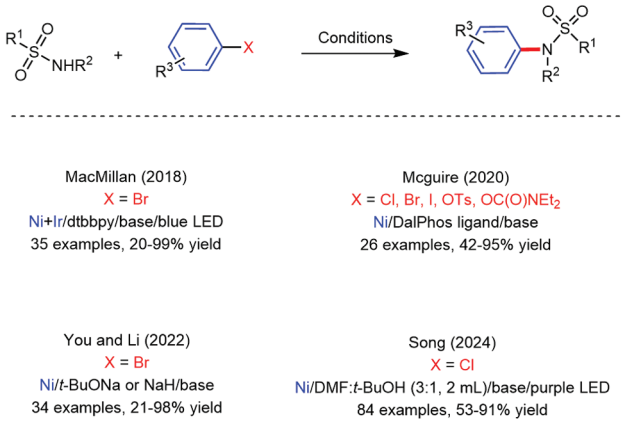

Fig. 20 Synthesis of sulfonamides by nickel-catalyzed cross-coupling of C–N.

N–H Functionalization

Pre-synthesis of sulfonamide groups through early C–N bond formation reactions may limit the type of functional groups on the sulfonamide substituents, resulting in incompatibility of downstream chemical functional groups. Post-functionalization of sulfonamide compounds offers an effective solution to this limitation. The functionalization of sulfonamides can be achieved by using different reactants, such as sodium arylsulfinate, ketones, alcohols, olefins, aldehydes, boric acid, etc.

For the later functionalization of sulfonamides, Fier's and Cornella's groups reported a general method for converting complex primary sulfonamides into various common functional groups by *in situ* formation of sulfinates under mild reaction conditions (►**Fig. 21**).[50,51] Based on the fact that sulfites are easily converted to other functional groups by electrophilic capture or loss of sulfur dioxide,[52] primary sulfonamides can be condensed with aldehydes to form sulfonylimide intermediates under mild conditions, and then release nitrile by-products, which are finally converted into sulfites. Notably, this late-stage functionalization method exhibits excellent selectivity, even in the presence of other

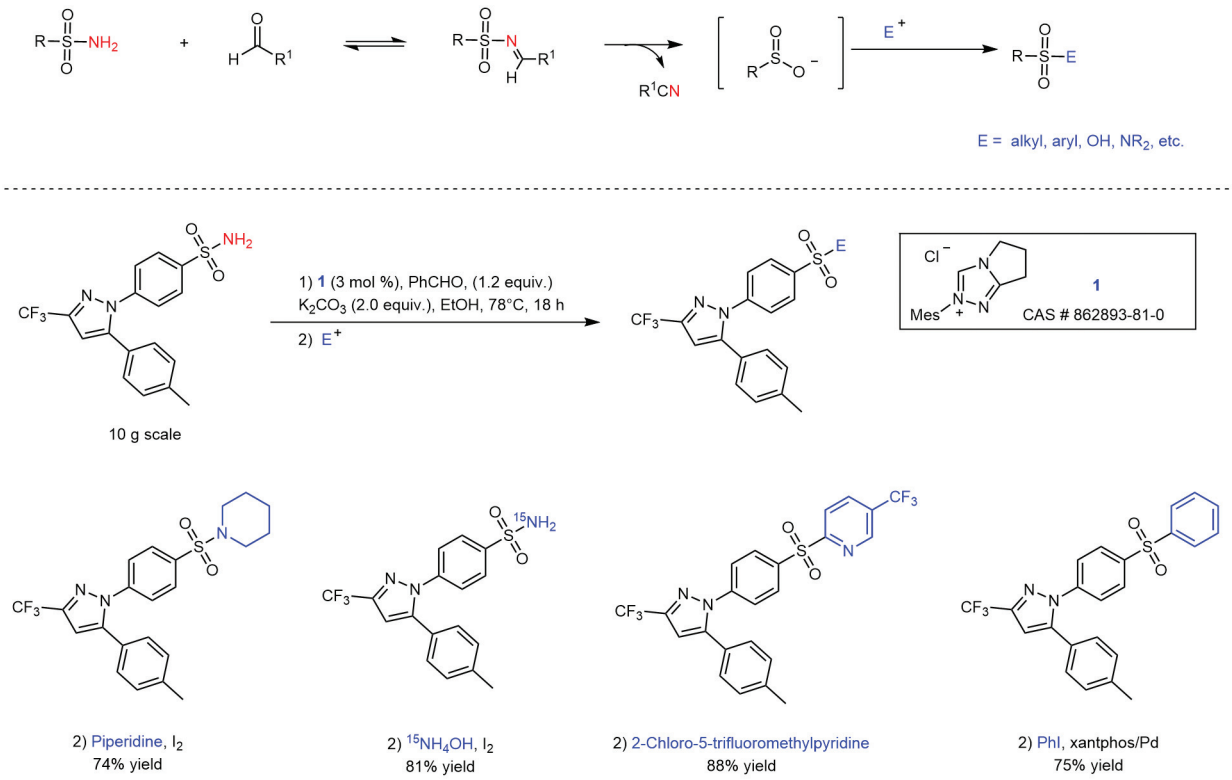

Fig. 21 Late-stage functionalization of primary sulfonamides.

amino groups in primary sulfonamides. This approach has been validated with several complex primary sulfonamide drugs. Additionally, it is suitable for the gram-scale preparation of new sulfonamide derivatives, illustrating the value of this predictable and high-yield post-functionalization technique. The method's utility is further highlighted by its ability to enable rapid access to ^{15}N-labeled sulfonamide drugs directly from their ^{14}N parent molecules, without requiring multistep syntheses. This capability is particularly valuable for supporting pharmacological studies in drug discovery.

In addition to the simple C–N bonding reaction, the secondary sulfonamide has been regarded as the terminal functional group because there is no other method to modify it later. In the same year, Fier's group developed a general method for the late functionalization of secondary sulfonamides (►**Fig. 22**),[53] and demonstrated the practicability of this method in drug discovery by applying it in the synthesis of metabolites and labeled compounds. The reaction initially produces an active phosphine intermediate from ethyl benzoylformate and tris(dimethylamino)phosphine, subsequently forming an *N*-sulfonylphenylglycine ester intermediate that features an acidic C–H bond adjacent to the nitrogen when combined with a secondary sulfonamide. The intermediate releases sulfinate anions under alkaline conditions and generates imines at the same time,

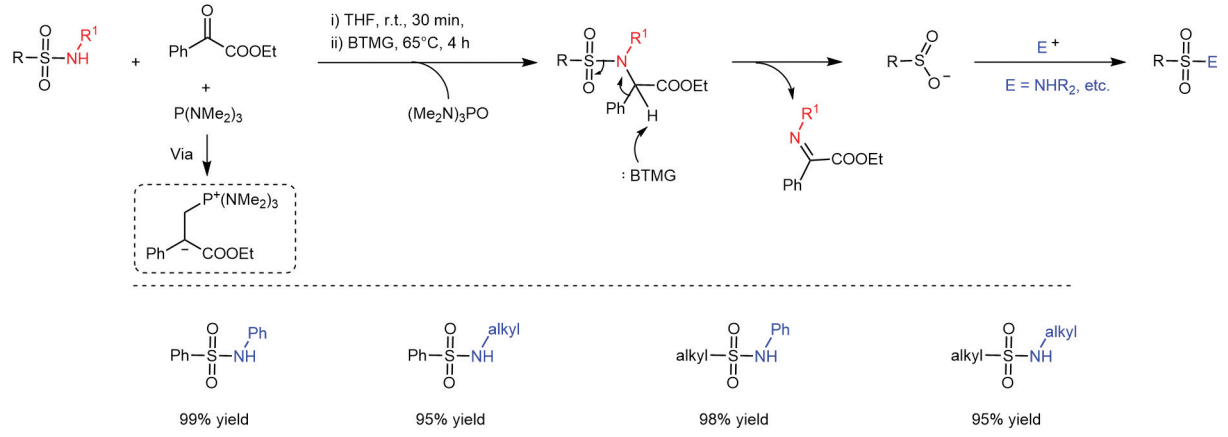

Fig. 22 Late-stage functionalization of secondary sulfonamides.

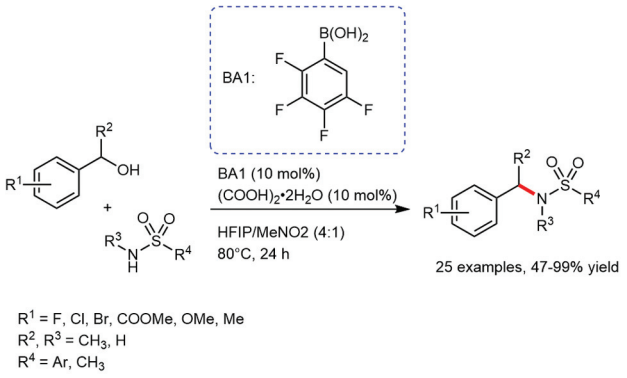

Fig. 23 Direct sulfonamidation of primary and secondary benzylic alcohols catalyzed by a boronic acid/oxalic acid system.

thereby achieving subsequent functionalization of sulfites or amines after imine cleavage.

