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Advances in photochemical and electrochemical incorporation of sulfur dioxide for the synthesis of value-added compounds

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Organic photochemistry and electrochemistry currently receive tremendous attention in organic synthesis as both techniques enable the reagent-less activation of organic molecules without using expensive and hazardous redox reagents. The incorporation of SO_2 into organic molecules is a relatively modern research topic, which likewise gains immense popularity since the discovery of the SO_2 surrogate DABSO. Sulfur-containing organic molecules are omnipresent in pharmaceuticals and agrochemicals. This review covers the recent progress in electrochemical and photochemical methodologies for the incorporation and uses of SO_2 in the synthesis of value-added compounds. Additionally, different work techniques are demonstrated for the synthetic application of SO_2.

Introduction

Reagent-less activation of organic molecules became increasingly popular in the past few decades. Photochemistry and the 21st century technique organic electrochemistry in particular have attracted growing interest,[1,2] which is attributed to numerous advantages in comparison to conventional synthetic approaches with expensive and hazardous redox reagents.[3] Inexpensive electricity or light,[2] derived from renewable energy sources,[4] is capable of activating organic molecules and beyond that achieving even novel and highly innovative reactivities.[5] From this follows waste reduction,[6] which is crucial during times of climate change,[1] and a decrease of synthetic steps for the target molecule.[7] Additionally, photochemistry and electrochemistry

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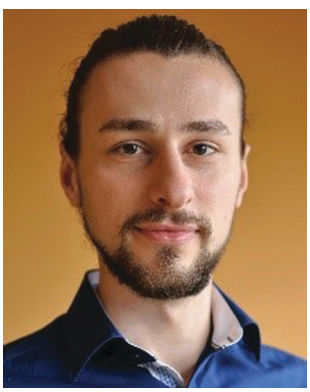
Stephan P. Blum

Stephan P. Blum received his BSc and MSc degrees from the Ludwig-Maximilians University of Munich. During his master studies, he participated in a student exchange at the City University of Hong Kong and completed an industrial internship at Boehringer Ingelheim in medicinal chemistry. His master thesis project was in organometallic chemistry supervised by Josep Cornellà at Max Planck Institute for Coal Research. In 2019, he started his PhD project on the electrochemical upcycling of sulfur dioxide to value-added products under the supervision of Prof. Dr Siegfried R. Waldvogel at Johannes Gutenberg University Mainz.



Kamil Hofman

Kamil Hofman was born in Frankfurt/Main (Germany) in 1990. He graduated with BSc and MSc degrees in chemistry from the Goethe-University Frankfurt (Germany). Since 2017, he has been working on his PhD thesis in the group of Georg Manolikakes. His current field of research focuses on novel multi-component reactions for the synthesis of sulfonamides.

increase the safety as the reaction can be easily interrupted by switching off the power and the reactions are mostly carried out under mild reaction conditions.[8] Overall, applying photochemistry[9] and electrochemistry[10] enables a more sustainable or "green" synthesis[11] of organic chemicals.

The feedstock chemical sulfur dioxide (SO_2) is annually generated in vast amounts by the incineration of sulfur and sulfur-containing waste, roasting of metal sulfides and subsequent washing of flue gases.[12,13] In the food industry, SO_2 is widely used as a preservative (E220) for nutritional products and beverages such as wines and dried fruits. Indeed, its preserving effect has already been utilized in the ancient world, *e.g.*, by the incineration of sulfur in wine vessels.[13,14] SO_2 is utilized as a bleaching agent for paper and cloth, and in gypsum production, corn processing, water and waste treatment, ore refining, oil extraction, metal and glass processes, and sulfonylation of oils and aromatic compounds.[13,15] However, the majority of the SO_2 produced annually is used for the synthesis of sulfuric acid production by the contact process, which has tremendous importance in the chemical industry.[16] In nature, SO_2 is released by volcanic eruptions. In the atmosphere, it is present in one part by parts per billion per volume (1 ppbv). Atmospheric SO_2 mainly stems from the combustion of sulfur-containing fossil fuels and is one of the major air pollutants with severe negative impacts on health and the environment.[17–19] Atmospheric oxidation of SO_2 to sulfuric acid is responsible for the formation of acid rain.[20] In industrialized countries, SO_2 emissions have been constantly reduced in the past few decades, whereas in developing countries, these emissions have currently increased significantly. Flue gas desulfurization (FGD) is commonly used for SO_2 removal from industrial exhausts.[17] Different processes, such as the wet sulfuric acid process (WSA), enable sulfur recovery from flue gas in the form of sulfuric acid.[21] The Wellman–Lord process recovers SO_2 from flue gas upon reaction with Na_2SO_3 to obtain the SO_2 surrogate $Na_2S_2O_5$.[12] From exhaust gases in water, collected SO_2 gas can be oxidized to H_2SO_4 by Br_2 leading to the formation of HBr. The latter can be recycled to Br_2 electrochemically. Alternatively, SO_2 can be oxidized electrocatalytically to SO_3 on Co phthalocyanines with gas diffusion electrodes.[22]

Currently, there is intense research interest in sulfur chemistry and the direct incorporation of SO_2 into organic molecules,[18,23–35] which originates from the broad bioactivity of sulfur-containing molecules making them extraordinarily interesting in drug discovery, agrochemicals, and medicinal chemistry.[24,36] Among the different approaches, radical processes are especially well-suited for the direct fixation of SO_2. Additionally, SO_2 is a very good trap for all kinds of carbon-based radicals and thereby the formed sulfonyl radicals are highly versatile intermediates for the construction of all kinds of SO_2 functionalities. As carbon-based radicals are commonly prepared from suitable precursors *via* single-electron-transfer (SET) processes,[26,33] photochemistry and electrochemistry are obvious choices for new SO_2 binding procedures. In the past few years, various photochemical methodologies for the fixation of SO_2 have been reported.[27,29] Surprisingly, this trend has not reached organic electrosynthesis yet. In this review, we give an overview of different working techniques for using SO_2 and the recent advances in its application in the electrochemical and photochemical preparation of organic products.

Working techniques for SO_2

SO_2 is a colorless, toxic, noxious and corrosive gas (boiling point: −10 °C; melting point: −75.5 °C). Due to its low boiling point, SO_2 can be easily liquified. Interestingly, SO_2 has a low vapor pressure (3.3 bar at 20 °C) and a high enthalpy of

Georg Manolikakes

Georg Manolikakes studied chemistry at the Ludwig-Maximilians University (LMU) Munich. At the LMU, he joined the group of Prof. Paul Knochel and received his PhD in 2009 in the field of organometallic chemistry. After a postdoctoral stay with Prof. Phil S. Baran at the Scripps Research Institute, he started his independent career at the Goethe-University Frankfurt in 2010. In 2017, he was appointed as an associate professor at the Technical University Kaiserslautern. His research interests cover multi-component and one-pot reactions, the synthesis of sulfonyl-containing molecules, asymmetric synthesis and medicinal chemistry.

Siegfried R. Waldvogel

Siegfried R. Waldvogel studied chemistry in Konstanz and received his PhD in 1996 from University of Bochum/Max Planck Institute for Coal Research with Prof. Dr M. T. Reetz as supervisor. After Postdoctoral research at Scripps Research Institute in La Jolla, CA (Prof. Dr J. Rebek, Jr), he started his own research career in 1998 at the University of Münster. After his professorship in 2004 at the University of Bonn, he became a full professor for organic chemistry at Johannes Gutenberg University Mainz in 2010. His research interests are novel electro-organic transformations including bio-based feedstocks from electrosynthetic screening to scale-up. In 2018, he cofounded ESy-Labs GmbH, which provides custom electrosynthesis and contract R&D services.

