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Metal- and base-free tandem sulfonylation/cyclization of 1,5-dienes with aryldiazonium salts *via* the insertion of sulfur dioxide†

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A metal- and base-free 5-*endo*-trig sulfonylative cyclization between 1,5-dienes, aryldiazonium salts and SO₂ (from SOgen) is presented. This method could successfully produce sulfonylated pyrrolin-2-ones in one pot with excellent regioselectivity and good-to-excellent yields. This strategy features mild reaction conditions and broad substrate scope. Moreover, a scale-up reaction and three synthetic applications demonstrate the practicality of this method. Lastly, control experiments indicate that the 5-*endo*-trig sulfonylative cyclization may proceed in a radical pathway.

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Introduction

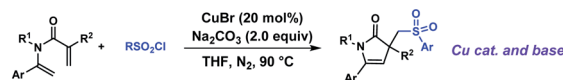
Pyrrolin-2-ones and their N-heterocyclic compound derivatives, widely exist in natural plants,¹ pharmaceuticals² and bioactive molecules.³ Similarly, sulfonyl groups are frequently found in pharmaceuticals⁴ and photoelectric materials⁵ due to their unique chemical properties. Numerous studies have indicated that the incorporation of sulfonyl groups into heterocycles could enhance their pharmacological activity.⁶ Therefore, great efforts have been devoted to explore efficient and straightforward methods to build sulfone-containing N-heterocyclic frameworks.

Radical cascade cyclization reactions represent a powerful strategy for the synthesis of functionalized cyclic structure, characterized by multiple C-C/C-X bond-forming in one step.⁷ The incorporation of sulfonyl group into heterocycles by radical cascade cyclization reactions has aroused extensive interest among scientists.⁸ In recent years, many sulfone-containing heterocyclic frameworks have been constructed by radical cascade cyclization reactions, such as sulfonylindoles,⁹ sulfonylindolines,¹⁰ sulfonylated pyrrolidines,¹¹ sulfonylated phenanthridines,¹² sulfonylated benzofurans,¹³ sulfonated oxazolines,¹⁴ sulfonylated spirocycles¹⁵ and others.¹⁶ In 2021, sulfonylated pyrrolinones were synthesized *via* sulfonylation/cyclization of 1,5-dienes with sulfonyl chlorides or sodium

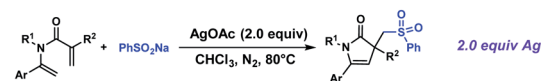
sulfonates by Wang and co-workers (Fig. 1a and b).¹⁷ However, due to the limited accessibility of sulfonyl chlorides and sodium sulfonates, these two methods suffered from a narrow range of substrates. Besides, transition metal (Cu and Ag), base and elevated temperature were essential in these transformations.

On the other hand, direct insertion of sulfur dioxide (SO₂) provides an alternative and efficient approach to introduce sulfonyl moiety into molecules.^{18,19} Recently, a cheap and bench-stable SO₂ surrogate (SOgen) has been developed by our group, which has been successfully applied in several sulfonylation reactions.²⁰ Inspired by Wang's work and our continuous

(a) Sulfonyl chlorides as sulfonylation reagents:



(b) Sodium sulfonates as sulfonylation reagents:



(c) SOgen as sulfonylation reagents (this work):

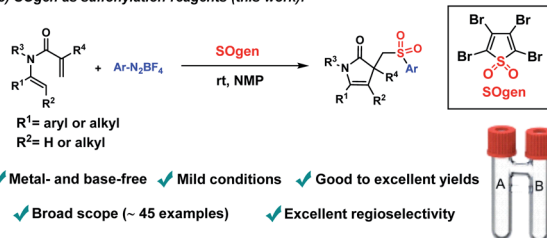


Fig. 1 Overview of tandem sulfonylative cyclization of 1,5-dienes: (a) sulfonyl chlorides as sulfonylation reagents; (b) sodium sulfonates as sulfonylation reagents; (c) SOgen as sulfonylation reagents (this work).