N-(Aryl)alkyl Sulfonamides

At present, *N*-alkyl sulfonamides can be synthesized by substituting alcohols with nitrogen nucleophiles under the catalysis of transition metals[54] and Lewis acids[55] or Brønsted acids,[56] producing water as the sole by-product. Verdelet et al developed a catalytic method for the direct conversion of primary and secondary benzyl alcohol into various sulfonamide compounds under mild conditions using 2,3,4,5-tetrafluorophenylboronic acid and oxalic acid dihydrate as co-catalyst systems (►**Fig. 23**).[57] In gram-scale preparations, this reaction is characterized by high yields and the excess sulfonamides can be recycled.

Subsequently, Morrill's group described the *N*-alkylation of sulfonamides by benzyl alcohol under $FeCl_2$-catalyzed conditions.[58] Given that the aforementioned methods predominantly utilize benzyl alcohol and require excess alkylating agents, Morrill's group developed a manganese-based PNP [$MnH(PNP^{NH}–iPr)(CO)_2$] pincer complex to catalyze the *N*-alkylation of primary sulfonamides using either benzyl alcohol or primary fatty alcohol, resulting in a series of aryl and alkyl sulfonamides with excellent separation yields (►**Fig. 24**).[59] A limitation on the substrate scope is that the *N*-alkylation of secondary sulfonamides has not been achieved. The author has explored its mechanism. First, the active manganese complex was formed in the dehydrogenation bromination reaction, which then reacted with alcohol to obtain an alkoxy complex. Subsequently, the aldehyde and manganese hydride complex formed by dehydrogenation condensed with *p*-toluenesulfonamide to form *N*-sulfonylimide. Finally, *N*-sulfonylimide was reduced by manganese hydride to provide *N*-alkylated products.

Although the above method exhibits good atom economy, it may involve toxic precious metals, high reaction temperature, and the use of excess amines or alcohols. To address these issues, Guru et al introduced a metal-free, green, and sustainable boron-catalyzed method for selective *N*-alkylation of sulfonamides with benzyl alcohols (►**Fig. 25**).[60] This method operates with a catalyst loading of 1 to 2 mol% and is compatible with functional groups such as carbonyl, cyano,

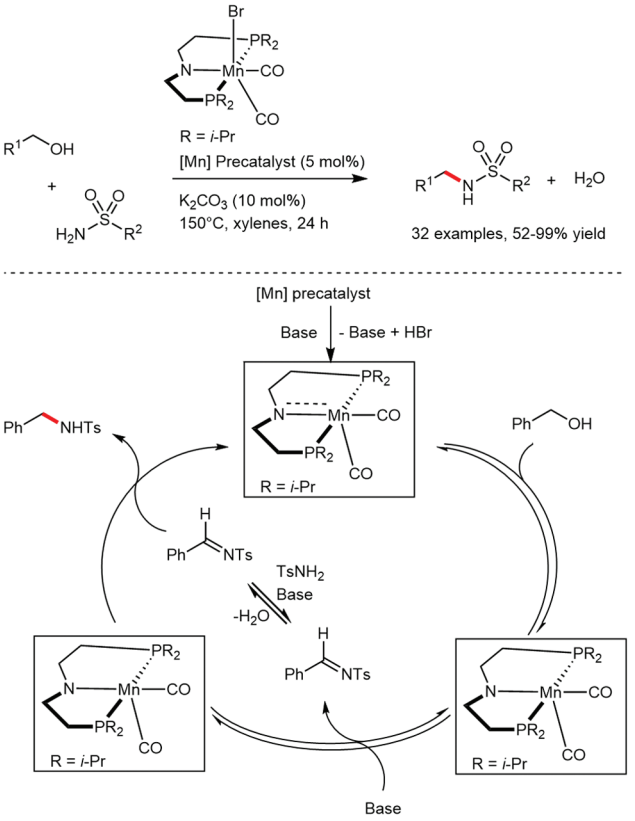

Fig. 24 Manganese-catalyzed *N*-alkylation of sulfonamides with alcohols.

carboxylic acid, halogen, and nitro. Recently, Ban et al have developed an improved protocol utilizing $In(OTf)_3$ as a Lewis acid catalyst for the direct sulfonamidation of unactivated alkyl alcohols, eliminating the need for preactivation (►**Fig. 25**).[61] This method efficiently transforms unactivated aliphatic alcohols into sulfonamides with good to excellent yields and is compatible with a diverse range of substrates, including allylic and benzylic alcohols. The procedure involves E1 elimination of alcohols to form alkenes, followed by hydroamination, demonstrating both scalability and practicality.

Jiang et al demonstrated a scheme for direct *N*-arylation of sulfonamides to *N*-arylsulfonamides by desulfitative protocols using sodium arylsulfinate as an effective aryl reagent (►**Fig. 26**).[62] This approach uses $CuCl_2$ as a catalyst and

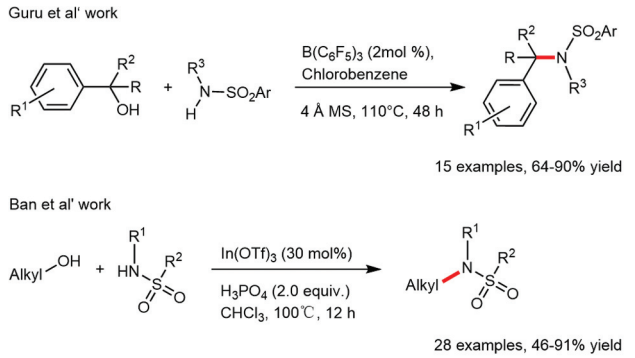

Fig. 25 *N*-Alkylation of sulfonamides with alcohols.

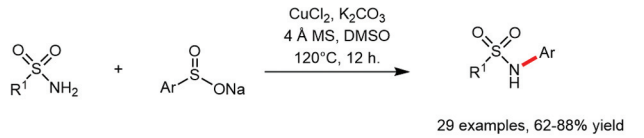

Fig. 26 *N*-Arylation of sulfonamides with sodium arylsulfinates.

demonstrates good functional group tolerance without the need for ligand participation, offering a novel and practical method for the synthesis of sulfonamides.

Song et al reported a palladium-catalyzed asymmetric reductive amination of ketones with weakly nucleophilic sulfonamides in the presence of a Brønsted acid (►**Fig. 27**).[63] This strategy employs *N*-*tert*-butyl-protected ketosulfonamide as the starting material, which avoids the need for removing protective groups and simplifies the separation of *N*-sulfonylimide intermediates by enabling a tandem reaction of amine deprotection and followed by asymmetric reduction amination. Finally, a large number of chiral γ-, ε-, and *δ*-sulfonamide compounds with high enantioselectivity (up to 99 %) can be obtained. Recently, Olu-Igbiloba et al presented a cobalt-catalyzed three-component synthesis of α-substituted *N*-sulfonyl amines, utilizing aryl aldehydes, primary sulfonamides, and (hetero)arenes (►**Fig. 27**).[64] This method enables the efficient construction of highly substituted sulfonamide frameworks via direct C(sp^2)–H activation, providing a more atom-economical alternative to traditional approaches such as the Petasis- or Mannich-type reactions.

Sulfonyl Amino Ketone Derivatives

Compared to aminoketones, the synthesis of *N*-sulfonylaminoketones is rarely reported due to the challenges in preparation and the use of hazardous chemicals. Mahato et al reported a highly selective method for the synthesis of α-sulfonamide derivatives by a coupling reaction of terminal alkynes with sulfonamides using diacetoxy iodobenzene (PIDA) as a catalyst (►**Fig. 28**).[65] This method showed good applicability in the gram-scale preparation. The mechanism study showed that alkynes reacted with $PhI(OAc)_2$ to form ethyl phenylethynyl iodate intermediate **A**, which was subjected to Michael's addition with AcOH to form intermediate **B**. After removing acetate ions, the intermediate carbene **C** was generated and was then reacted with acetyloxynucleophiles or acid. The diacetoxy olefin intermediate **D** was generated, and the final product was obtained by the reaction between α-acetoxy ketone and sulfonamide.

Hong's group introduced a new gold-catalyzed method for synthesizing *N*-sulfonyl amino ketones (►**Fig. 29**),[66] utilizing sulfonamides and alkynes as starting materials to achieve two different *N*-sulfonyl enaminone isomers through chemically controlled and stereoselective synthesis. As the first example of transition metal-catalyzed synthesis of enamines from sulfonamides and alkynes, it showed moderate to excellent yield and selectivity.

In addition, Liang et al reported a method for the synthesis of *N*-sulfonyl enaminones in high yields by copper-catalyzed N–H olefination of sulfonamides using saturated ketones as olefin sources and TEMPO derivatives and O_2 as oxidants (►**Fig. 30**).[67] This method introduces an unsaturated structure by modifying β-carbon, offering a novel approach to the functionalization of ketones.

Axially Chiral Sulfonamide Compounds

Non-biaryl C–N axially chiral compounds often exist in drugs and bioactive natural products, which can be used as chiral organic catalysts or ligands (►**Fig. 31**). The direct functionalization of benzenesulfonamides is usually used as the most direct strategy for obtaining axially chiral sulfonamides. Due to their significant application potential in the pharmaceutical industry, these chiral sulfonamides have been extensively studied.