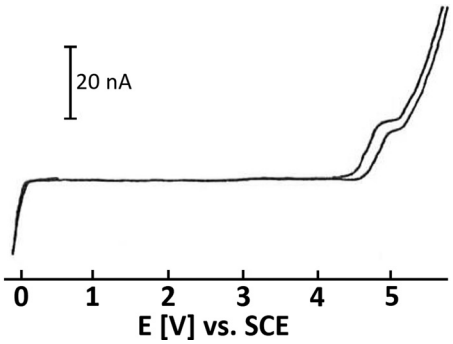


Fig. 1 Cyclic voltammogram of liquid SO_2 and $CsAsF_6$ (~4 mM); conditions: Pt working electrode, T = 203 K; SCE = saturated calomel electrode. Figure adopted from Bard (refurbished).[40] Depicted upon permission from John Wiley & Sons.

vaporization (5960 cal mol^{-1} (~24.9 kJ mol^{-1}) at approx. −10 °C).[13,37,38] Therefore, it is not only simple to liquify SO_2, but also to keep it in its liquid state, either by cooling or using pressure vessels. Indeed, SO_2 is well-known as a dipolar aprotic solvent in organic synthesis.[15,37,39] Liquid SO_2 readily dissolves organic and inorganic salts due to its high dipole moment of 1.61 D with a dielectric constant that varies from 15.6 at 0 °C to 17.3 at −30 °C. At low temperatures, liquified SO_2 can be safely transferred using precooled syringes. Additionally, this gas is easy to recover/recycle. SO_2 is commercially available. The cost of high-purity SO_2 gas (99.98%; water content: ≤50 ppm; costs: ~5 € per kg) is relatively low compared to many other organic solvents at the same level of purity, such as acetonitrile (MeCN), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) or tetrahydrofuran (THF).[13,37]

Beyond that, SO_2 proved to be an excellent solvent in electrochemical oxidation studies as a molecule with pronounced low nucleophilicity, and it poorly solvates cations. It is reported to offer the widest known anodic regime for the electrochemical studies of highly oxidized species.[40,41] The potential window of SO_2 with the supporting electrolyte $CsAsF_6$ is displayed in Fig. 1,[40] which indicates that SO_2 is hard to oxidize but facile to reduce to SO_2 anion radicals. However, as a toxic, foul-smelling and corrosive gas, the use of SO_2 in a typical academic laboratory setup is associated with safety issues and the necessity for specialized equipment. For this reason, various solid, easy-to-handle SO_2 surrogates have been introduced (Fig. 2). The most prominent example is the SO_2 surrogate DABSO (1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct), which has led to a significant boost in organic SO_2 chemistry in the past decade.[18,31,32,42] However, it has certain drawbacks such as the high cost (Sigma Aldrich: 31.20 € per g)[43] or significantly reduced overall atom economy.[44] Other rather inexpensive SO_2 surrogates are sodium and potassium metabisulfite. In particular, $K_2S_2O_5$ has been applied in various transformations.[30,45] However, solubility issues occur in organic solvents so that the application of inorganic SO_2 surrogates is rather limited and elevated temperatures are mostly required.[30] Just recently, a novel surrogate (SOgen) has been designed, which is based on the Diels–Alder reaction of 4-methylstyrene, and 1.2 eq. of SOgen (Fig. 2) generates only 1 eq. of SO_2 *ex situ* in a two-compartment system at elevated temperatures.[25] Although this system has been well-proven in various transformations, its atom economy is very low. Alternatively, SO_2 can be generated *ex situ* from Na_2SO_3 and sulfuric acid with a subsequent introduction of gas into the reaction mixture.[46]

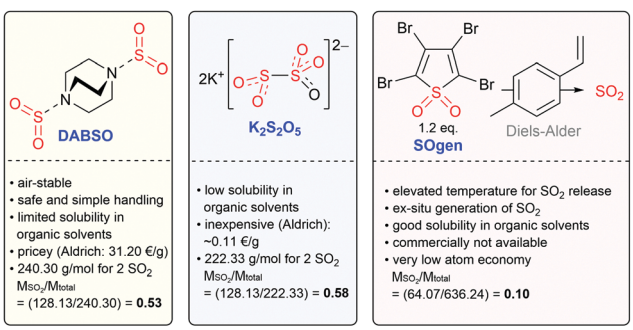


Fig. 2 Selection of SO_2 surrogates in organic synthesis.[25,30,31,43]

However, this technique seems rather non-practicable and reproducibility might be challenging as the SO_2 concentration of the reaction mixture cannot be determined. Other SO_2 surrogates are sodium dithionite ($Na_2S_2O_4$) and thiourea dioxide, which have been used in various transformations in the incorporation of SO_2 into organic molecules. $Na_2S_2O_4$ in solution disproportionates into the SO_2 anion radical and thiourea dioxide gives SO_2^{2-} (upon reaction with hydroxide), both of which are considered as reduced SO_2 species.[34,35] However, sodium dithionite can be considered as an ex-cell electrochemical product of SO_2. Consequently, these surrogates comprise different reactivities in comparison to classical SO_2 surrogates shown in Fig. 2, which release gaseous SO_2.

Stock solutions provide another opportunity for the safe handling of SO_2 in an academic laboratory. SO_2 readily dissolves in various organic solvents[47] and some stock solutions are even commercially available (SO_2 in THF and SO_2 in CH_2Cl_2).[48] However, THF is not the solvent of choice in electrochemical reactions due to its low oxidation potential.[49] The most prominent example of SO_2 stock solutions is arguably the Karl–Fischer reagent, a 15–20% solution of SO_2 in MeOH (albeit also containing pyridine as the base).[50] Although DABSO has been successfully employed in various photochemical processes, it is unfortunately unsuitable for electrosynthesis due to its quite low oxidation potential for 1,4-diazabicyclo[2.2.2]octan (DABCO), which will lead to competitive oxidation pathways in anodic processes.[51] In photochemistry, the limited solubility of DABSO in organic solvents can cause further challenges, as the resulting suspensions drastically interfere with irradiation (scattering, absorption, *etc.*). Such stock solutions in dipolar aprotic solvents (*e.g.* MeCN) provide a superior alternative, which additionally drastically increases the atom economy of the desired reaction. The SO_2 concentration can be easily determined by iodometry[52] and the handling proved to be simple and safe.[44,53,54] For instance, such stock solutions have been used in MeCN, DMSO or DMF in cathodic SO_2 reduction studies or the synthesis of

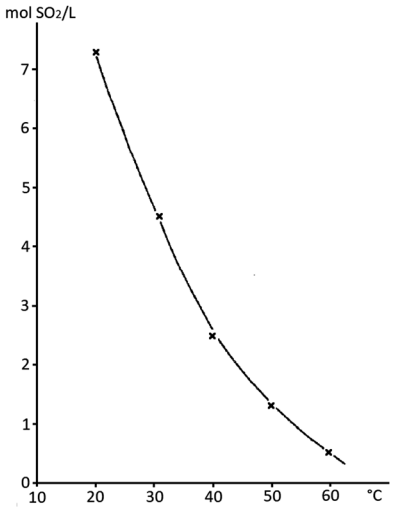


Fig. 3 Saturation points of SO_2 in mol SO_2/L at different temperatures. System: 0.1 M NEt4Br in acetonitrile. Figure adopted from Knittel (refurbished).[60] Depicted upon permission from Springer Nature.

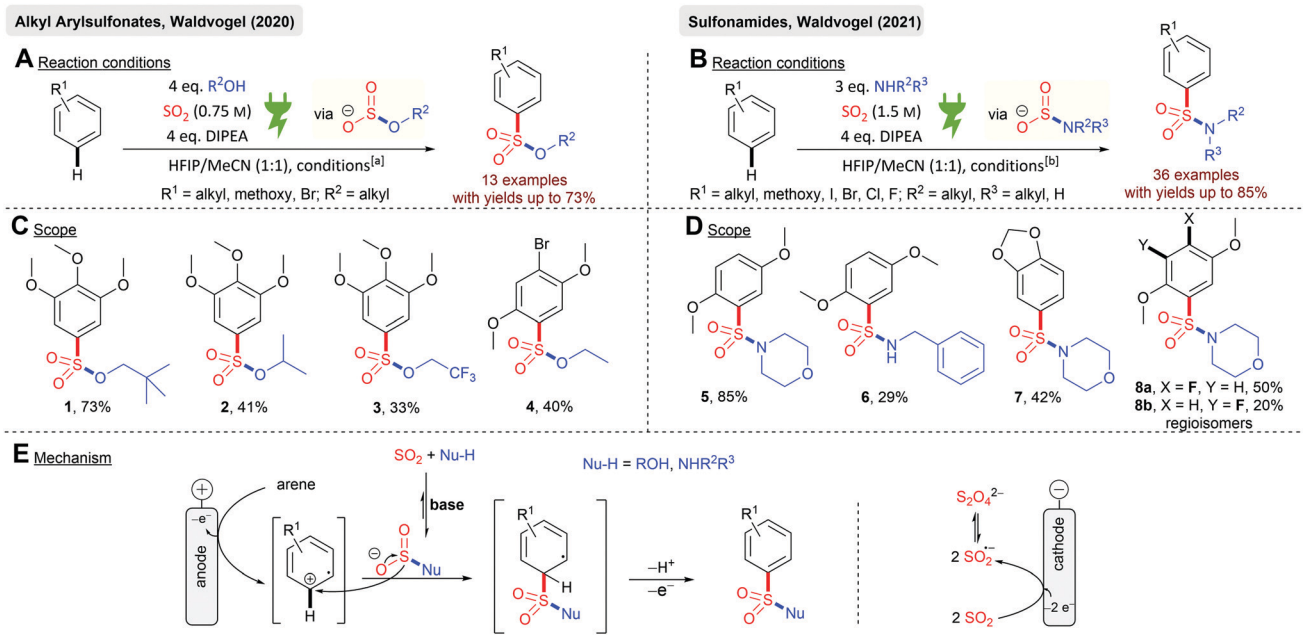
sulfones from alkyl halides.[55–60] It was determined that a 6 M saturation of SO_2 in MeCN/0.1 M NEt_4Br at room temperature can be reached (Fig. 3, NEt_4Br was used as the supporting electrolyte and can be added optionally).[60] For simple and safe handling of these stock solutions, Waldvogel *et al.* recommended maintaining the SO_2 concentration in acetonitrile below the saturation point (for example, 3–4 M in pure MeCN) and storing the stock solution at around +4 °C.[44]