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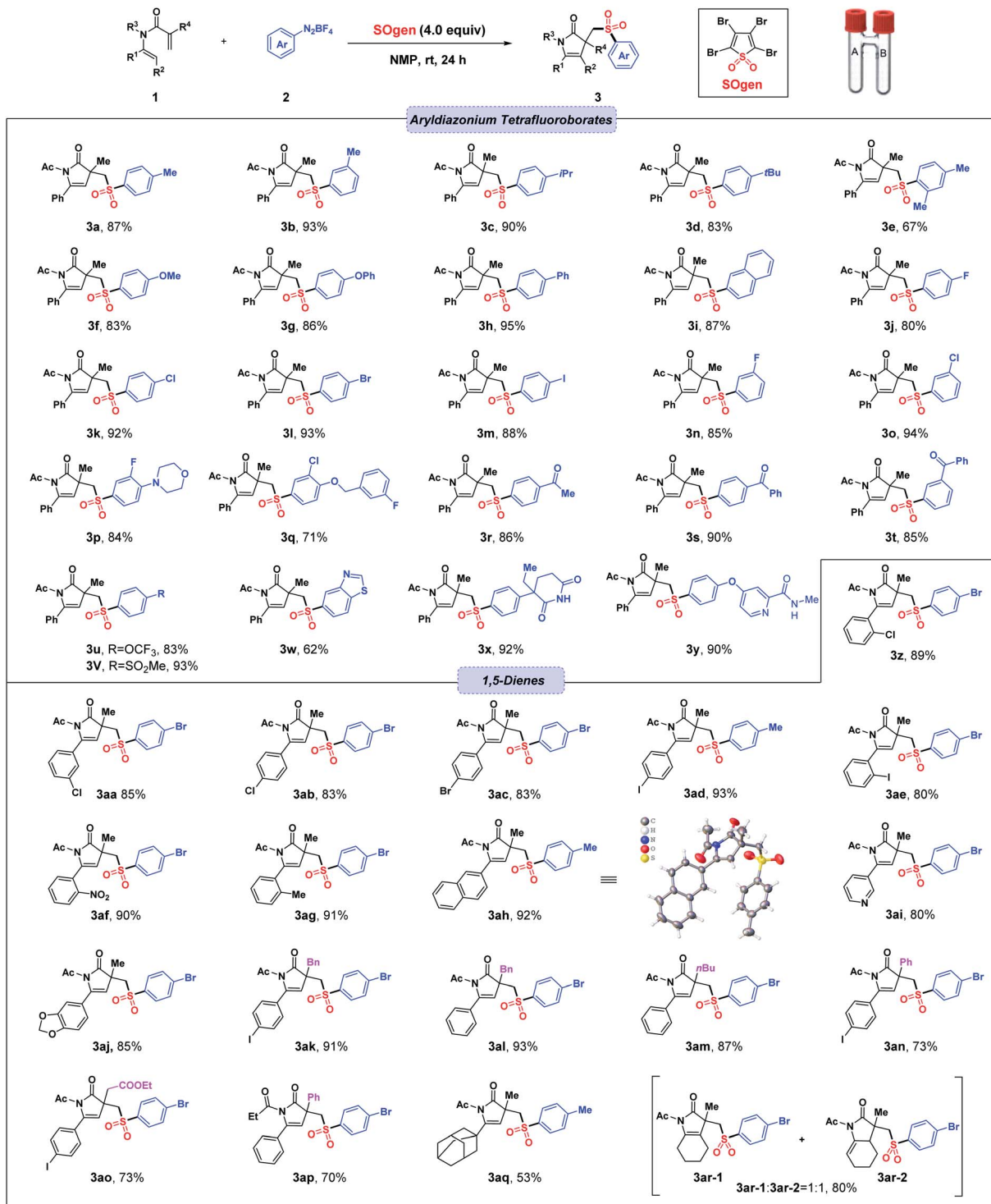
other sulfur dioxide surrogates were examined. The use of DABSO and inorganic SO_2 surrogates ($\text{Na}_2\text{S}_2\text{O}_5$ and $\text{K}_2\text{S}_2\text{O}_5$) could both lead to the formation of product **3a** but with lower yields (Table 1, entries 14–16). Unfortunately, rongalite reagent ($\text{HOCH}_2\text{SO}_2\text{Na}\cdot\text{H}_2\text{O}$) would hamper the reaction (Table 1, entry 17).