Kikuchi's group first synthesized optically active *N*-allyl sulfonamide derivatives with the N–C axial chiral structure in the presence of (*S*,*S*)-trost ligand and $(allyl–Pd–Cl)_2$ catalyst (►**Fig. 31**).[68] The reaction of allyl acetate with various *N*-(2-*tert*-butylphenyl) sulfonamides shows high

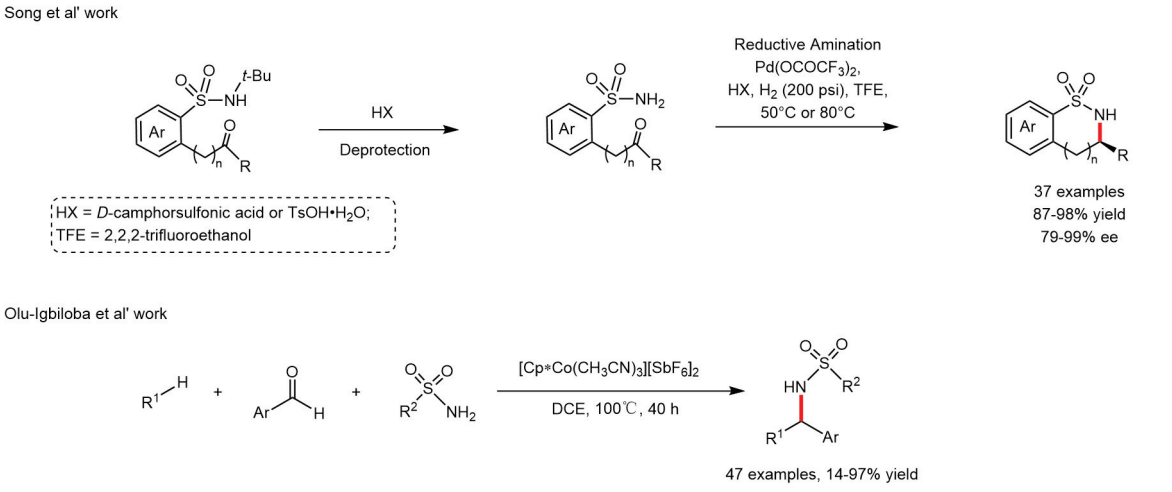

Fig. 27 Amination of ketones and aromatic aldehydes.

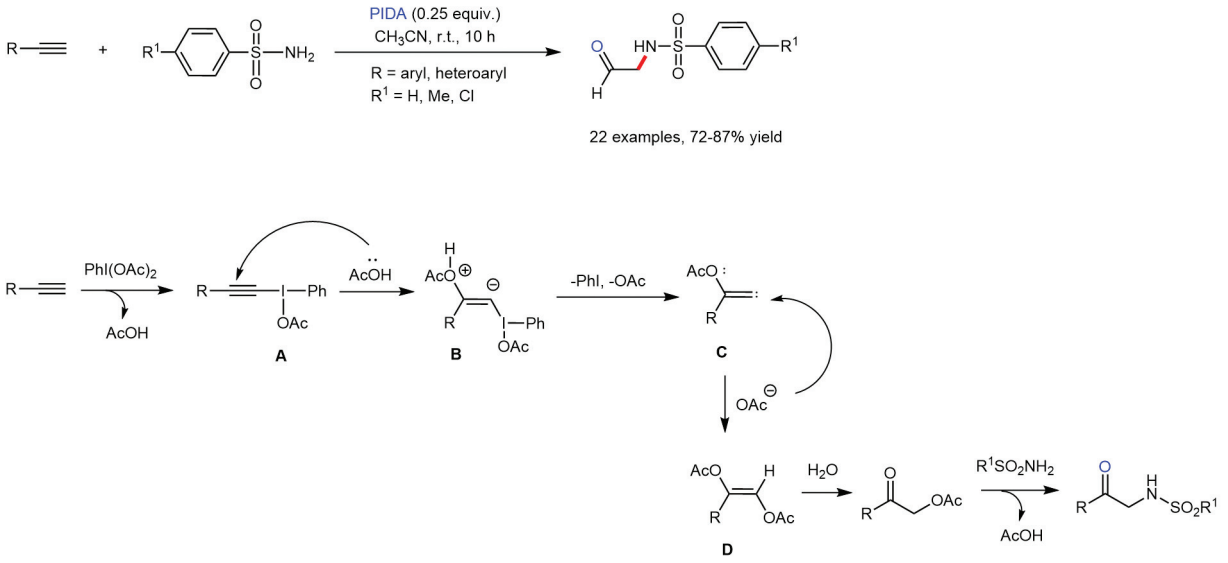

Fig. 28 Metal-free amidation reactions of terminal alkynes with benzenesulfonamide.

yield and enantioselectivity (95% ee), and it has been found that the spatial properties of the substrate can significantly affect the enantioselectivity. In addition, the absolute configuration of the main enantiomers was determined by single-crystal X-ray structure analysis, and the reason for enantioselectivity was explained.

In addition, Zhao's group proposed a commercial chiral amine catalyst for the *N*-alkylation of sulfonamides (►**Fig. 31**).[69] This method has advantages such as simple operation and direct recovery of the chiral catalyst used. This method efficiently converts benzenesulfonamides into axially chiral *N*-arylsulfonamides with excellent yield and

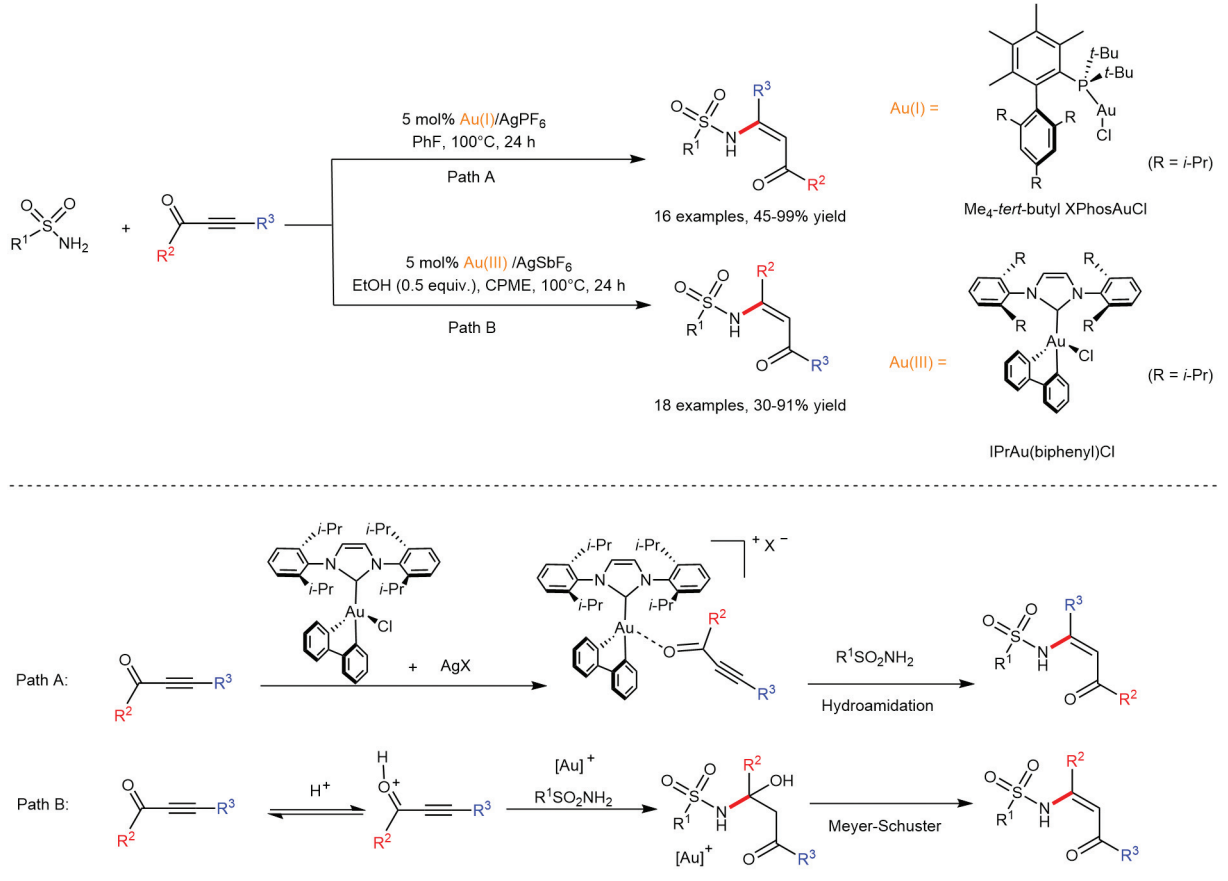

Fig. 29 Gold-catalyzed selective synthesis of *N*-sulfonyl enaminone isomers.

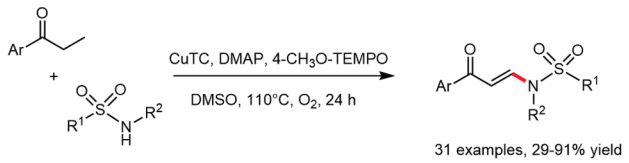

Fig. 30 Copper-catalyzed N–H olefination of sulfonamides.

enantioselectivity and can be easily amplified. It was found that the presence of halogen substituents on the benzene ring was the key to this catalytic system, and the practicability of the catalytic system was further proved by the derivatization reaction.

