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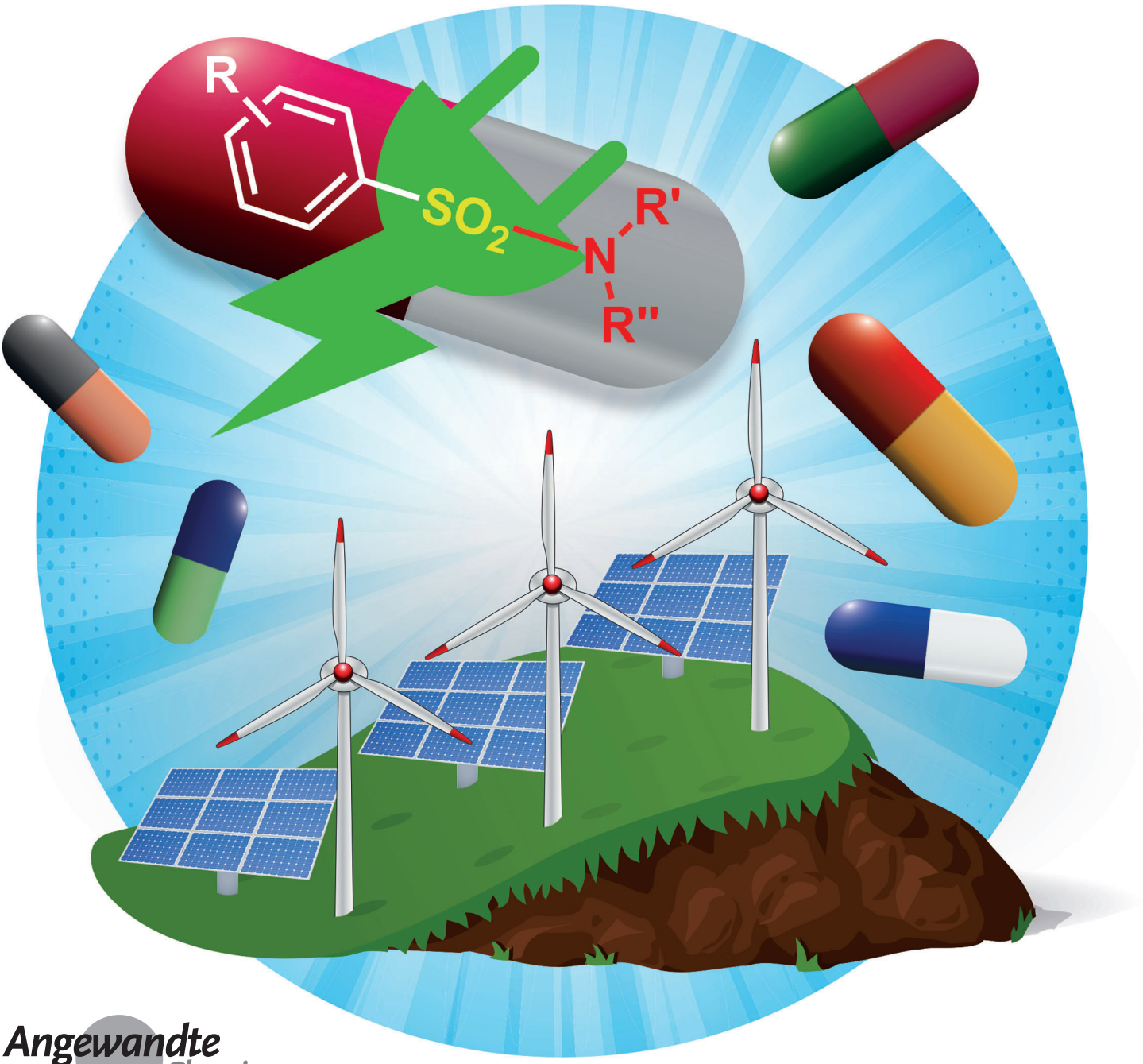
Electrochemistry | Hot Paper

Metal-Free Electrochemical Synthesis of Sulfonamides Directly from (Hetero)arenes, SO_2, and Amines

*Stephan P. Blum, Tarik Karakaya, Dieter Schollmeyer, Artis Klapars, and Siegfried R. Waldvogel**