Factors increasing the solubility of SO_2 in organic solvents are the high basicity and polarity of the medium of choice. However, the cohesion effects of the solvent lower the dissolution of SO_2 due to energy consumption in forming a void within the liquid. The formation of donor–acceptor complexes is decisive for the absorption of SO_2 in organic solvents. Surprisingly, aromatic hydrocarbons comprise relatively high dissolution of SO_2 possibly due to the formation of complexes between the electron acceptor SO_2 and the π-electron system.[47,61]

Overall, different alternatives for the utilization of SO_2 in organic synthesis exist. The direct use of SO_2 gas itself is straightforward and 100% atom-economic. Although safe handling of SO_2 gas should not pose any problem for a trained chemist, issues and concerns associated with this toxic and corrosive gas can impede its use in a typical academic or medicinal chemistry laboratory. In such cases, solid, bench-stable SO_2 surrogates provide a safe and easy-to-handle alternative, albeit connected with a lower atom-economy. In addition, these surrogates can contain additional components, which might interfere with the desired process. Stock solutions of SO_2 in typical organic solvents, preferably available from commercial suppliers, can offer a good balance between atom-economy and safety. However, in the end, one has to evaluate and balance all factors and risks. The ideal reagent for a safe and efficient introduction of SO_2 will always depend on the envisioned transformation, the available experimental setup and also the scale of the planned process.

Electrochemistry – anodic reactions with SO_2

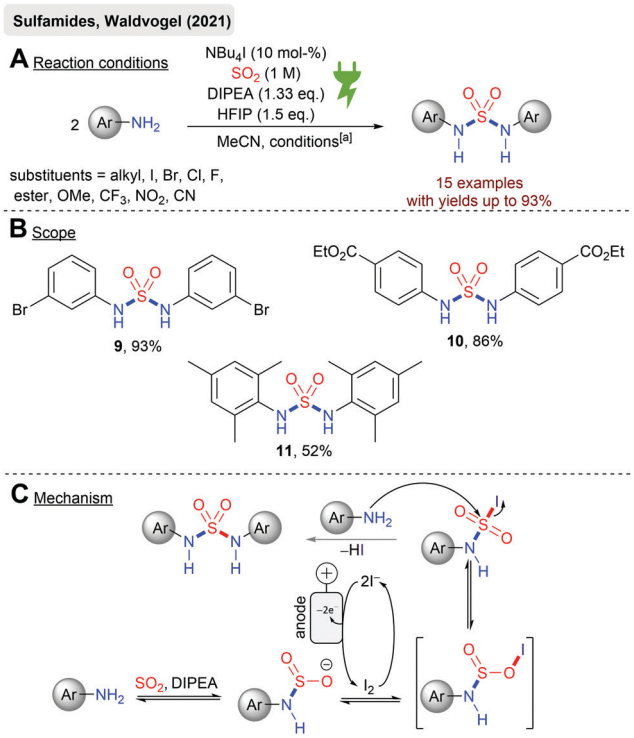
Electrochemistry with SO_2 can be divided into anodic and cathodic processes. Cathodic reductions feature the formation



Scheme 1 Electrochemical synthesis of alkyl arylsulfonates (left) and electrochemical synthesis of sulfonamides (right); DIPEA = *N*,*N*-diisopropylethylamine; HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol; BDD = boron-doped diamond; [a]: BDD electrodes, r.t., 14 h, 11.25 mA cm^{-2} (galvanostatic), 3.5 F, divided cell (glass frit); [b]: BDD electrodes, r.t., 14 h, 12 mA cm^{-2} (galvanostatic), 3.5 F, divided cell (glass frit).

of SO_2 anion radicals[59,62–65] and the synthetic exploitation thereof. Anodic processes imply the incorporation of SO_2 into electrochemically activated organic molecules as oxidation of SO_2 is practically impossible. However, such conversions have not been the center of attention so far. This could be due to the fact that the cathodically generated SO_2 anion radicals can interfere in the anodic process due to the possible reoxidation and interference of this species or the consumption of SO_2 in an undivided cell. Waldvogel and coworkers reported the first anodic reaction with SO_2 as the reactant in the electrochemical synthesis of alkyl arylsulfonates and sulfonamides (Scheme 1). Both chemical motifs are highly based on bioactive molecules and therefore have tremendous importance in medicinal chemistry. Initially, the electrolysis was conducted in undivided cells but the application of the divided cells resulted in higher overall yields. SO_2 was used from a stock solution in acetonitrile, which significantly increases the atom economy. Further highlights are the mild reaction conditions and the requirement of not needing any additional supporting electrolytes (Scheme 1A and B). Various electron-rich arenes were successfully converted with yields up to 73% (**1**) for the sulfonate esters and yields up to 85% (**5**) for the sulfonamides (Scheme 1C and D). Primary and secondary alcohols (**2**, 41%) as well as fluoroalcohols (**3**, 33%) are eligible for this protocol. Secondary and primary amines gave the corresponding sulfonamides, although primary amines resulted in significantly lower yields (**6**, 29%). Heterocyclic structures, such as 1,3-benzodioxole (**7**, 42%), are also suitable for this protocol. Most importantly, halogen substituents are tolerated offering complementarity to transition metal-catalyzed reactions (**4**, 40%; **8a**, 50% and **8b**, 20%). The electrochemical synthesis of sulfonamides proved to be scalable as a 13-fold scale-up reaction of **5** resulting in 85% yields, which is slightly higher than that at the smaller scale. The reaction mechanism (Scheme 1E) of both conversions is based on the reaction of a nucleophile (alcohol or amine) with SO_2 in the presence of an organic base rendering in the formation of monoalkyl sulfites or amidosulfinates, respectively. Both species provide excellent electrical conductivity and therefore are well suited for electrochemical synthesis. Initial anodic oxidation of the arene forms the corresponding radical cation, with a subsequent nucleophilic attack of the *in situ* formed monoalkyl sulfite or amidosulfinate. Hydrogen bonding between the O-atom of these species with HFIP is considered to promote the sulfur-directed nucleophilic attack. Finally, a second anodic oxidation step accomplishes the desired product.[53,54]

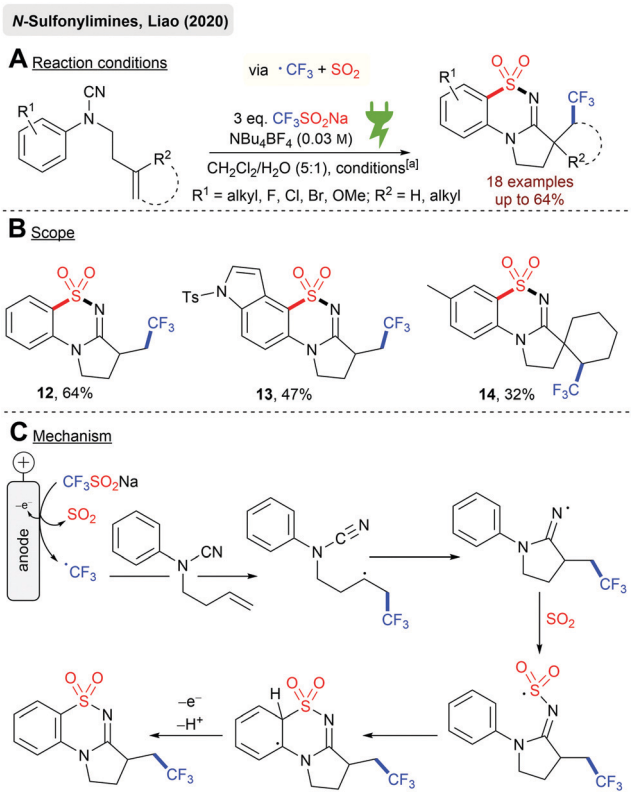
Just recently, the first electrochemical synthesis of sulfamides mediated by catalytic amounts of iodide[44] has been reported (Scheme 2) with yields up to 93% (**9**). Sulfamides are an emerging functionality in drug design and medicinal chemistry due to their versatile biological activities. Platinum electrodes in a divided cell (glass frit) were utilized with SO_2 in acetonitrile. Stoichiometric amounts of DIPEA and HFIP are required for the success of this reaction (Scheme 2A). HFIP is considered to weaken the interaction between DIPEA and SO_2 as these form charge transfer complexes. The reaction comprises broad functional group tolerance to numerous anilines with excellent yields. For example, the local anesthetic agent benzocaine