Then, the group turned to the asymmetric acylation of axially chiral sulfonamides, and reported a commercial isothiourea catalyst (*S*)-HBTM for the selective *N*-acetylation of

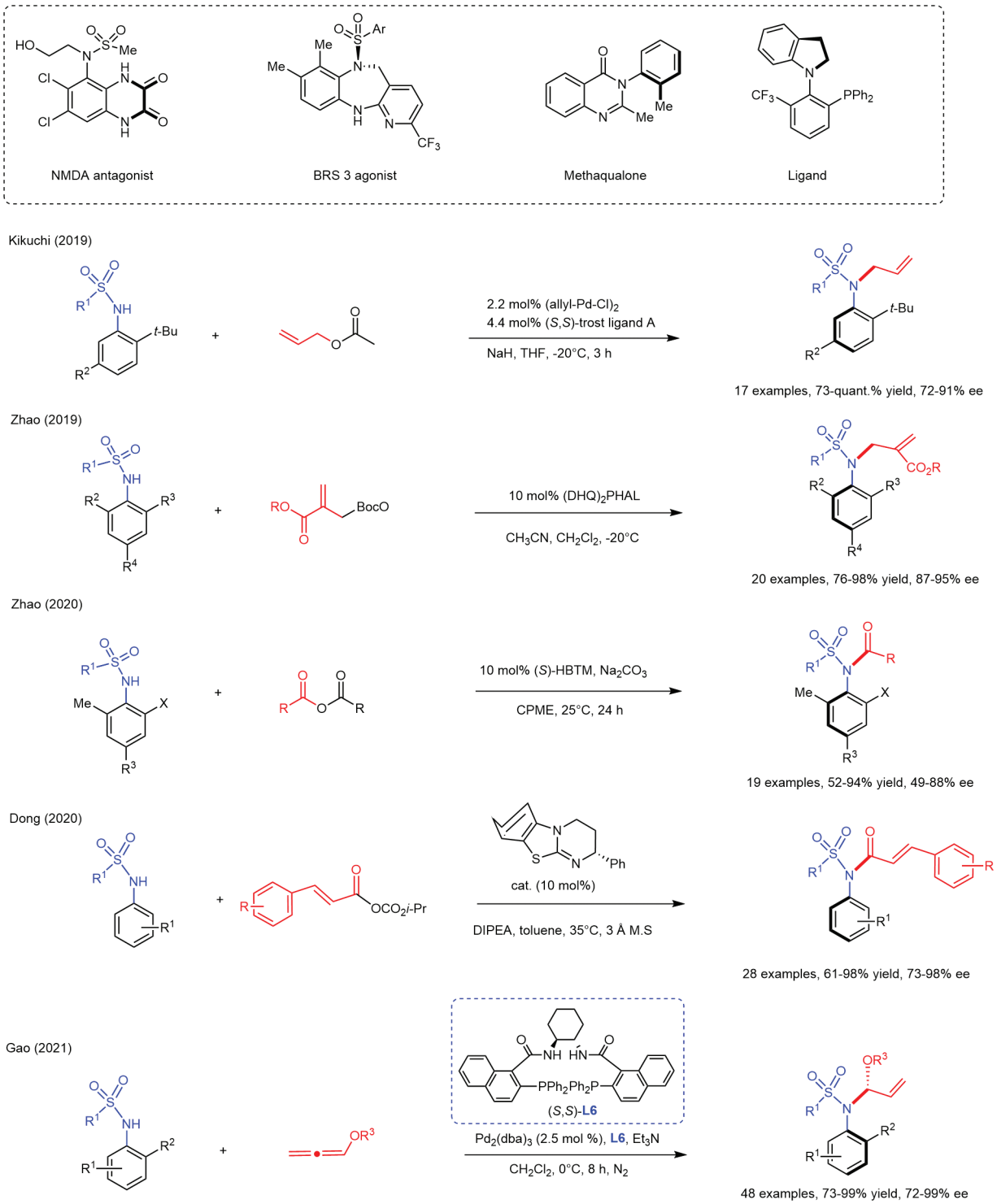

Fig. 31 Asymmetric synthesis of axially chiral benzenesulfonamide.

sulfonamides (►**Fig. 31**),[70] and obtained *N*-arylbenzenesulfonamides with high enantiomeric purity. The product was successfully used as a chiral iodine catalyst for asymmetric α-hydroxybenzenesulfonylation of phenylpropanone. Notably, an *ortho*-methyl substituent on the aryl group is essential for the reaction, as its absence reduces the enantioselectivity.

In the same year, Dong's group also developed a new method for the synthesis of axially chiral benzene sulfonamides by isothiourea-catalyzed *N*-acetylation of sulfonamides with α,β-unsaturated carbonic anhydride (►**Fig. 31**).[71] This method achieves high yields and enantioselectivity for axially chiral sulfonamide compounds, irrespective of the substituent configuration and electronic properties of the aryl group, and allows for gram-scale production. Until recently, methods for synthesizing axially chiral benzene sulfonamides have been rather limited in obtaining highly enantioselective products with various *ortho*-substitutions, such as *tert*-butyl, iodine, and bromine, on the benzene ring. Recently, Gao et al reported a palladium-catalyzed enantioselective hydroamination of olefins (►**Fig. 31**),[72] achieving effective conversion with various *ortho*- groups, including ester, ketone, nitro, chlorine, fluorine, methoxy, and *tert*-butyl, iodine, and bromine. This method provides an efficient synthetic route for axially chiral unnatural amino acids and eight-membered ring sulfonamides.

C–H Amination

Sulfonamidation of C–H bonds offers high atomic economy, directly functionalizing C–H substrates without pre-synthesis of sulfonamide groups, thereby improving overall conversion efficiency. Recently, the direct sulfonamide reaction of (hetero)aromatic C–H bonds with sulfonyl azides become an effective method for synthesizing *N*-(heteroaryl)aryl sulfonamides, with nitrogen as the only by-product.[73] Given that the C–H amination strategy typically selectively targets the desired C–H bond under an efficient catalyst system, this section will discuss three aspects: metal catalysis, enzyme catalysis, and metal-free catalysis.

Metal-Catalyzed C–H Sulfonamidation

Metal-catalyzed direct C–H sulfonylation allows for the introduction of sulfonamides at the ideal position on the substrate. Late transition metal catalysts, in particular, exhibit high reactivity and excellent selectivity in amination reactions.

Iridium-Catalyzed C–H Sulfonamidation

In metal catalysis applications, iridium is widely used for synthesizing sulfonamides through C–H sulfonamide and sulfonyl azide denitrogenation coupling. Kim et al utilized a catalytic system with an $IrCp^*(OAc)_2$ catalyst combined with $AgNTf_2$ to selectively amidate N-protected indole derivatives with various sulfonyl azides, yielding the expected sulfonyl amidation products in moderate to good yields (►**Fig. 32**).[74] Electron-donating groups on the indole ring were found to enhance the efficiency of the C–N bond formation reaction.

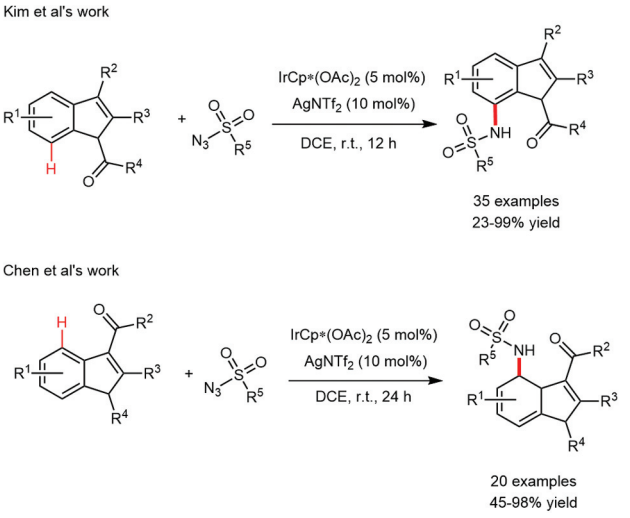

Fig. 32 Iridium-catalyzed C–H amidation of indoles with organic azides.

Inspired by this work, Chen et al[75] demonstrated that sulfonyl azides selectively amidate indoles with carbonyl directing groups (such as aldehydes, ketones, esters, and amides) at the C3 position in DCE (►**Fig. 32**). Notably, indoles with or without N protection exhibit good functional group tolerance and can be easily scaled up. Additionally, Lanke and Prabhu[76] described the synthesis of C4-sulfonamidoindoles from corresponding indole-3-carbaldehydes and sulfonyl azides.

In this context, several research teams have developed *ortho*-C–H sulfamidation reactions for aromatic hydrocarbons with various directing groups (such as amide,[77] sulfonamide,[78] sulfonylimide,[79] 1,2-diaminobenzenes,[80] triazole *N*-oxide,[81] *N*-sulfonyl ketimines,[82] quinazolinone,[83] and tetrazine[84]) using the standard $[IrCp^*Cl_2]_2$ as a catalyst (►**Fig. 33**).