In memory of François Diederich

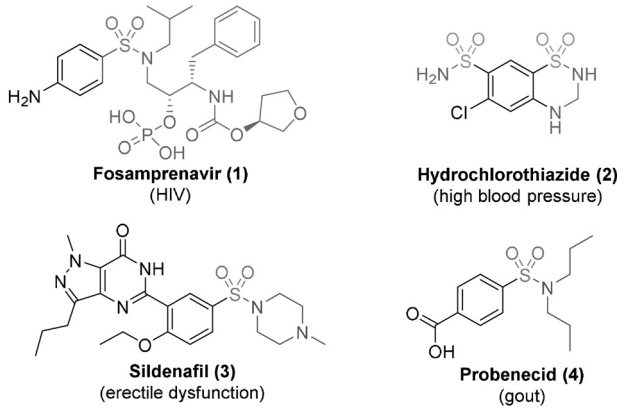


Abstract: *Sulfonamides are among the most important chemical motifs in pharmaceuticals and agrochemicals. However, there is no methodology to directly introduce the sulfonamide group to a non-prefunctionalized aromatic compound. Herein, we present the first dehydrogenative electrochemical sulfonamide synthesis protocol by exploiting the inherent reactivity of (hetero)arenes in a highly convergent reaction with SO_2 and amines via amidosulfinate intermediate. The amidosulfinate serves a dual role as reactant and supporting electrolyte. Direct anodic oxidation of the aromatic compound triggers the reaction, followed by nucleophilic attack of the amidosulfinate. Boron-doped diamond (BDD) electrodes and a HFIP–MeCN solvent mixture enable selective formation of the sulfonamides. In total, 36 examples are demonstrated with yields up to 85 %.*

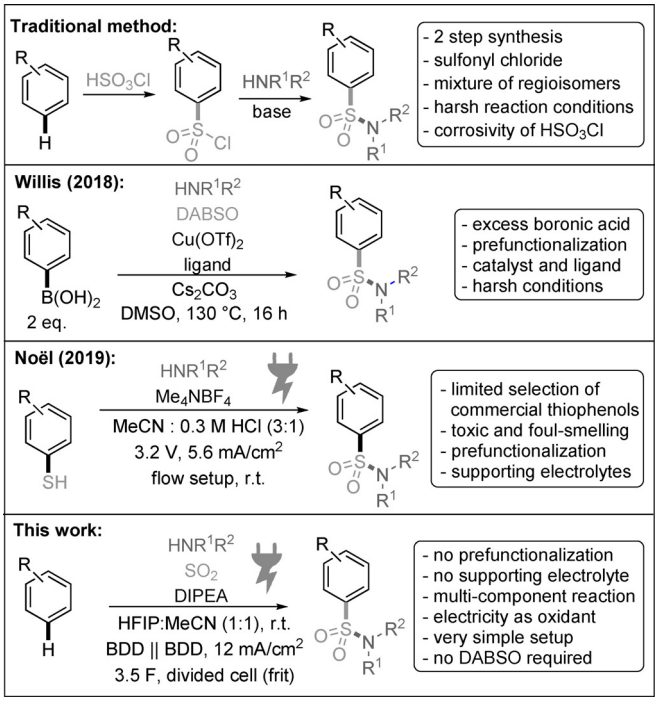
Sulfonamides exhibit unique antibacterial properties[1–3] and are classified as "highly important antimicrobials" by WHO.[4] Gerhard Domagk was awarded the Nobel prize in 1939 for introducing them as antibacterial chemotherapeutic agents.[2] Even though sulfonamides rarely occur in nature,[5–7] it was later on discovered that they reveal numerous other biological activities.[8,9] Anti-tumoral,[10] anti-obesity,[11] and anti-inflammatory[8,12] activity are just a few examples.

The protease inhibitor Fosamprenavir (**1**) is an anti-HIV prodrug (Scheme 1).[13,14] Hydrochlorothiazide (**2**) is used against high blood pressure.[14,15] The vasodilatory drug Sildenafil (**3**) became well-known for the treatment of erectile dysfunction[14,16] and Probenecid (**4**) is a well-established drug to medicate gout.[14,17] Additionally, sulfonamides are common chemical motifs in agrochemicals,[5,18] plasticizers,[19] dyes/pigments,[20] and polymers.[21] The high chemical and metabolic stability[6,7,22] combined with the interesting physicochemical properties[23] makes sulfonamide functionalities highly important in bioactive molecules.[3,22] For this reason, extensive research effort has been put into the development of more efficient syntheses of sulfonamides.[24]