After determining the optimal reaction conditions, we began to explore the substrate scope of this reaction, and the results are summarized in Scheme 1. We first investigated the functional group compatibility of aryldiazonium tetrafluoroborates in the transformation. Alkyl substituted aryldiazonium tetrafluoroborates at the *meta*- or *para*-position of the phenyl ring proceeded well and afforded corresponding products **3b–3d** in good yields (83–93%). While a methyl substituent at the *ortho*-position could lead to a lower yield (67%, **3e**), possibly due to the steric hindrance. In addition, substrates with methoxy or phenoxy group delivered desired products **3f** and **3g** in 83% and 86% yield, respectively. Substrates bearing a biphenyl or 2-naphthyl group showed good reactivity, producing expected products (**3h** and **3i**) in excellent yields. Notably, halogen groups were found to be well tolerated under the standard conditions (**3j–3q**). Moreover, substrates with electron-withdrawing groups such as MeCO–, PhCO–, CF₃O–, MeSO₂– were subject to the reaction conditions, and gave corresponding products (**3r–3v**) in good yields. In addition, heterocyclic diazonium salt was found to be compatible in the transformation (**3w**). Finally, aryldiazonium tetrafluoroborates with complicated substituent structures could also work smoothly to afford **3x** and **3y** in 92% and 90% yield, respectively.

Next, the substrate scope of 1,5-dienes was investigated. The results showed that halogen groups (–Cl, –Br and –I) on 1,5-dienes had little effect on the reaction, and the corresponding products **3z–3ae** were formed in 80–93% yields. Notably, 1,5-diene with a strongly electron-withdrawing group (–NO₂) could deliver desired products **3af** in an excellent yield (90%). Meanwhile, the one with an electron-donating group (–Me) could also give products **3ag** in a similar yield (91%). Naphthalene ring was well tolerated, achieving **3ah** in 92% yield and the configuration of compound **3ah** was confirmed by X-ray crystallography. Pyridine moiety was also adapted to the reaction conditions and generated **3ai** in 80% yield. In addition, it was found that benzodioxole moiety (**3aj**) could be well tolerated under the standard conditions. When R⁴ group was replaced by other substituents, such as benzyl, phenyl, *n*-butyl and –CH₂COOEt, desired products (**3ak–3ap**) could still be made in good-to-excellent yields. When R¹ group was alkyl, the sulfonation reaction could still proceed, demonstrated by two successful examples (**3aq** and **3ar**). It was worth noting that compound **3ar** contained two isomers (**3ar-1** : **3ar-1** = 1 : 1).

Then we explored the influence of other solvents on this reaction, the target product (**3a**) was not obtained in most solvents, such as THF, MeCN, DCM, toluene and MeOH (Table 1, entries 2–6). When the solvent was DMA, DMF and DMSO, **3a** was formed in only poor yields (Table 1, entries 7–9). Next, the amount of SO₂ (from 2.5 equiv. to 4.0 equiv.) was investigated, and the results indicated that 4.0 equiv. was the best choice (Table 1, entries 10–12). Although this reaction could work under an air atmosphere, argon atmosphere proved to be more beneficial for the transformation (Table 1, entry 13). Finally,

^a Standard conditions: chamber A, SOgen (0.80 mmol), 1-methyl-4-vinylbenzene (0.81 mmol), tetradecane (1.0 mL), at 100 °C for 10 min; chamber B, **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.44 mmol, 2.2 equiv.), NMP (1.0 mL), at room temperature for 24 h under argon atmosphere.
^b Yields were determined by ¹H-NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. ^c Isolated yield in the parentheses. ^d The reaction was set up in a 4 mL vial.

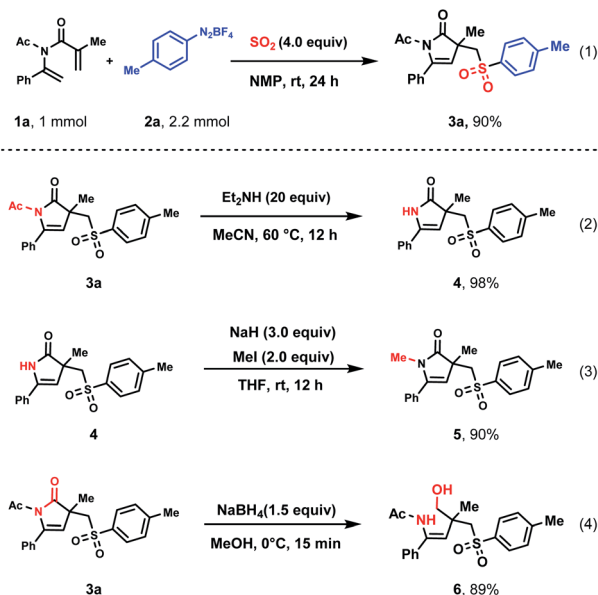


Scheme 1 Substrate scope^a. ^aReaction conditions: chamber A, SOgen (0.80 mmol), 1-methyl-4-vinylbenzene (0.81 mmol), tetradecane (1.0 mL), at 100 °C for 10 min; chamber B, **1** (0.2 mmol, 1.0 equiv.), **2** (0.44 mmol, 2.2 equiv.), NMP (1.0 mL), at rt for 24 h under argon atmosphere. All yields are isolated yields.