Xu et al demonstrated that 1-(sulfonyl)-2-aryl-1*H*-benzimidazoles could be synthesized through C–H activation, sulfonyl amidation, and cyclization of phenylbenzylimidazole derivatives with sulfonyl azides in the presence of $[IrCp^*Cl_2]_2/AgNTF_2$/phenylacetic acid (►**Fig. 34**).[85] Additionally, Das and Samanta recently achieved a regioselective synthesis of C3 sulfonamide isoquinolones from 2-pyridyl-protected isoquinolones and sulfonyl azides in moderate to excellent yields using catalytic amounts of $[IrCp^*Cl_2]_2$ and $AgSbF_4$, with NaOAc as an additive (►**Fig. 34**).[86]

Recent studies have shown that this catalytic strategy enables the efficient synthesis of fluorescent sulfonamide compounds, which hold significant promise as optical imaging agents. For instance, Choi and colleagues reported the direct C–H amidation polymerization of disulfonyl azides and dibenzamides (►**Fig. 35**, top).[87] This results in a fluorescent polysulfonamide compound due to the formation of a unique intramolecular hydrogen bond between the protons on the sulfonamide group and the adjacent carbonyl group along the polymer backbone. Moreover, Hwang and Choi also introduced a robust method for synthesizing various fluorescent sulfonamides via iridium-catalyzed direct C–H amidation of *p*-toluenesulfonyl azides under uniform conditions

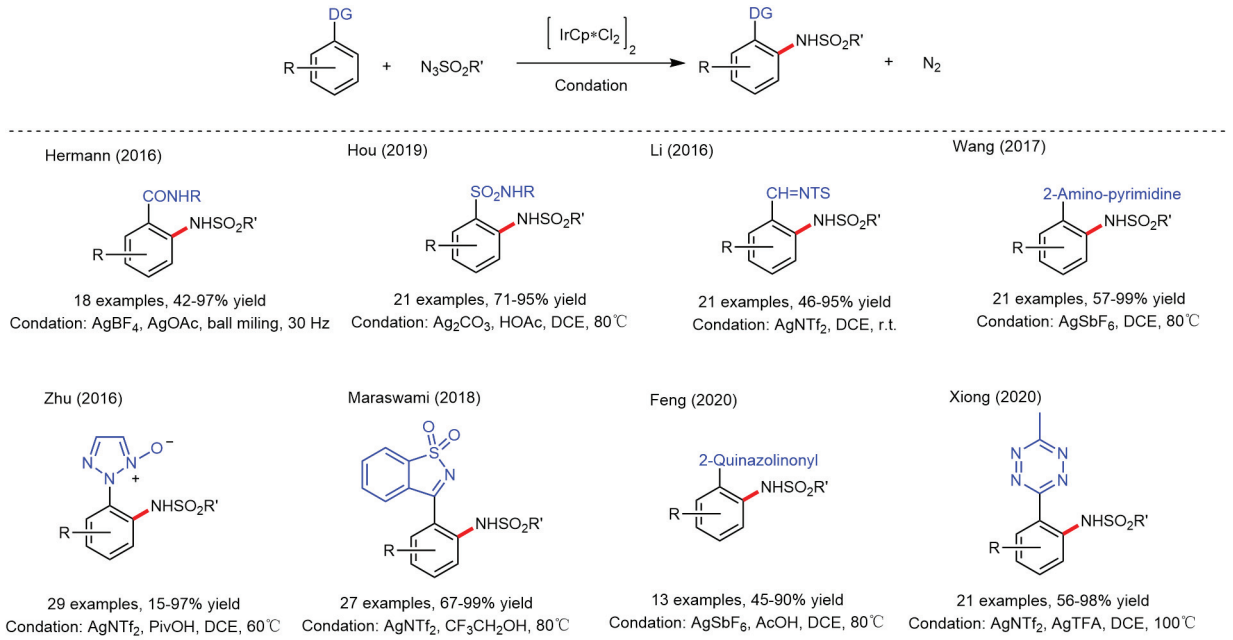

Fig. 33 Iridium-catalyzed selective C–H amidation.

(►**Fig. 35**, bottom).[88] This method achieves excellent luminescence efficiency across the visible spectrum with yields up to 99%. Additionally, the synthesis of multicolor fluorescent sulfonamides can be fine-tuned by modifying the electronic properties of the substituents.

Although sulfonyl azides are highly reactive, their post-processing and storage are cumbersome and unfavorable. In contrast, sulfonamides are more stable. The hydroamination of olefins can yield anti-Markovnikov addition products.[89] Based on the proton-coupled electron transfer (PCET) of the N–H bond of sulfonamides, Knowles and colleagues reported a method for the co-catalyzed intermolecular anti-Markovnikov hydroamination of unactivated olefins using primary and secondary sulfonamides, facilitated by an iridium(II) photocatalyst, dialkyl phosphate, and thiol hydrogen atom donors under room temperature illumination (►**Fig. 36**).[90] Building on these results, the research group also achieved enantioselective hydroamination of various substituted olefins with complex sulfonamide substrates, producing pyrrolidine products with high enantioselectivity (►**Fig. 36**).[91] Recently, Knowles and colleagues have developed an innovative light-driven method for anti-Markovnikov hydroamination of alkenes using primary sulfonamides. This method employs a ternary catalytic system consisting of an iridium (III) chromophore, a fluorinated alkoxide base, and a thiol hydrogen atom donor (►**Fig. 36**).[92] The reaction operates via a PCET mechanism, where the alkoxide base aids in activating strong N–H bonds to generate N-centered radicals. These radicals facilitate C–N bond formation with various alkenes. This protocol demonstrates a broad substrate scope and functional group tolerance, underscoring excited-state PCET as a versatile platform for catalytic radical generation. In addition, Sihag and Jeganmohan proposed a possible reaction mechanism involving π-allyl intermediates and thus achieved Ir(III)-catalyzed direct allyl C–H amidation of unactivated substituted ene with substituted sulfonamides (►**Fig. 36**).[93]

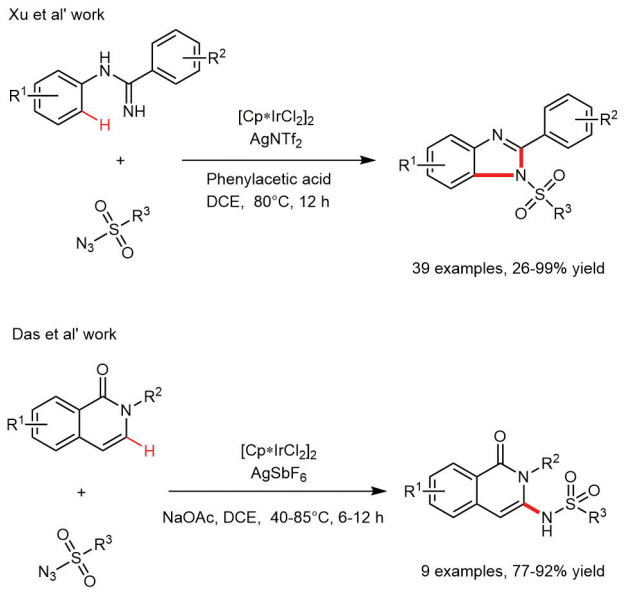

Fig. 34 Iridium-catalyzed selective C–H amidation of imidamides and isoquinolones.

Other Mental-Catalyzed C–H Sulfonamidation

Other late-transition metals have also made great progress in the study of C–H amidation reactions. Recently, Shi's team discovered that nitrazine [Ar(R)C=N–N=C(R)Ar] can serve as an ideal directing group for C–H amidation via C–H activation, leading to the first development of a mild and efficient rhodium(III)-catalyzed *ortho*-amidation of sulfonamides with nitrazines (►**Fig. 37**).[94] Azine can be obtained from the corresponding acetophenone and hydrazine in the laboratory, and it is easy to remove from the reaction. The

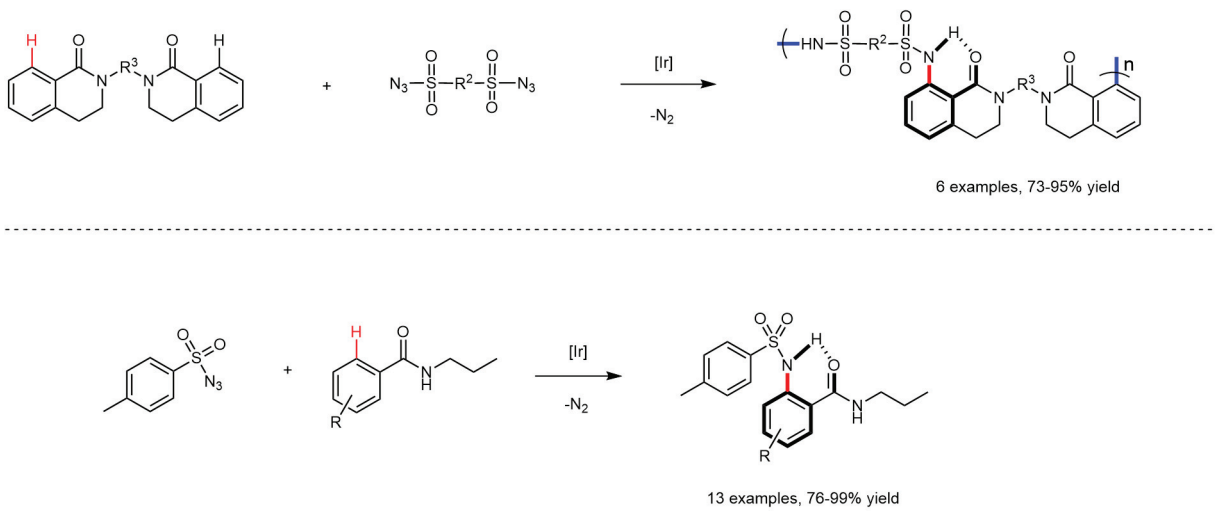

Fig. 35 Iridium-catalyzed C–H amidation for synthesizing fluorescent sulfonamides.