Traditionally, sulfonamides are directly prepared by reaction of an amine with a sulfonyl chloride (Scheme 2). However, sulfonyl chlorides are moisture-sensitive[25] and many may not be amenable to long-term storage.[3] They can be obtained by treatment of chlorosulfuric acid with the corresponding aromatic compound. Harsh reaction conditions and multiple equivalents[26] of the corrosive chlorosulfuric acid are often required and the selectivity is limited to the inherent reactivity of the aromatic compound, which can result in regioisomer mixtures.[27,28] An interesting alternative method was reported by Willis and co-workers featuring the Cu^{II}-catalyzed synthesis of sulfonamides starting from the corresponding arylboronic acid with DABSO as SO_2 source.[6] However, harsh reaction conditions, the cost of DABSO, necessary prefunctionalization of the arene and excess of the boronic acid component are drawbacks in this approach. Just recently, Noël and co-workers published the electrochemical conversion of thiophenols to sulfonamides in presence of an amine.[7] Despite the convergent nature, this methodology suffers from certain disadvantages, such as the need of



Scheme 1. Sulfonamide-containing drugs.



Scheme 2. Selected strategies for the synthesis of sulfonamides. DABSO = 1,4-diazabicyclo[2.2.2]octane–bis(sulfur dioxide) adduct; DIPEA = *N*,*N*-diisopropylethylamine.

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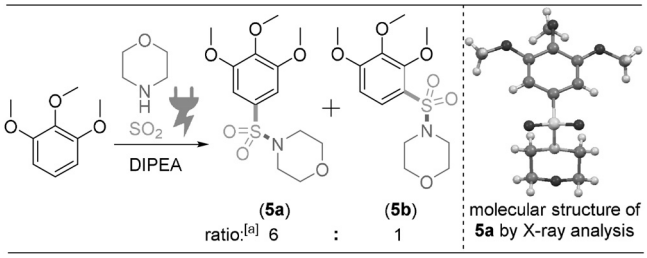
a supporting electrolyte. Furthermore, thiophenols are considered air sensitive, toxic and foul-smelling and only a limited selection is available commercially.[29] In the past decades, numerous other publications dealing with sulfonamide syntheses were reported.[3,22,27,30,31] Once again, all methods are based on prefunctionalized scaffolds. Herein, we present the first one-step synthesis of sulfonamides, directly from (hetero)arenes, SO_2, and amines in a multi-component reaction via electrochemical C–H activation.[32] An amine and SO_2 are proposed to form the amidosulfinate intermediate, which takes a dual role as nucleophile and supporting electrolyte. The feedstock chemical SO_2[31,33] is incorporated into the substrate in an atom-economical way, avoiding the use of expensive SO_2 surrogates. Inexpensive electricity serves as "green" oxidant—electrochemical reactions in general are considered sustainable, inherently safe, and scalable.[34,35] BDD electrodes[36] and the solvent 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP),[37] important to the success of this transformation, enable novel electrochemical reactivity.[38] Moreover, the robustness of such transformations[39] and the long life-time of BDD electrodes[40] in combination with the possibility of HFIP recovery[35,41] make this approach even more environmentally friendly. Just recently, our group reported the electrochemical synthesis of alkyl arylsulfonates from arenes, alcohols, and SO_2 in a multi-component reaction,[28] and this encouraged us to explore the possibility of a direct electrochemical synthesis of sulfonamides.

Guided by our previous studies on arylsulfonates,[28] we chose 1,2,3-trimethoxybenzene as arene model substrate for reaction optimization in combination with morpholine as amine. We were delighted to observe the formation of the desired sulfonamide as two regioisomers **5a** and **5b** in a 6:1 ratio as depicted in Scheme 3. Reaction optimization showed that a 1:1 solvent mixture of HFIP/MeCN was superior (Table 1, entry 1) in comparison to excess HFIP (Table 1, entry 2) or excess MeCN (Table 1, entry 3). HFIP/DMSO (1:1) proved to be unsuitable for this reaction (Table 1, entry 4), whereas HFIP/CH_2Cl_2 (1:1) gave 57% combined yield (Table 1, entry 5). Electrolysis in undivided cells resulted in lower product formation (Table 1, entry 6). Slight increase of the SO_2 concentration to 1.5 M (Table 1, entry 7) had no significant influence on the reaction. Likewise, the increase to 12 mA cm^{-2} current density also did not show any remarkable difference (Table 1, entry 8). The modulation of the applied amount of charge to 3.5 F increased



Scheme 3. General reaction scheme for the electrochemical synthesis of sulfonamides during the optimization process. [a] The 6:1 regioisomeric ratio was determined according to the crude NMR of entry 9 (Table 1).