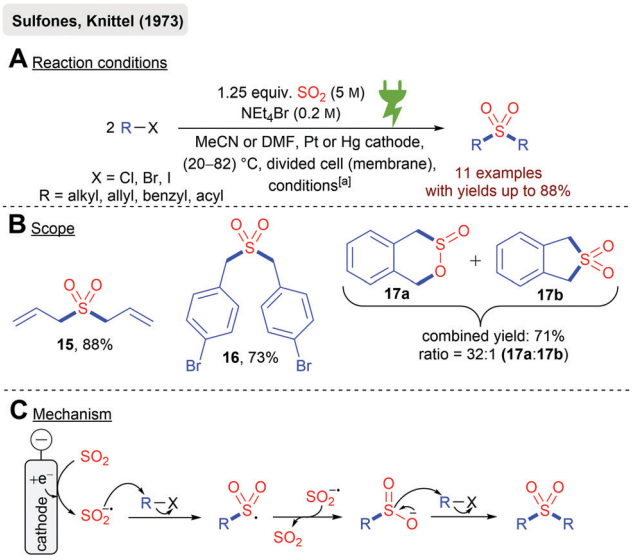
Scheme 2 Electrochemical synthesis of symmetric sulfamides; [a]: Pt electrodes, r.t., 14 h, 7.5 mA cm^{-2} (galvanostatic), 2.5 F, divided cell (glass frit).

resulted in **10** in 86% yield (Scheme 2B), but the sterically hindered mesidine gave **11** in moderate yield (52%). The mechanistic concourse (Scheme 2C) is postulated to proceed *via* the formation of amidosulfinates from the aniline, SO_2 and the sterically hindered base DIPEA in an equilibrium reaction. The electrochemically generated iodine is ionized by DIPEA. The subsequent reaction of the amidosulfinate with the *in situ* generated iodonium ion forms the sulfamoyl iodide, which is most likely stabilized by HFIP by hydrogen bonding. A second nucleophilic attack finally results in the formation of sulfamide. As a cathodic reaction, SO_2 reduction to the SO_2 anion radical was identified by cyclovoltammetry studies even though platinum electrodes were applied, which actually exhibit a low overvoltage for H^+ discharging to hydrogen gas.[66]

Liao and coworkers reported the electrochemical cyclization reaction of *N*-aryl cyanamides with the terminal alkene to *N*-sulfonylimines (Scheme 3A) *via* trifluoromethylation and SO_2 insertion by using Langlois' reagent (CF_3SO_2Na) as the CF_3 and SO_2 sources. A series of rather electron-rich *N*-arylcyanamides were successfully converted to the corresponding products with moderate yields, although electron-withdrawing substituents (CF_3, CO_2Et) on the arene moiety resulted in no product formation. The highest yields were achieved with the model substrate giving **12** (64%, Scheme 3B). Halogen substituents are tolerated and remarkably, indole derivative **13** was isolated in 47% yield. Finally, several spirocyclic structures were obtained as sole diastereomers (**14**, 32%) from *N*-aryl cyanamides containing cyclopentene or cyclohexene moieties. The proposed reaction



Scheme 3 Electroctrochemical synthesis of cyclic *N*-sulfonylimines; [a]: C_{gr}||Pt (anode||cathode), 30 °C, 6 h, 2.2–3.7 mA cm^{-2} (galvanostatic), 2.2–3.7 F, 14 h, undivided cell.



Scheme 4 Electrochemical synthesis of symmetric sulfones; [a]: potentiostatic conditions: −0.7 V *vs.* Ag/AgCl, 1 F mol^{-1} or galvanostatic conditions: 300 mA cm^{-2} and 500 mA cm^{-2}, 2000–10 000 C.

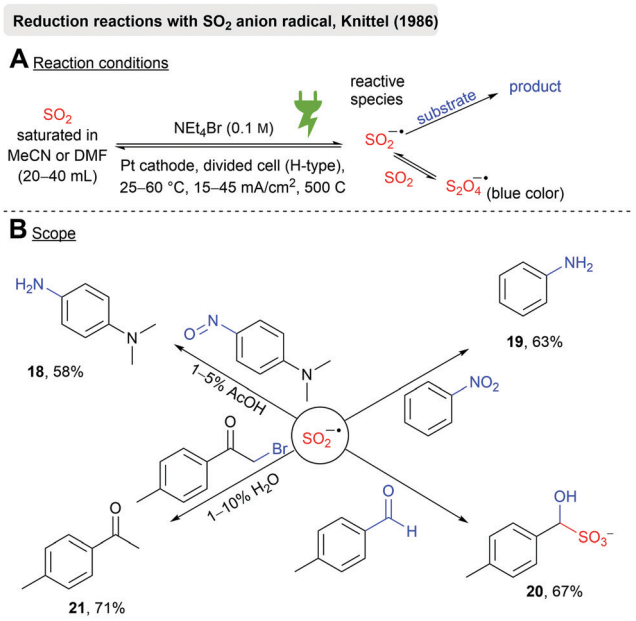
mechanism (Scheme 3C) suggested the initial anodic oxidation of CF_3SO_2Na under the cleavage of SO_2 to form the CF_3 radical, which undergoes radical addition to the terminal alkene. A subsequent intramolecular cyclization renders the iminyl radical, followed by SO_2 capture and a second cyclization step on the aromatic ring. A second anodic oxidation step results in the corresponding *N*-sulfonylimine.[67,68] The authors have not investigated this reaction in a divided cell set-up. Eventually, higher yields could have been achieved as this system suggests SO_2 reduction as a cathodic side reaction, which could be one reason for the moderate yields.

Electrochemistry – cathodic reductions of SO_2

The reduction of SO_2 in dipolar aprotic solvents (MeCN, DMF, DMSO) to the SO_2 radical anion is considered as quite stable, and is well described in the literature.[59,62–64] The synthetic exploitation of this electrochemically generated species has been first described by Knittel and coworkers in 1973 in their protocol for the synthesis of symmetric sulfones in the presence of organic halides (Scheme 4). Cyclic voltammetry experiments suggested that the SO_2 reduction occurs at −0.7 V *vs.* Ag/AgCl (in MeCN). A galvanostatic and potentiostatic protocol has been established (Scheme 4A), whereas in the latter cathode, fouling was observed. This problem was avoided under galvanostatic conditions in combination with the replenishing of the reactants periodically. Several alkyl, allyl, benzyl, and acyl halides were successfully transformed to their corresponding sulfone in good yields (Scheme 4B). Diallylsulfone (**15**) even gave 88% yield. Bromo substituents on aromatic moieties were tolerated in **16** (73%) and remarkably an intramolecular reaction resulted in sultine **17a** with sulfone **17b** as the side product (71% combined yield). It is noteworthy that previous studies with sodium dithionite ($Na_2S_2O_4$) and alkyl halides resulted in significantly lower yields (10–15%), which demonstrates that the electrochemical synthesis in this example is superior. Cyclic voltammetry experiments and SO_2 anion radical titration experiments (with the alkyl halide) suggest the nucleophilic attack of the SO_2 anion radical to the alkyl halide as the rate-determining step resulting in the R–SO_2 radical according to the mechanism depicted in Scheme 4C. An electron transfer from another equivalent of the SO_2 anion radical renders the sulfinate anion, which undergoes another S-directed nucleophilic substitution reaction with R–X yielding the symmetric sulfone.[55,57]