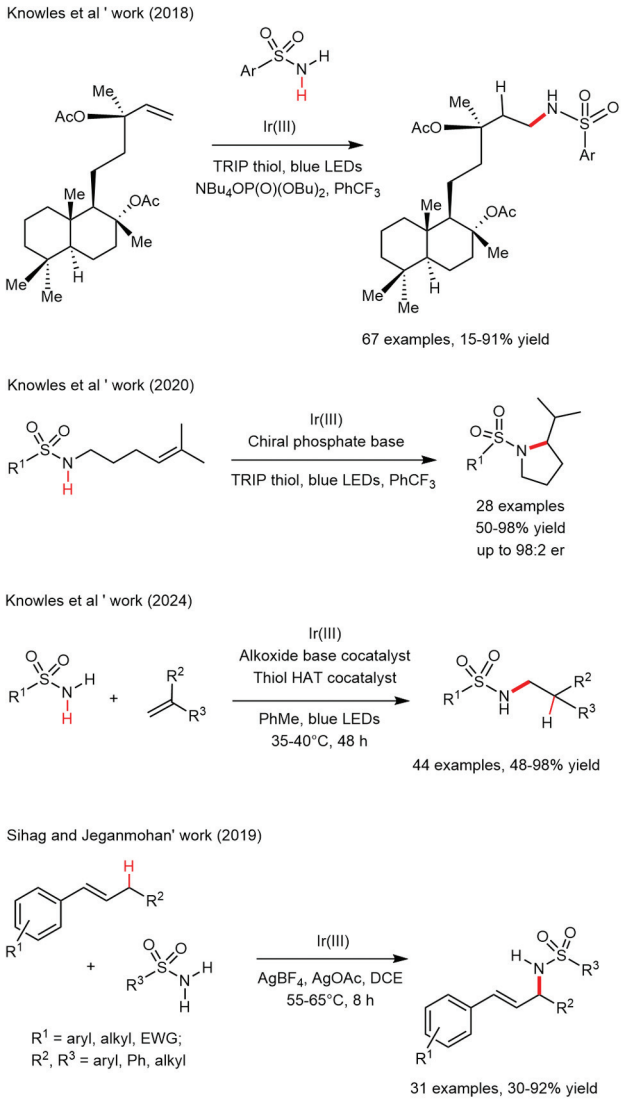

Fig. 36 Iridium-catalyzed C–H amidation of alkenes with sulfonamides.

method is highly regioselective, and has a broad substrate range and good functional group tolerance, providing a simple method for the synthesis of sulfonamide derivatives.

Moreover, Kumar et al reported a simple and effective copper-mediated cross-dehydrogenative coupling reaction of indoles with sulfonamides (►**Fig. 38**).[95] The reaction demonstrated good functional group tolerance, accommodating a range of substitutions on the sulfonamide scaffold. Both electron-donating and electron-withdrawing substituents were compatible, resulting in the desired benzenesulfonamide products in moderate to good yields. Notably, the substitution pattern (*ortho*-, *meta*-, and *para*-) had minimal effect on the yield, consistently producing similar results. Additionally, halogenated sulfonamides were also successfully incorporated. This methodology was effectively utilized for the synthesis of the sulfonamide derivative antiproliferative agent, ER-67836. Recently, Hajra et al introduced a novel protocol for copper(II)-mediated, picolinamido-directed C8–H sulfonamidation of 1-naphthylamine derivatives (►**Fig. 38**),[96] celebrated for its simplicity, broad substrate range, and excellent yields with precise site selectivity. Mechanistic studies highlight the role of organometallic chelation. These advancements pave the way for efficient synthesis of *N*-arylated and alkylated sulfonamide derivatives.

Cyclosulfonamide compounds are often introduced into target molecules as stable lactam compounds in medicinal chemistry. For example, Zhong et al reported a method for

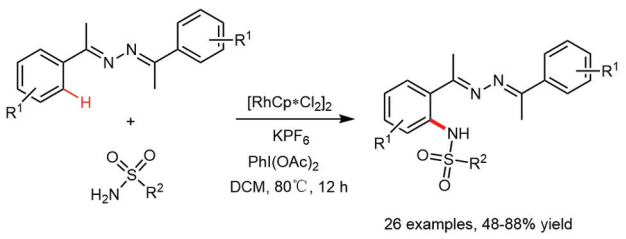

Fig. 37 Rhodium-catalyzed C–H amidation of azine with sulfonamides.

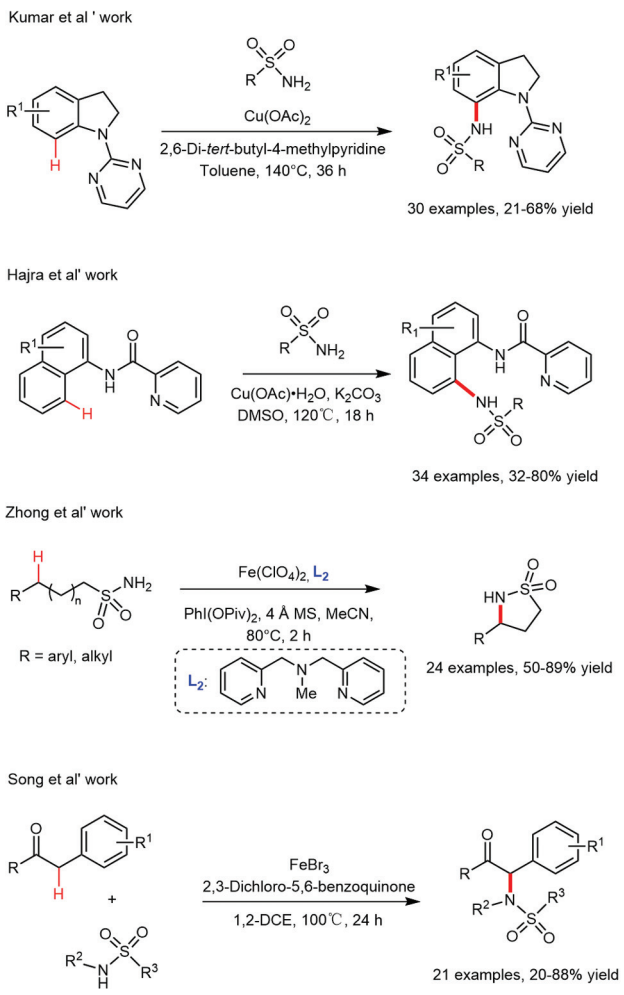

Fig. 38 Cu(II)-mediated and iron-catalyzed C–H amination.

direct synthesis of cyclosulfonamides by intramolecular C(sp^3)–H amidation reaction using iron complexes formed by easily available $Fe(ClO_4)_2$ and aminopyridine ligands as raw materials (►**Fig. 38**).[97] This method can achieve gram-scale preparation and product derivatization reaction, so it has good practicability. Recently, Song et al have developed an iron-catalyzed α-amination of ketones using sulfonamides through an oxidative coupling process, effectively eliminating the necessity for pre-functionalization (►**Fig. 38**).[98] The method successfully employs both primary and secondary sulfonamides as efficient partners. This innovative approach enables the direct amination of benzyl ketones with a variety of sulfonamide substituents under oxidative conditions. Current studies are focused on elucidating the underlying reaction mechanism.

Qian et al provided a method for the direct synthesis of bicyclic sulfonamide compounds by ruthenium-catalyzed intermolecular coupling reaction of alkynes with alkenyl sulfonamides (►**Fig. 39**).[99] In this scheme, a ruthenium(II)-catalyzed tandem reaction involving cyclization and amination enables the synthesis of [3.3.0] and [4.3.0] bicyclic sulfonamides with high enantioselectivity.

In addition, Zhang's group developed a Co(II)-based metal system as an effective catalyst for the enantioselective 1,5-

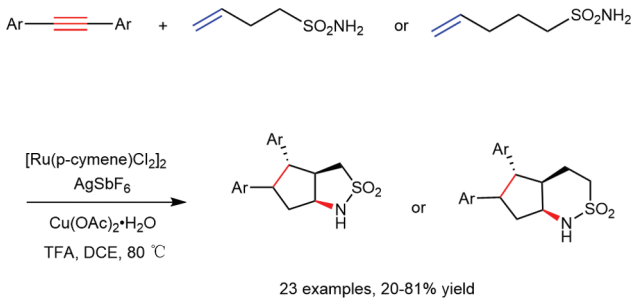

Fig. 39 Ruthenium(II)-catalyzed C–H amidation of alkenyl sulfonamides with alkynes.