Table 1: Optimization reactions of the model substrates.

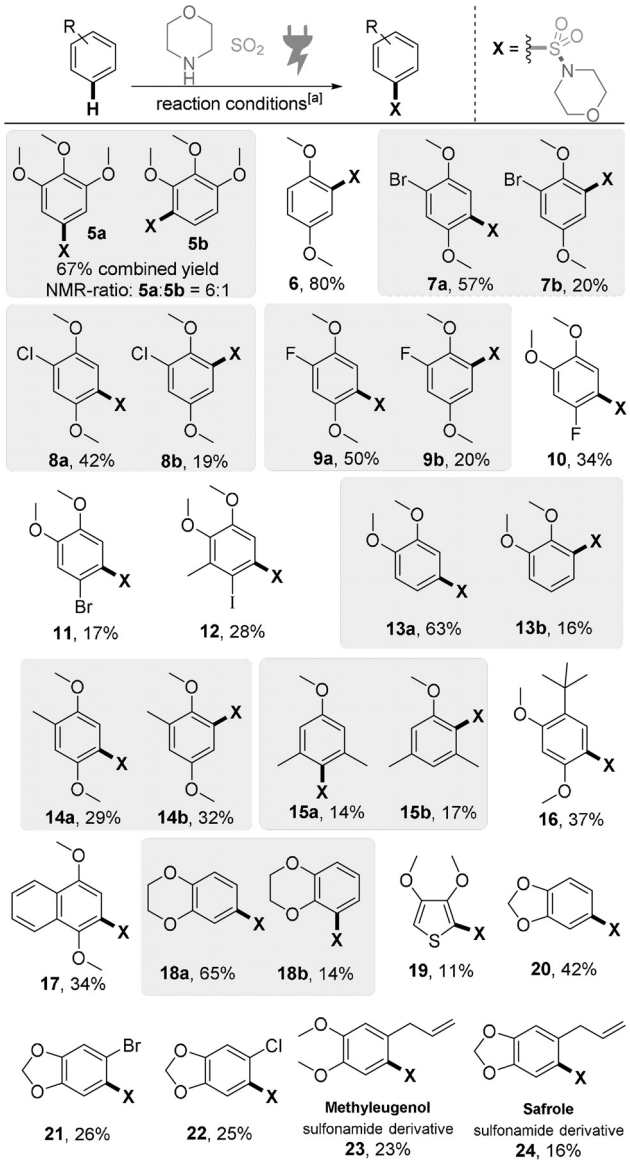
Entry	Deviation from the standard conditions[a]	Yield [%][b]
1	none	54
2	HFIP/MeCN (9:1)	39
3	HFIP/MeCN (1:9)	traces
4	HFIP/DMSO (1:1)	traces
5	HFIP/CH_2Cl_2 (1:1)	57
6	undivided cell	13
7	1.5 M SO_2	53
8	1.5 M SO_2, 12 mA cm^{-2}	55
9	1.5 M SO_2, 12 mA cm^{-2}, 3.5 F	72
10	1.5 M SO_2, 12 mA cm^{-2}, 5.5 F	40
11	1.5 M SO_2, 12 mA cm^{-2}, 3.5 F, no DIPEA	31
12	1.5 M SO_2, 12 mA cm^{-2}, 3.5 F, Pt electrodes	59
13	1.5 M SO_2, 12 mA cm^{-2}, 3.5 F, graphite electrodes	49
14	1.5 M SO_2, 12 mA cm^{-2}, 3.5 F glassy carbon electrodes	72
15	1.5 M SO_2, no electricity	0

[a] Standard conditions: 1,2,3-trimethoxybenzene (0.6 mmol, 0.1 M), morpholine (3 eq.), DIPEA (4 eq.), SO_2 (1.2 M), HFIP/MeCN = 1:1 (vol%), r.t., divided cell (glass frit), BDD electrodes, j = 7 mA cm^{-2}, Q = 2.5 F. [b] Combined yield of **5a** and **5b** determined by internal NMR standard (1,3,5-trimethoxybenzene); DMSO = dimethylsulfoxide.

the yield to 72% (Table 1, entry 9), though 5.5 F resulted in less product formation due to overoxidation of the sulfonamide (Table 1, entry 10). Omitting of DIPEA decreased the yield and resulted in lower conductivity of the electrolyte (Table 1, entry 11). Graphite and platinum electrodes (Table 1, entries 12 and 13) provided worse results, but it is noteworthy that glassy carbon showed similar reactivity compared to BDD electrodes (Table 1, entry 14). No product was found when the electricity was omitted (Table 1, entry 15). Finally, the conditions from Table 1, entry 9 were chosen for further reactions.