This protocol has been refined in 1980 to a paired electrolysis process with SO_2, propyl alcohol and NEt_4Br by the generation of propyl bromide in the anodic compartment *via* the formation of HBr from the electrochemically generated Br_2 with SO_2 and H_2O.[58] In 1982, this methodology was further developed by the synthesis of various sulfur-containing heterocycles, such as oxathiolane-, oxathiane-, thiane- and thiepane-oxides upon the reaction of the SO_2 anion radical with 1,ω-dihalides.[56]

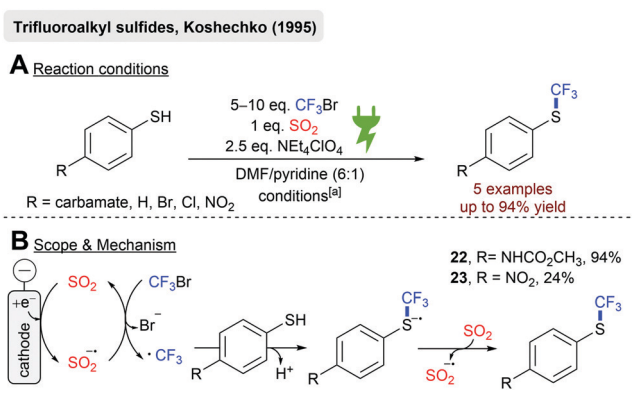
Knittel further investigated the chemical behaviour of the electrochemically generated SO_2 anion radicals in MeCN or DMF towards reducible substrates (Scheme 5). It is postulated that the SO_2 anion radical is in equilibrium with the S_2O_4 anion radical, whereas the former is the reactive species. Several molecules bearing different reducible functional groups were



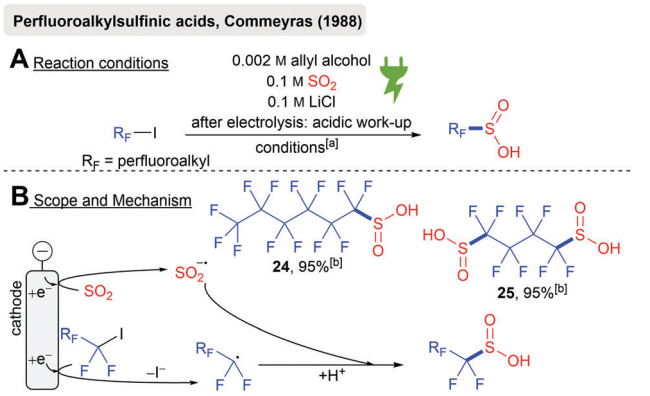
Scheme 5 Reactivity of the electrochemically generated SO_2 anion radical towards reducible substrates.

investigated (Scheme 5B), such as nitrosobenzenes, which resulted in the reduction to the corresponding aniline (**18**, 58%) in the presence of acetic acid. The author claims that the SO_2 anion radical is moderately suitable for the reduction of nitrobenzene, as the hydroxylaminosulfonate intermediate gets formed. Elevated temperatures are required, which is in conflict with the solubility of SO_2 in MeCN (Fig. 3). However, aniline (**19**) was obtained in 63% at 30 °C. The reduction of aldehydes to alcohols is unsuitable due to the formation of hydroxysulfonates (**20**, 67%). Dehalogenation of α-bromoketones occurred readily (**21**, 71%) in the presence of H_2O.[60]

In 1995, Koshechko and coworkers reported the electrochemical synthesis of trifluoroalkyl sulfides from CF_3Br and several 4-substituted thiophenols in an electrocatalytic fashion (Scheme 6).[69] The electrochemical reduction of SO_2 to the SO_2 anion radical lowers the activation barrier for CF_3Br reduction



Scheme 6 Electrochemical synthesis of trifluoroalkyl sulfides catalyzed by the SO_2 anion radical; [a]: r.t., Pt||Pt, divided cell (glass frit), −0.9 to −1.0 V (potentiostatic) *vs.* Ag/$AgNO_3$, 0.125–1 F.



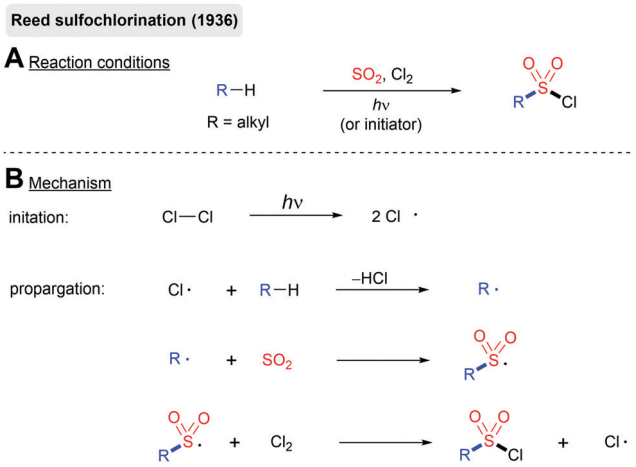
Scheme 7 Electrochemical synthesis of perfluoroalkylsulfinic acids; [a]: DMF/H_2O (9 : 1), 20 °C, carbon fiber electrodes, divided cell (glass frit), 1–12 mA cm^{-2} (galvanostatic), ~1.05 F; [b]: yield determined by NMR integration (^{19}F NMR).

to form the trifluoromethyl radical under bromide abstraction, which has been described earlier.[70] Radical addition to the thiolate anion, followed by an electron transfer to SO_2, gives the desired product and regenerates the SO_2 anion radical. The carbamate substituent resulted in the highest yields (**22**, 94%), whereas strongly electron-withdrawing substituents, such as the nitro-group, diminished the yield significantly (**23**, 24%).[68,69,71]

The electrochemical synthesis of perfluoroalkylsulfinic acids from perfluoroiodoalkanes and SO_2 was reported in 1988 by Commeyras and coworkers (Scheme 7A). Cyclic voltammetry studies suggested the simultaneous cathodic reduction of the model substrate $C_6F_{13}I$ (−1.38 V *vs.* SCE) to the corresponding perfluoroalkyl radical and the reduction of SO_2 (−1.4 V *vs.* SCE) to the SO_2 anion radical with a subsequent radical recombination (Scheme 7B). Subsequent acidic work-up gives the perfluoroalkysulfinic acids **24** (from $C_6F_{13}I$) and **25** (from $I(CF_2)_4I$) with 95% calculated NMR yield, respectively. Lower water content resulted in the formation of carbonic acids upon the reaction with DMF when $I(CF_2)_4I$ was used.[72] The initial reduction of perfluoroiodoalkanes prior to SO_2 seems unlikely when considering the studies of Knittel (reduction potential for SO_2 at −0.7 V *vs.* Ag/AgCl).[55] A SO_2 mediated process could be more likely.

Photochemistry – early examples

The photochemical fixation of SO_2 into organic molecules dates back to the development of the Reed sulfochlorination of simple alkanes in the 1930s (Scheme 8).[73] This reaction proceeds *via* a radical chain mechanism initiated by a UV-light induced homolysis of chlorine. Similar to the classical free-radical halogenation, the chlorine atom abstracts hydrogen from the alkane. The formed alkyl radical is intercepted by SO_2 leading to the corresponding sulfonyl radical. The reaction of the sulfonyl radical with Cl_2 delivers the sulfonyl chloride product and a new chlorine atom, which can take part in another chain propagation step. As with other free-radical halogenation reactions, the Reed sulfochlorination only tolerates a small



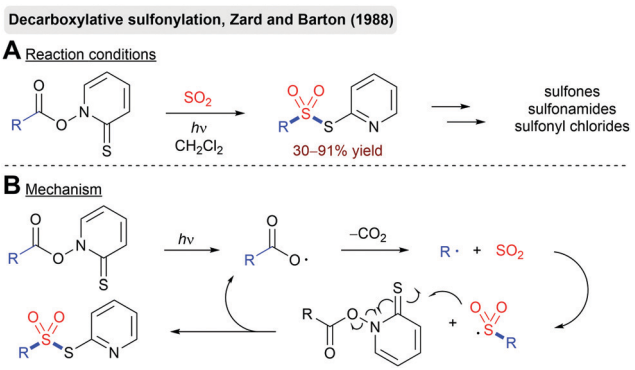
Scheme 8 Reed sulfochlorination.

number of functional groups. In most cases, a mixture of regioisomers is formed. Nevertheless, the Reed process has been employed on a large scale for the production of sulfonic acid-based detergents and chlorosulfonated polyethylene.[74]