C–H amination of sulfonyl azides to synthesize chiral five-membered cyclic sulfonamides (►**Fig. 40**).[100] The catalytic system achieves asymmetric C–H amination through free-radical reactions under neutral and nonoxidative conditions. It is effective not only for arylsulfonyl azides but also for the more challenging alkylsulfonyl azides, yielding chiral five-membered ring sulfonamide compounds with high yields and excellent enantioselectivity.

Enzyme-Catalyzed C–H Sulfonamidation

While developing catalytic C–H amination reactions, progress has also been made in enzyme-catalyzed C–H amination. An enzymatic strategy enables intermolecular benzyl C–H amination with *p*-toluenesulfonyl azides.[101] Additionally, genetically engineered iron-containing enzymes have shown good catalytic effects in the C–H sulfonamide reaction of azides.[102] Hartwig's team developed an asymmetric intramolecular C–H amination reaction of sulfonyl azides, using a CYP119 variant with an iridium engineering P450 enzyme, achieving chiral benzene sulfonamides with good chemical selectivity (►**Fig. 41**).[103]

Metal-Free C–H Sulfonamidation

For metal-free C–H amination of sulfonamides, Michael's group reported a widely used selenium-catalyzed allyl C–H amination reaction (►**Fig. 42**).[104] This method offers unique regioselectivity, introduction of new C–N bonds at the allyl position of olefins, from monosubstituted to tetrasubstituted, with sulfonamides, successfully applied to synthesize terpenoids with high yields and regioselectivity.

The excited 1,5-hydrogen atom transfer (HAT) process based on acyl radicals can selectively replace C(sp^3)–H with C(sp^3)–N bonds in medicinal chemistry. Muñiz's group developed a nonpolluting iodine redox catalysis combined with light for intramolecular radical C–H amination reaction (►**Fig. 43**),[105–107] achieving highly regioselective amination between sulfonamides and aliphatic molecules.

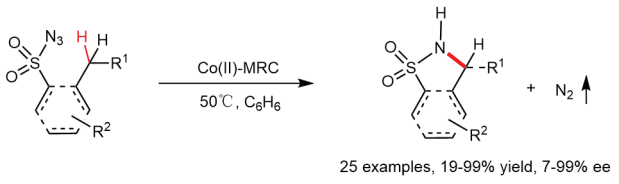

Fig. 40 Co(II)-catalyzed C–H amination.

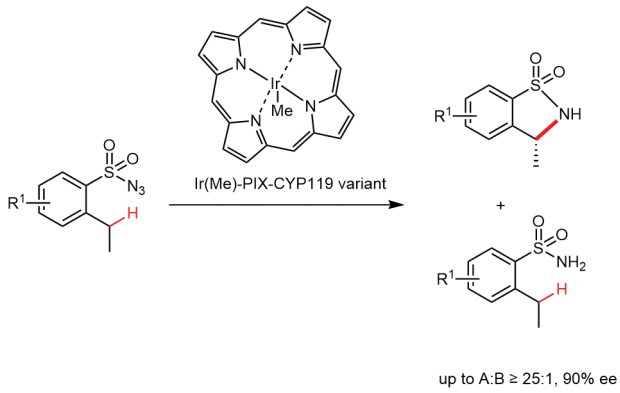

Fig. 41 Ir(Me)-PIX-CYP119-catalyzed intramolecular C–H amination.

Additionally, Wu et al used photochemical methods to induce sulfonamides to form nitrogen radicals via halogen-bonded charge-transfer complexes, thereby stimulating the HAT process for regioselective C–H amination of alkanes (►**Fig. 44**).[108] This approach enabled the synthesis of pyrrolidine compounds through two consecutive C (sp^3)–H amination steps, offering a novel way for halogen-enhanced charge transfer complexes to participate in chemical reactions. Yu et al introduced an effective metal-free method for synthesizing *N*-(2-quinolinyl) sulfonamides (►**Fig. 45**).[109] The intermolecular amidation of quinoline *N*-oxides with sulfonamides was accomplished via a 1,3-dipolar [3 + 3]-cycloaddition reaction in the presence of $PhI(OAc)_2$ and PPh_3, yielding the desired *N*-(2-quinolinyl) sulfonamides in high yields. This method also addresses the challenge of poor reactivity of sulfonamide compounds as nucleophiles.

Other Methods

Luo et al reported a novel and practical method for the synthesis of sulfonamides from sulfamoyl chloride (►**Fig. 46**).[110] First, the *N,N*-disubstituted sulfamoyl chlorides were catalyzed by photoredox to generate sulfonyl radicals, which then were attacked by 1-phenyl-1-trimethylsiloxane to generate enol silyl ether radical intermediates. Finally, β-ketosulfonamides were obtained by oxidation and deprotonation. This method can be conducted under mild and economical conditions, featuring a broad substrate range and good functional group compatibility. At the same time, this method has been successfully applied in the synthesis of antiepileptic drug zonisamide. At present, its detailed mechanism is being further studied. Recently, Sookezian and Molander presented a groundbreaking multicomponent reaction for the 1,2-difunctionalization of olefins, incorporating both a sulfonamide

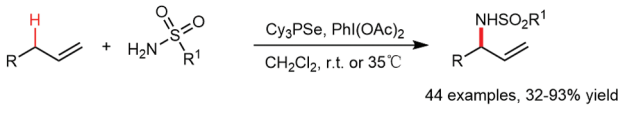

Fig. 42 Se-catalyzed allylic C–H amination of terpenoids.

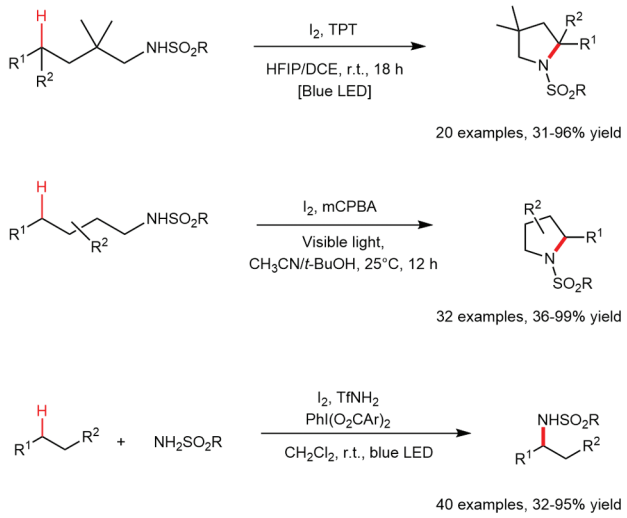

Fig. 43 Iodine-catalyzed C–H amination.

moiety and an additional functional group. By utilizing radical/polar crossover, the method leverages commercially available sulfamoyl chlorides and organotrifluoroborates as coupling partners (►**Fig. 46**).[111] The process initiates with the generation of sulfur-centered radicals, which react with alkenes to produce sulfamoylated intermediates. These intermediates undergo oxidation to form benzylic carbocations that are then trapped by various nucleophiles, including organotrifluoroborates and heterocycles. This versatile approach effectively accommodates a wide range of functional groups and represents the first direct use of chlorosulfonamide species in a three-component reaction.

Nguyen and Retailleau described a catalyst-free method for the synthesis of sulfonamides from 2-nitrochalcone and elemental sulfur in the presence of 3-methylpyridine or *N*-methylmorpholine (►**Fig. 47**).[112] Under heating conditions, two oxygen atoms from the 2-nitro group migrate to the sulfur atom, facilitating the formation of S–N, C–S, and S–O bonds between the nitrogen atom, α-carbon of chalcone, and elemental sulfur. Since the structure of nitrochalcone is easy to construct and the reaction is easy to operate, and sulfur as a sulfur source shows a strong atomic economy, it provides a more effective synthesis method for sulfonamide compounds.

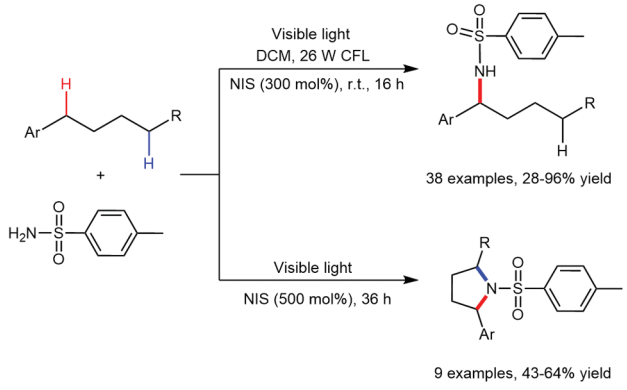

Fig. 44 Halogen-bond-induced consecutive C(sp^3)–H aminations.

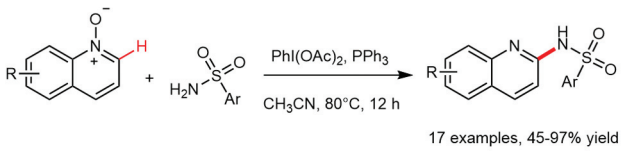

Fig. 45 Amidation of quinoline N-oxide with benzenesulfonamide derivatives under metal-free conditions.