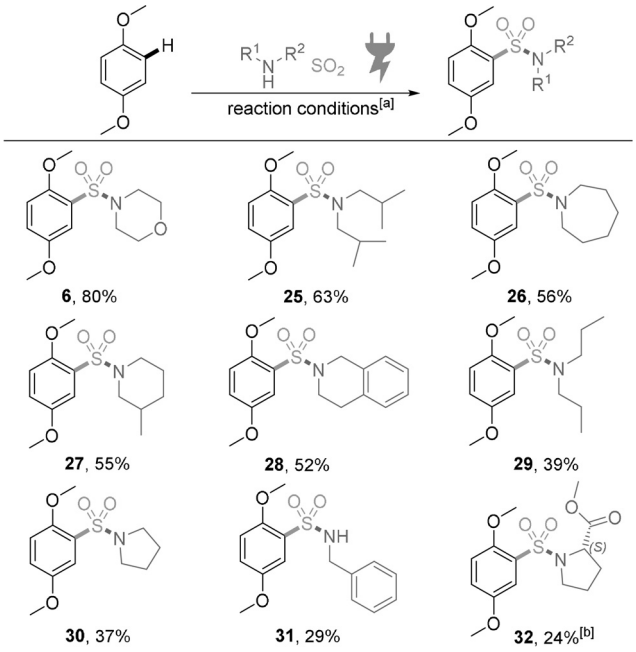
After completion of the optimization process, the substrate scope was expanded in regard to different arenes in combination with morpholine (Scheme 4). Amazingly, sulfonamide **6** was isolated in 80% yield. Remarkably, bromo, chloro, fluoro, and iodo substituents were tolerated in **7a/7b**–**12**, which provides an opportunity for further functionalization via metal-catalyzed coupling reactions.[42] The sulfonamide derivatives (**13a/13b**) of veratrole were obtained in 79% combined yield.

Two further regioisomers with roughly the same ratio were formed with 2-methyl-1,4-dimethoxybenzene as starting material, giving **14a/14b** in 61% combined yield and anisole derivatives **15a/15b** were obtained in 31% yield. The sulfonamides **16** (37%) and **17** (34%) were in similar yield range, whereas benzodioxane derivatives **18a/18b** gave 79%. Thiophene-derived heterocyclic structure **19** only provided 11% yield and benzodioxole derivative **20** gave 42%. Further halogen-containing benzodioxoles provided lower yields (**21**, 26%; **22**, 25%). Finally, two natural products (methyleugenol and safrol) containing potentially sensitive alkene functionality were successfully converted to their sulfonamide derivative (**23**, 23%; **24**, 16%). In general, less electron-rich arenes were ineligible for this reaction.



Scheme 4. Sulfonamide substrate scope of different (hetero)arenes. Grey background: isolated regioisomers. [a] Reaction conditions: arene substrate (0.6 mmol, 0.1 M), morpholine (3 equiv.), DIPEA (4 equiv.), SO_2 (1.5 M), HFIP/MeCN = 1:1, divided cell (glass frit), r.t., BDD electrodes, $j = 12\ mA\,cm^{-2}$, $Q = 3.5$ F.

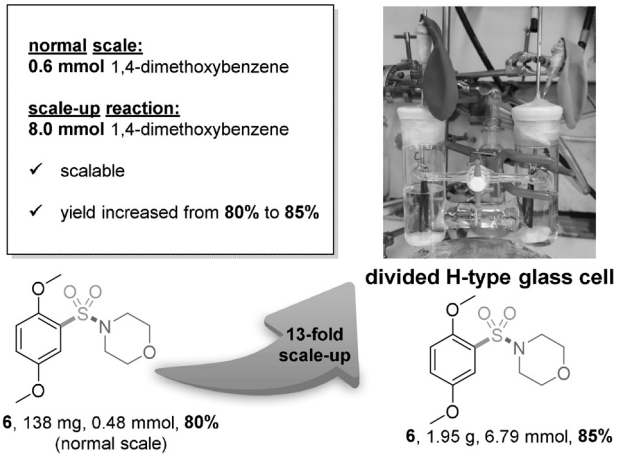
Thereupon, the amine substrate scope was investigated by using 1,4-dimethoxybenzene as arene substrate (Scheme 5). Several secondary amines were implemented, such as diisobutylamine, which provided sulfonamide **25** (63%). Comparable yields ranging from 52–56% (**26**, 56%; **27**, 55%; **28**, 52%) were achieved with azepine, 2-methylpiperidine, and tetrahydroisoquinoline. Dipropylamine and pyrrolidine provided slightly lower yields (**29**, 39%; **30**, 37%). Primary amines in general suffered from poor conversion. However, benzylamine derivative **31** was isolated in 29% yield. Sulfonamide **32** with L-proline methyl ester hydrochloride as amine substrate was obtained in 24% yield (the lower yield is potentially due to precipitation of the amine–SO_2 complex in the electrolyte). A list of substrates that were tried can be retrieved from the Supporting Information.