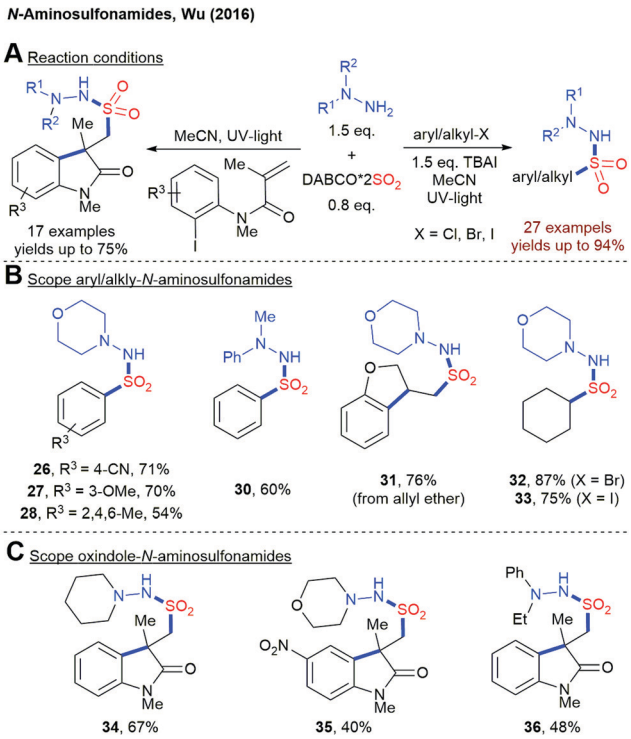
Another noteworthy example is the decarboxylative sulfonylation of so-called Barton esters reported by Zard and Barton (Scheme 9).[75] Photolysis of the labile N–O bond of the thiohydroxamic ester using UV irradiation affords an acyloxy radical. Extrusion of CO_2 furnishes an alkyl radical, which is again intercepted by SO_2. The formed sulfonyl radical reacts with another molecule of the Barton ester, leading to the formation of the thiosulfonate product and the propagation of the radical chain. The obtained products can be readily transformed into sulfones, sulfonyl chlorides or sulfonamides. The reaction proceeds through the generation of an aryl radical, trapping of this radical with SO_2 and a final back electron transfer.

Photochemistry using UV irradiation

Although the photochemical fixation of SO_2 has been known for almost 100 years, its application in organic synthesis has been sparsely studied.[76] Only in the last ten years, the photochemical



Scheme 9 Photochemical decarboxylative sulfonylation by Barton.



Scheme 10 UV-light mediated insertion of SO_2 into organic halides, TBAI = tetrabutylammonium iodide.

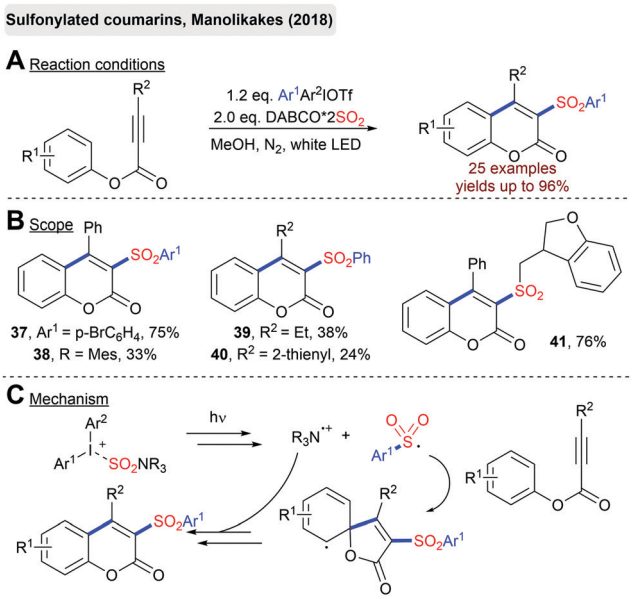
insertion of SO_2 into organic molecules has gained more attention. In 2016, Wu and coworkers reported a UV-light mediated synthesis of *N*-aminosulfonamides from aryl or alkyl halides, DABSO and hydrazines (Scheme 10).[77] Mechanistic investigations indicate the formation of a sulfonyl radical as the key intermediate. Later on, the same group extended this methodology to the construction of oxindole scaffolds.[78]

The same group also described a couple of other reactions for the synthesis of sulfones exploiting a UV-light mediated insertion of SO_2.[79] However, the use of high-energy UV-light in organic synthesis is associated with several disadvantages. It can lead to undesirable side reactions or decomposition of the product. UV-light only constitutes a minor part of natural sunlight, necessitating the use of specialized equipment for such transformations.

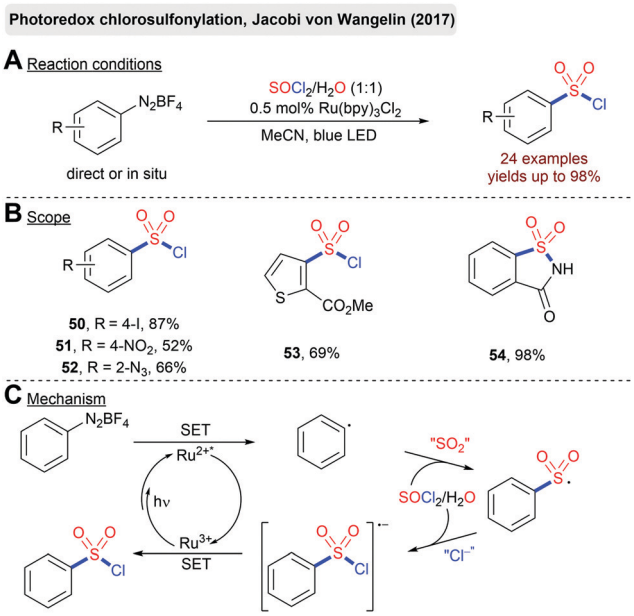
Photochemistry using visible light

The Manolikakes group described the synthesis of sulfonylated coumarins from arylpropinoates, DABSO and diaryliodonium salts (Scheme 11).[80] Interestingly, this transformation is solely driven by visible light and proceeds in the absence of any external photosensitizer. Presumably, the excitation of a charge transfer complex between the iodonium salt and DABSO initiates this radical transformation and the generation of a sulfonyl radical.

This combination of diaryliodonium salt and DABSO has been utilized for a visible-light mediated synthesis of sulfonylated oxindoles and azaspiro[4,5]-trienone using either *N*-arylacrylamide



Scheme 11 Photoinitiated synthesis of sulfonylated coumarins.



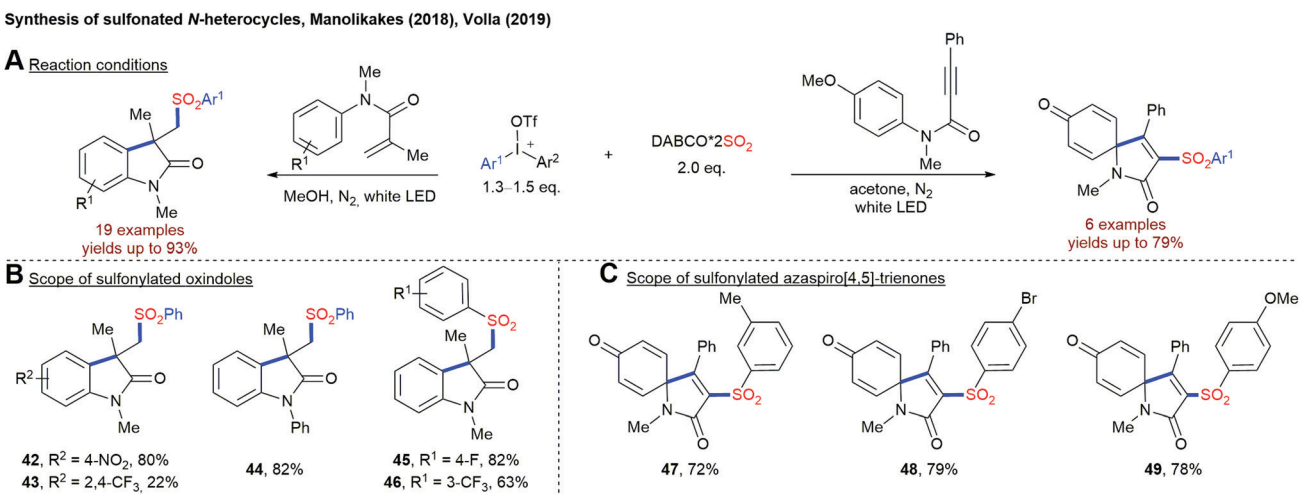
Scheme 13 Photoredox-catalyzed synthesis of sulfonyl chlorides.

or *N*-arylpropiolamides as the third reaction partner (Scheme 12).[81] So far, the direct utilization of visible light for the fixation of SO_2 in the absence of any external photosensitizer is limited to the reactions employing diaryliodonium salts as radical precursors. Other substrate classes have not been utilized successfully by now.