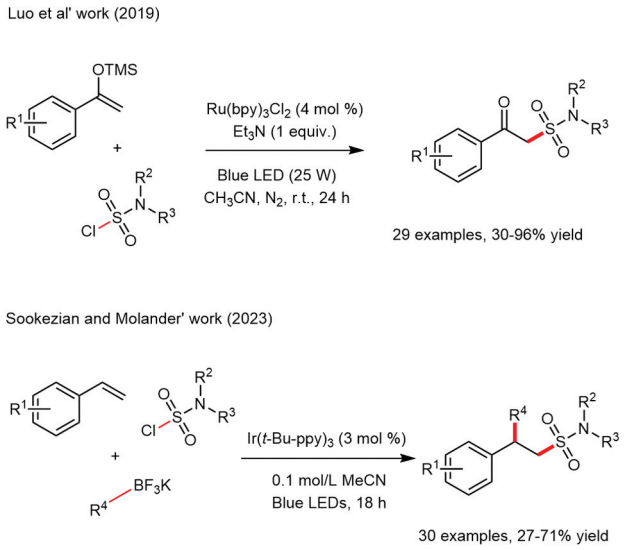

Fig. 46 Sulfonamidation of enol silyl ether with chlorosulfonamide.

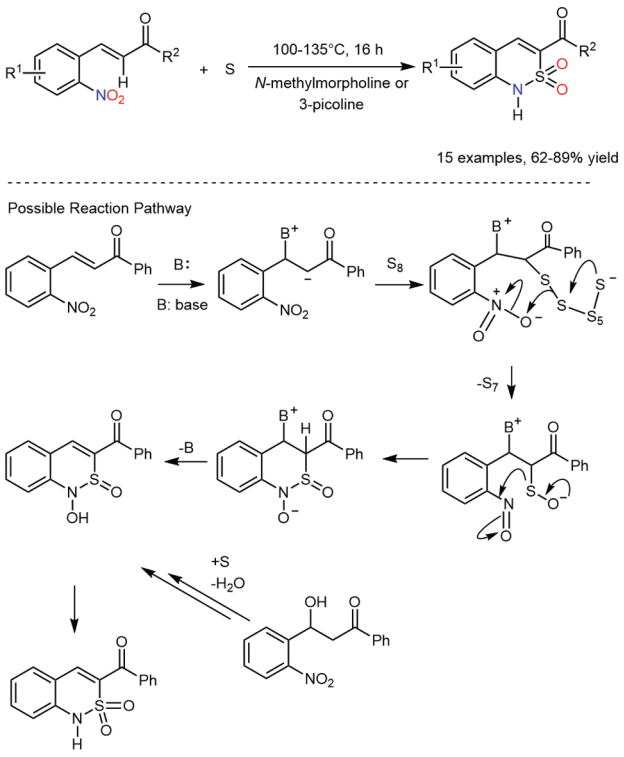

Fig. 47 Synthesis of sulfonamides from 2-nitrochalcones with sulfur.

Willis' group reported a method for direct synthesis of primary sulfonamides from organometallic reagents and a new sulfonamide reagent *t*-BuONSO (►**Fig. 48**, top).[113] It is worth noting that *t*-BuONSO can be prepared on a 10-gram scale using commercially available *O*-*tert*-butylhydroxylamine hydrochloride, thionyl chloride, and triethylamine. Reactions with various (hetero)aryl or alkyl organometallic nucleophiles (such as Grignard reagents or organic lithium reagents) can obtain primary sulfonamide compounds in good to excellent yields and are well applied to the synthesis of the drug celecoxib. The authors explain that initially, the Grignard reagent reacts with *t*-BuONSO to form sulfinamide intermediate **I**, which is then converted into sulfinimide ester anion **II** through a sulfinyl nitro intermediate or N→S *o*-migration, accompanied by intramolecular proton transfer to the nitrogen atom. After the elimination of isobutene, the sulfonamide anion **III** was obtained, and the final sulfonamide product was obtained by the quenching process. Recently, Willis' group has developed a scalable and versatile methodology for synthesizing sulfonamides from a wide array of alkyl carboxylic acids (►**Fig. 48**, bottom).[114] By employing acridine photocatalysts in conjunction with 400 nm light, the process efficiently generates alkyl radicals. These radicals subsequently react with the sulfinylamine reagent *t*-BuONSO to form *N*-alkoxy sulfinamide intermediates. Through treatment with sodium hydroxide, these intermediates can be selectively transformed into sulfonamides. This method is robust, accommodating a diverse range of functional groups, and applies to complex biologically active compounds.

Summary

Sulfonamide drugs are popular in the field of drug research and development. Despite significant progress, urgent issues remain in meeting sustainable development goals in chemical production: (1) reducing the reaction times, lowering the reaction temperatures, avoiding the use of toxic solvents, and minimizing the catalyst loading. These methods offer significant potential for further improvement, such as the use of green, recyclable solvents and catalysts. (2) Improving the reaction safety and chemical selectivity and reducing waste generation by improving the reaction catalytic system is also one of the important development directions in the future, such as the use of green synthesis technologies like enzyme catalysis, photocatalysis, and electrocatalysis. (3) Exploring green production processes remains an important challenge, such as designing process routes that reduce or eliminate the use and production of hazardous substances. This article systematically reviews the ideas and methods for synthesis and structural modification of sulfonamide structural drugs and drug intermediates in the past 5 years. Four strategies for the synthesis of sulfonamide structural compounds are presented: S–N construction, C–N cross-coupling, N–H functionalization, and C–H sulfonamidation. In particular, efficient, practical, and green new synthetic schemes are summarized, and the related reaction conditions, mechanisms, and applications are discussed. Herein, we hope that this review can provide new ideas and reference value for

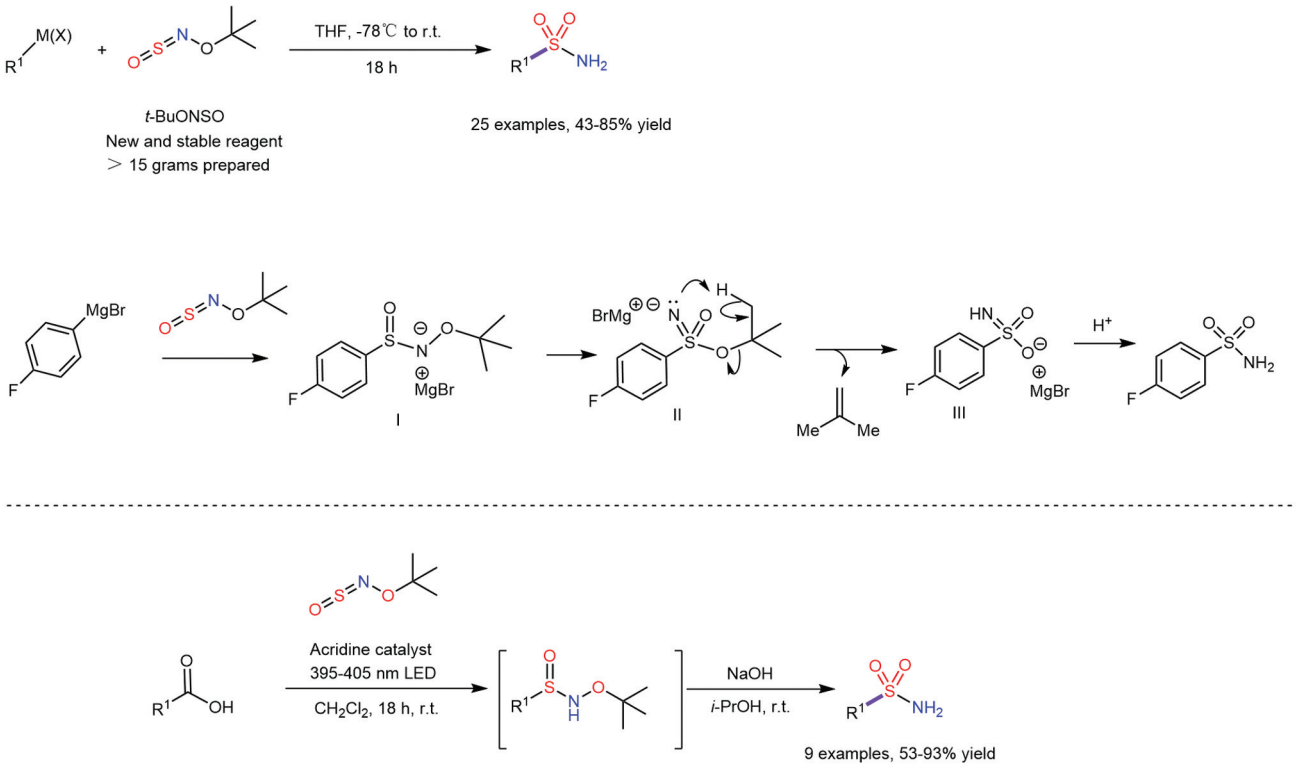

Fig. 48 Primary sulfonamide synthesis using the sulfinylamine reagent *t*-BuONSO.

green and efficient preparation technology of sulfonamides and their intermediates.

Conflict of Interest
None declared.

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