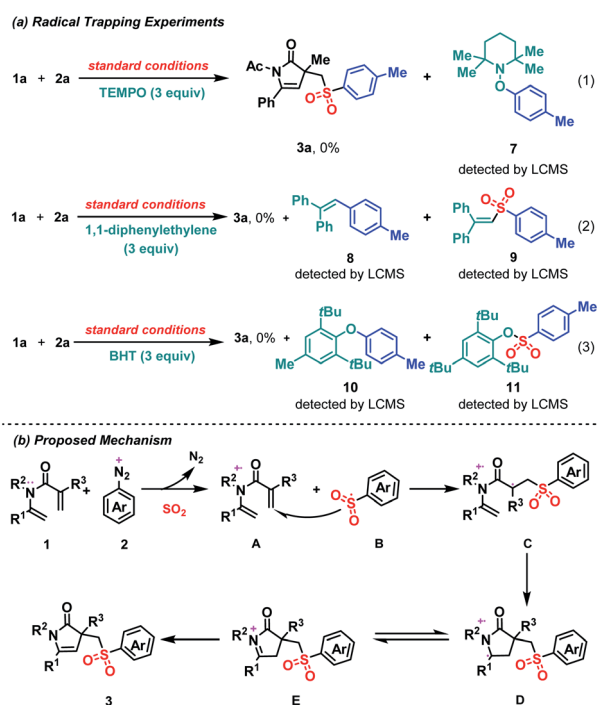
transferred to N-Me (**5**) in 90% yield in a mixture of sodium hydride and iodomethane (Scheme 2(3)). In addition, the amide moiety of **3a** could be reduced to hydroxy amine (**6**) *via* ring-opening by NaBH₄ in excellent yield (Scheme 2(4)).

In order to understand the mechanism of this reaction, three control experiments with radical scavengers were carried out. Firstly, in the presence of radical scavenger (TEMPO), the desired product (**3a**) was totally quenched and TEMPO adduct **7**





Scheme 2 Scale-up reaction and synthetic applications.



Scheme 3 (a) Control experiments and (b) proposed mechanism.

was identified by LC-MS (Scheme 3a(1)). Secondly, when 1,1-diphenylethylene or BHT was added, the reaction showed similar result and corresponding aryl radicals adduct (8 or 10) sulfonyl radicals adduct (9 or 11) were identified, respectively (Scheme 3(2) and (3)). These results indicated that this transformation might proceed through a radical pathway.

Base on the control experiments and literature,^{20c} a plausible reaction mechanism is proposed herein (Scheme 3b). One of lone-pair electrons on the N atom of 1,5-diene is transferred to

aryldiazonium tetrafluoroborate, which leads to the formation of nitrogen radical cation species (A) and aryl radical. Then aryl radical is trapped by sulfur dioxide and gives aryl sulfone radical (B). Sulfonyl radical B selectively adds to the double bond of 1,5-diene and produces alkyl radical species C. Subsequently, intramolecular 5-*endo*-trig cyclization produces intermediate D, which has an equilibrium with E. Finally, the desired product (3) is produced *via* tautomerization from E.