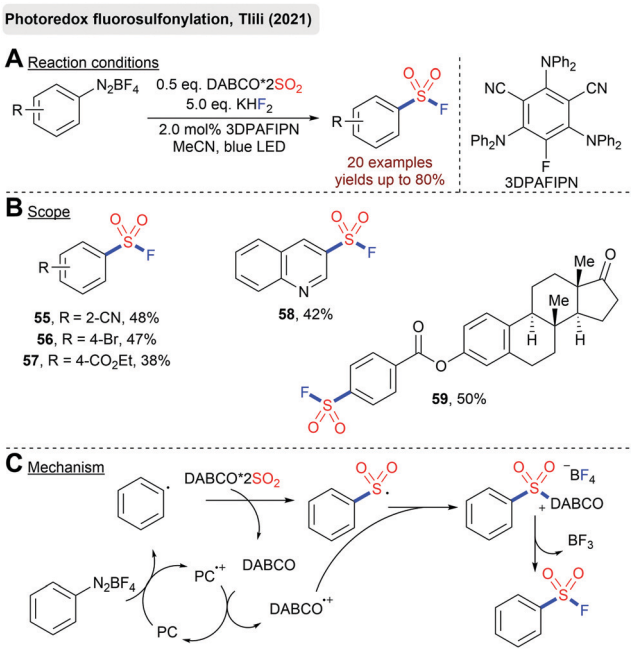
Photoredox-catalysis using visible light

The recent advent of photoredox-catalysis has opened intriguing possibilities to directly use (low-energy) visible-light for the activation of a plethora of different substrates.[82] Inevitably, other methods for the construction of C–S bonds mediated by visible-light have also attracted considerable attention.[83] The first examples employed sulfinates or sulfonyl chlorides as precursors for the generation of sulfonyl radicals.[84] Later on, the *in situ* generation of these reactive intermediates from an organic building block and SO_2 mediated by photoredox-catalysis emerged as a highly attractive opportunity for the fixation of SO_2 in any type of sulfonyl functionality.[27,28,30] Herein, we will highlight some selected pioneering examples as well as the most recent advances, from the last few years, in the photoredox-catalyzed synthesis of sulfonyl halides, sulfones and sulfonamides from SO_2 or a suitable surrogate.

Jacobi von Wangelin and coworkers described a $Ru(bpy)_3Cl_2$-catalyzed chlorosulfonylation of arenediazonium salts mediated by visible light (Scheme 13).[85] Interestingly, both SO_2 and the required HCl are generated by the hydrolysis of thionyl chloride ($SOCl_2$) in the reaction.



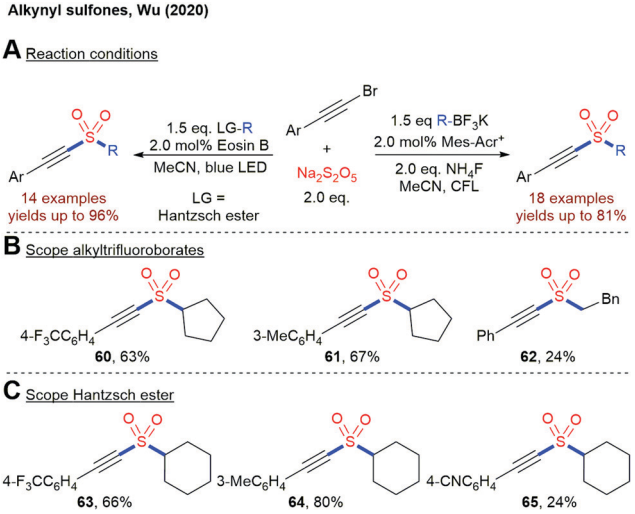
Scheme 12 Synthesis of sulfonylated oxindole and azaspiro[4,5]-trienone using either *N*-arylacrylamide or *N*-arylpropiolamides.



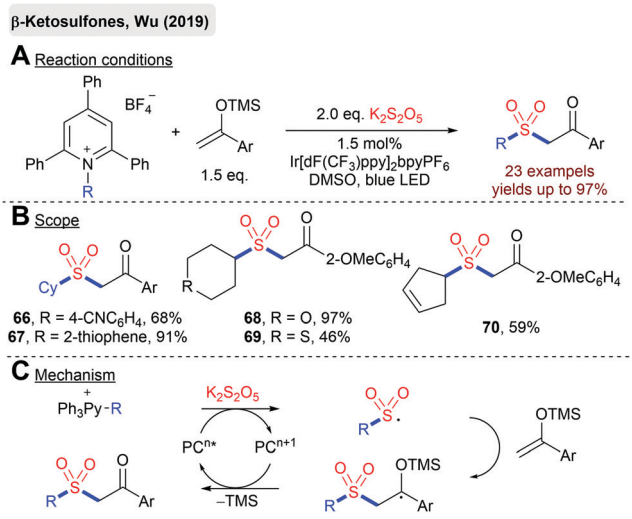
Scheme 14 Photoredox-catalyzed synthesis of sulfonyl fluorides.

Just recently, Tlili's group reported a light mediated synthesis of arylsulfonyl fluorides from arenediazonium salts and DABSO-catalyzed by an organic photoredox-catalyst (Scheme 14).[86] Interestingly, DABSO plays a twofold role in this reaction. On the one hand, it serves as the SO_2-source to trap the formed aryl radical. On the other hand, the thereby-released DABCO regenerates the active photocatalyst in its ground state and takes part in the generation of a highly electrophilic sulfonium salt. Although better yields are obtained with the addition of KHF_2, the BF_4^- counterion can serve as a fluoride source itself.

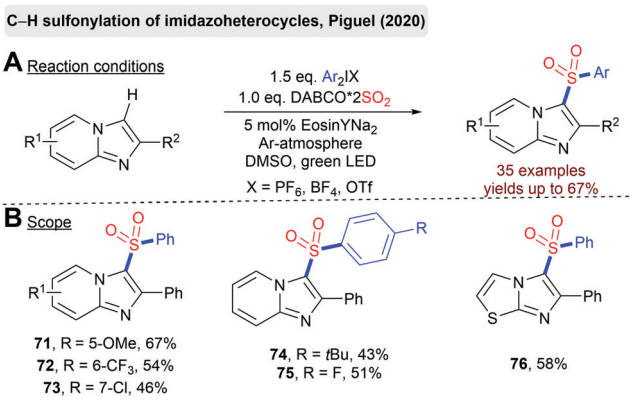
In 2020, Wu and coworkers disclosed two closely related methods for the construction of alkynyl sulfones from alkynyl bromides, $Na_2S_2O_5$ and alkyltrifluoroborates or 4-alkyl Hantzsch esters, respectively (Scheme 15).[87] A sulfonyl radical is postulated as the key intermediate in both processes.



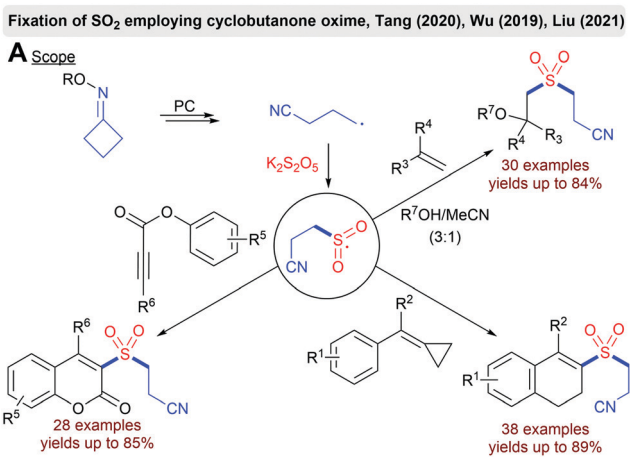
Scheme 15 Photoredox-catalyzed insertion of SO_2 into alkynyl sulfones; CFL = compact fluorescent lamp.