Conclusions

In conclusion, a metal- and base-free sulfonylative cyclization of 1,5-dienes with aryldiazonium salts *via* the insertion of SO₂ (from SOgen) has been developed. This method can work under mild conditions and provide the desired products in good yields with excellent regioselectivity. In addition, this approach greatly expands the substrates scope compared with previous reported work. Preliminary mechanism studies indicate that this 5-*endo*-trig sulfonylative cyclization may proceed in a radical pathway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- For selected examples, see: (a) N. Dev, A. K. Das, M. A. Hossain and S. M. M. Rahman, Chemical Compositions of Different Extracts of *Ocimum Basilicum* Leaves, *J. Sci. Res.*, 2011, **3**, 197–206; (b) S. Chu, S. Liu, W. Duan, Y. Cheng, X. Jiang, C. Zhu, K. Tang, R. Wang, L. Xu, X. Wang, X. Yu, K. Wu, Y. Wang, M. Wang, H. Huang and J. Zhang, The Anti-Dementia Drug Candidate, (–)-Clausenamide, Improves Memory Impairment Through Its Multi-target Effect, *Pharmacol. Ther.*, 2016, **162**, 179–187.
- For selected examples, see: (a) R. Kontnik and J. Clardy, Codinaeopsin, an Antimalarial Fungal Polyketide, *Org. Lett.*, 2008, **10**, 4149–4151; (b) S. Castellano, H. D. G. S. Fijj, S. S. Kinderman, M. Watanabe, P. deLeon, F. Tamanoi and O. Kwon, Small-Molecule Inhibitors of Protein Geranylgeranyltransferase Type I, *J. Am. Chem. Soc.*, 2007, **129**, 5843–5845.
- For selected examples, see: (a) S. S. Ariya, J. Baby, V. Santhanam and H. Waheeta, Computational Analysis of Compounds from *Ocimum Sanctum* for Anticancer Activity Against Oral Squamous Cell Carcinoma, *Asian J. Pharm.*