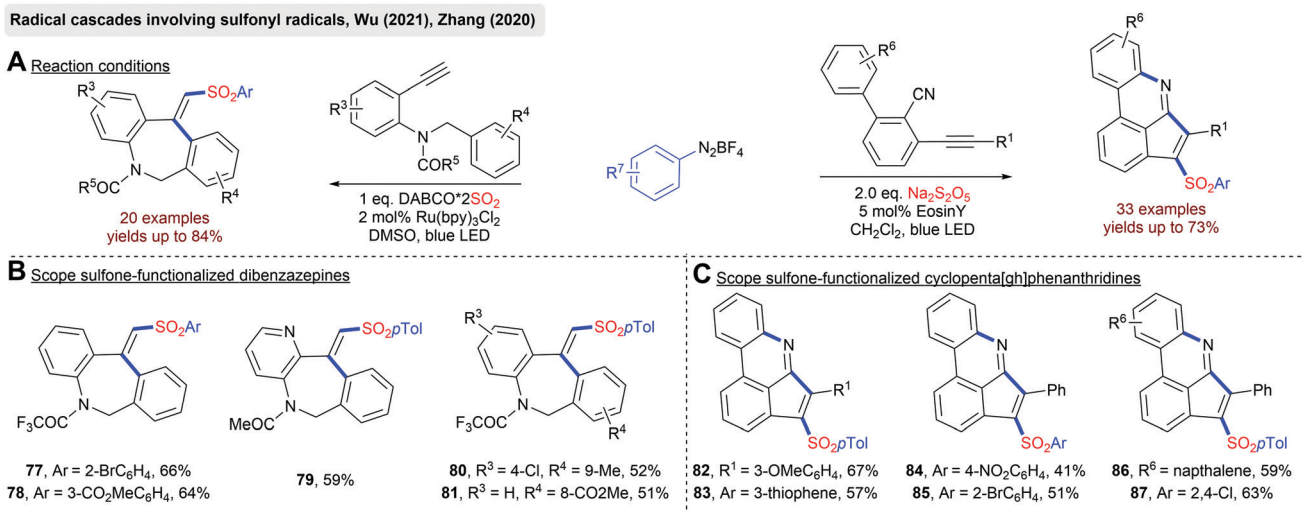
Scheme 16 β-Ketosulfones from silylenolethers and alkylpyridinium salts.



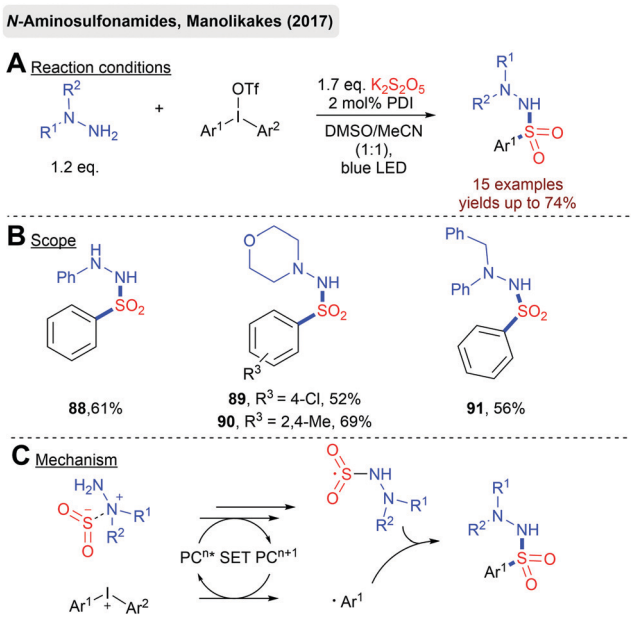
Scheme 17 Direct sulfonylation of imidazoheterocycles.



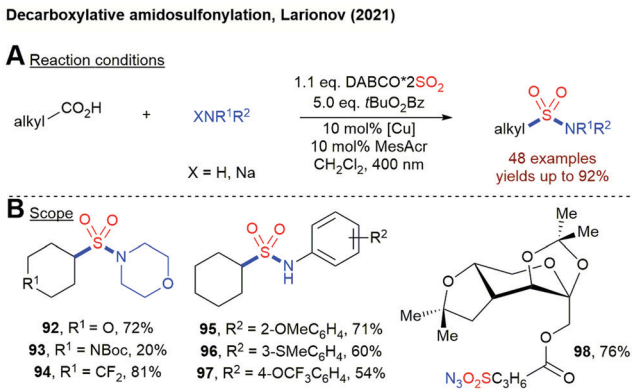
Scheme 18 Photoredox-catalyzed fixation of SO_2 employing cyclobutanone oxime.



Scheme 19 Photoredox-catalyzed cascades towards sulfonylated heterocycles.



Scheme 20 Photoredox-catalyzed synthesis of *N*-aminosulfonamides.



Scheme 21 Decarboxylative aminosulfonylation of free carboxylic acids using a dual catalyst system.

The same group described a photoredox-catalyzed synthesis of β-ketosulfones from silylenolethers, $K_2S_2O_5$ and alkylpyridinium salts as radical precursors (Scheme 16).[88] Sulfonyl radicals are generated by the SET reduction of pyridinium salts, followed by the homolytic fragmentation and addition of the generated alkyl radical to SO_2. Later on, Wu and coworkers described an analogous method with difluorinated silyl enol ethers.[89]

Piguel *et al.* reported the C–H sulfonylation of imidazoheterocycles with DABSO and diaryliodonium salts catalyzed by the organic dye Eosin Y (Scheme 17).[90] This transformation provides an attractive opportunity for a direct installation of a sulfonyl moiety onto a non-functionalized heterocyclic scaffold.

Several groups described a ring-opening approach for the visible-light mediated fixation of SO_2.[91] The SET reduction of cyclobutanone oxime with an excited photocatalyst leads to a ring-opening and a cyanoalkyl radical. After the addition to SO_2, the formed sulfonyl radical can be intercepted by various trapping agents such as alkenes, methylenecyclopropanes or alkynoates (Scheme 18).

In general, radical cascades involving sulfonyl radicals enable the facile synthesis of (hetero)cyclic scaffolds bearing a sulfonyl functionality. In Scheme 19, two transformations for a photoredox-catalyzed construction of sulfone-functionalized dibenzazepines and cyclopenta[*gh*]phenanthridines are depicted.[92] In both cases, sulfonyl radicals are generated from aryldiazonium salts and a solid SO_2 surrogate. The Manolikakes group described a photoredox-catalyzed synthesis of *N*-aminosulfonamides from diaryliodonium salts, in-situ generated SO_2 and hydrazines (Scheme 20).[93] Mechanistic investigations indicate that contrary to previous reactions, aryl sulfonyl radicals are not formed. Instead, the SET oxidation of a hydrazine–SO_2 adduct affords an S-centered radical as the key intermediate. Unfortunately, this method is limited to

hydrazines and the synthesis of aminosulfonamides. Reactions with simple amines failed.

In 2021, Larinov and coworkers reported a decaboxylative aminosulfonylation of free carboxylic acids using DABSO, a hydroxylamine derivative and a dual catalyst system consisting of an acridine photocatalyst and CuOTf (Scheme 21).[94] By using anilines or NaN_3 together with tBuO$_2$Bz as terminal oxidant, sulfonamides and sulfonyl azides can be accessed directly. This method is also amenable to the late-stage functionalization of natural products.

Conclusion and outlook

The photochemical incorporation of SO_2 into value-added compounds has been used for almost 100 years. Although all the first methods, such as the Reed chlorosulfonylation, relied on the use of UV-light, the recent achievements in the field of photoredox-catalysis have led to significant advances towards the fixation of SO_2 with visible-light mediated in the last few years. This field has become an active area of research and new methods have been developed at an astonishing rate. However, further progress towards the utilization of more common building blocks, in particular from renewable resources, is still needed. In particular, the lack of efficient methods for the synthesis of highly relevant sulfonamide motifs has to be addressed. On the other hand, the electrochemical incorporation of SO_2 is a very new and modern research topic, although Knittel and coworkers did some pioneering work in 1973 featuring the electrochemical synthesis of symmetrical sulfones. Anodic processes involving SO_2 are scarce. This could be due to the fact that it is hard to find a suitable system as the cathodically formed SO_2 anion radical might interfere in anodic oxidations/reactions. Currently, divided cells are an elegant solution to circumvent this problem. Cathodic reductions of SO_2 in a mediated fashion are rather established in electroorganic synthesis although not much work has been reported in this field in the past. We expect a significant increase of electrochemical methodologies involving SO_2 incorporation in the near future. Other future research topics could be paired electrolysis systems involving SO_2 reduction coupled with anodic oxidation processes in the synthesis of value-added products.

Conflicts of interest

The authors declare no conflict of interests.

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