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- allylamides through the Insertion of Sulfur Dioxide, *Org. Chem. Front.*, 2022, **9**, 364–369.
- 15 W. Dong, L. Qi, J. Y. Song, J. M. Chen, J. X. Guo, S. Shen, L. J. Li, W. Li and L. J. Wang, Direct Synthesis of Sulfonylated Spiro[indole-3,3'-pyrrolidines] by Silver-Mediated Sulfonylation of Acrylamides Coupled with Indole Dearomatization, *Org. Lett.*, 2020, **22**, 1830–1835.
- 16 (a) Z. C. Chen, H. Zhang, S. F. Zhou and X. L. Cui, $K_2S_2O_8$ -Initiated Cascade Cyclization of 2-Alkynynitriles with Sodium Sulfinates: Access to Fused Cyclopenta[gh]phenanthridines, *Chin. J. Org. Chem.*, 2020, **40**, 3866–3872; (b) Z. Cao, Q. Zhu, Y. W. Lin and W. M. He, The Concept of Dual Roles Design in Clean Organic Preparation, *Chin. Chem. Lett.*, 2019, **30**, 2132–2144; (c) K. D. Zhou, J. Zhang, G. Y. S. Qiu and J. Wu, Copper(II)-Catalyzed Reaction of 2,3-Allenic Acids, Sulfur Dioxide, and Aryldiazonium Tetrafluoroborates: Route to 4-Sulfonylated Furan-2(5H)-ones, *Org. Lett.*, 2019, **21**, 275–278; (d) F. Herrera, P. Esteban, A. Luna and P. Almendros, Metal-Catalyzed Reactivity Reversal in the Sulfonylation Reaction of α -Allenols: Controlled Synthesis of 4-(Arylsulfonyl)-2,5-Dihydrofurans, *Adv. Synth. Catal.*, 2021, **363**, 3952–3956.
- 17 (a) R. Ding, M. H. Mao, W. Z. Jia, J. M. Fu, L. Liu, Y. Y. Mao, Y. Guo and P. L. Wang, Synthesis of Sulfonylated Pyrrolines and Pyrrolinones via Ag-Mediated Radical Cyclization of Olefinic Enamides with Sodium Sulfinates, *Asian J. Org. Chem.*, 2021, **10**, 366–370; (b) R. Ding, Y. L. Liu, H. Hao, C. Y. Chen, L. Liu, N. S. Chen, Y. Guo and P. L. Wang, Regioselective, Copper(I)-Catalyzed, Tandem Sulfonylation-Cyclization of 1,5-Dienes with Sulfonyl Chlorides, *Org. Chem. Front.*, 2021, **8**, 3123–3127.
- 18 For selected reviews, see: (a) E. J. Emmett and M. C. Willis, The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry, *Asian J. Org. Chem.*, 2015, **4**, 602–611; (b) G. S. Qiu, K. D. Zhou, L. Gao and J. Wu, Insertion of Sulfur Dioxide Via a Radical Process: An Efficient Route to Sulfonyl Compounds, *Org. Chem. Front.*, 2018, **5**, 691–705; (c) K. Hofman, N. W. Liu and G. Manolikakes, Radicals and Sulfur Dioxide: A Versatile Combination for the Construction of Sulfonyl-Containing Molecules, *Chem.-Eur. J.*, 2018, **24**, 11852–11863; (d) D. Joseph, M. A. Idris, J. Chen and S. Lee, Recent Advances in the Catalytic Synthesis of Arylsulfonyl Compounds, *ACS Catal.*, 2021, **11**, 4169–4204.
- 19 For selected examples, see: (a) D. Q. Zheng, Y. Y. An, Z. H. Li and J. Wu, Metal-Free Aminosulfonylation of Aryldiazonium Tetrafluoroborates with $DABCO \cdot (SO_2)_2$ and Hydrazines, *Angew. Chem., Int. Ed.*, 2014, **53**, 2451–2454; (b) B. Nguyen, E. J. Emmett and M. C. Willis, Palladium-Catalyzed Aminosulfonylation of Aryl Halides, *J. Am. Chem. Soc.*, 2010, **132**, 16372–16373; (c) Y. Meng, M. Wang and X. Jiang, Multicomponent Reductive Cross-Coupling of an Inorganic Sulfur Dioxide Surrogate: Straightforward Construction of Diversely Functionalized Sulfones, *Angew. Chem., Int. Ed.*, 2020, **59**, 1346–1353; (d) W. Li, H. Li, P. Langer, M. Beller and X. F. Wu, Palladium-Catalyzed Aminosulfonylation of Aryl Iodides by using Na_2SO_3 as the SO_2 Source, *Eur. J. Org. Chem.*, 2014, 3101–3103; (e) H. B. Zhu, Y. J. Shen, D. H. Wen, Z. G. Le and T. Tu, Selective Synthesis of *ortho*-Substituted Diarylsulfones by Using NHC-Au Catalysts under Mild Conditions, *Org. Lett.*, 2019, **21**, 974–979; (f) Y. Wang, L. L. Deng, J. Zhou, X. C. Wang, H. B. Mei, J. L. Han and Y. Pan, Synthesis of Chiral Sulfonyl Lactones via Copper-Catalyzed Asymmetric Radical Reaction of $DABCO \cdot (SO_2)$, *Adv. Synth. Catal.*, 2018, **360**, 1060–1065; (g) A. Shavnya, K. D. Hesp, V. Mascitti and A. C. Smith, Palladium-Catalyzed Synthesis of (Hetero)Aryl Alkyl Sulfones from (Hetero)Aryl Boronic Acids, Unactivated Alkyl Halides, and Potassium Metabisulfite, *Angew. Chem., Int. Ed.*, 2015, **54**, 13571–13575; (h) N. von Wolff, J. Char, X. Frogneux and T. Cantat, Synthesis of Aromatic Sulfones from SO_2 and Organosilanes Under Metal-free Conditions, *Angew. Chem., Int. Ed.*, 2017, **56**, 5616–5619.
- 20 (a) X. W. Jia, S. Kramer, T. Skrydstrup and Z. Lian, Design and Applications of a SO_2 Surrogate in Palladium-Catalyzed Direct Aminosulfonylation between Aryl Iodides and Amines, *Angew. Chem., Int. Ed.*, 2021, **60**, 7353–7359; (b) Y. Li, L. Shen, M. Zhou, B. J. Xiong, X. M. Zhang and Z. Lian, Copper-Catalyzed Chloro-Arylsulfonylation of Styrene Derivatives via the Insertion of Sulfur Dioxide, *Org. Lett.*, 2021, **23**, 5880–5884; (c) L. Chen, M. Zhou, L. Shen, X. C. He, X. Li, X. M. Zhang and Z. Lian, Metal- and Base-Free $C(sp^2)$ -H Arylsulfonylation of Enamides for Synthesis of (*E*)- β -Amidovinyl Sulfones via the Insertion of Sulfur Dioxide, *Org. Lett.*, 2021, **23**, 4991–4996; (d) G. Chen, J. Xu, B. J. Xiong, H. Z. Song, X. M. Zhang, X. L. Ma and Z. Lian, Copper-Catalyzed Trifluoromethylthio-arylsulfonylation of Styrene Derivatives via the Insertion of Sulfur Dioxide, *Org. Lett.*, 2022, **24**(5), 1207–1212; (e) X. W. Jia, C. X. Huang, X. M. Zhang and Z. Lian, Metal-free Sulfonylative Annulations of Alkyl Diiodides with Sulfur Dioxide: Synthesis of Cyclic Aliphatic Sulfones, *Org. Chem. Front.*, 2021, **8**, 5310–5315.