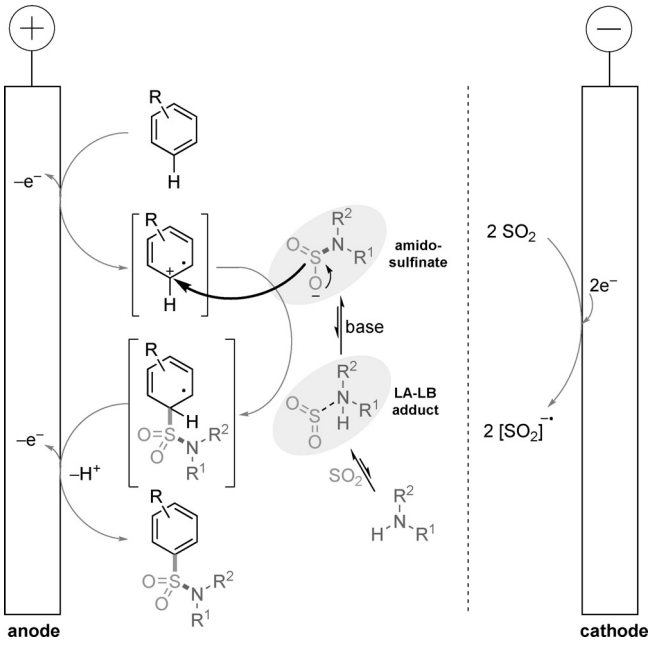
Scheme 5. Sulfonamide substrate scope of different amines. [a] Reaction conditions: 1,4-dimethoxybenzene (0.6 mmol, 0.1 M), amine substrate (3 equiv.), DIPEA (4 equiv.), SO_2 (1.5 M), HFIP/MeCN = 1:1, divided cell (glass frit), r.t., BDD electrodes, $j = 12\ mA\,cm^{-2}$, $Q = 3.5$ F; [b] L-proline methyl ester hydrochloride (3 equiv.) and DIPEA (5 equiv.) were used.

Next, the scalability of the reaction was investigated. A simple H-type glass cell, divided by a glass frit (Scheme 6), was used for this purpose. The synthesis of **6** was scaled up from 0.6 mmol to 8.0 mmol (13-fold increase). To our delight, the yield of this reaction increased to 85% in this scale-up reaction with 1.95 g isolated product.

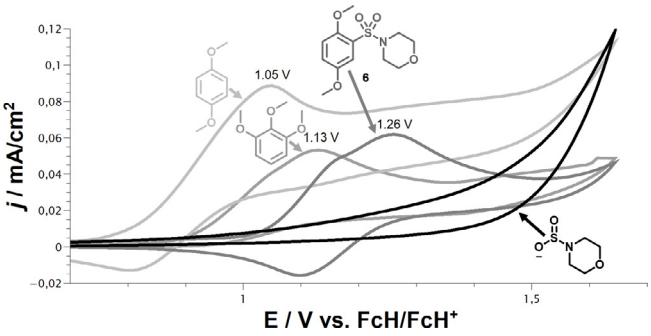
Finally, the reaction mechanism was considered. Sulfur dioxide and the amine form Lewis acid–base adducts, generating amidosulfinates in an equilibrium reaction after deprotonation by an organic base (Scheme 7). Likewise,



Scheme 6. Scale-up reaction. Comparison between screening cell (normal scale) and H-type glass cell (scale-up reaction).



Scheme 7. Postulated reaction mechanism.



Scheme 8. Cyclic voltammetry results. Black graph: morpholine (0.3 M), DIPEA (0.4 M), SO_2 (1.5 M), HFIP/MeCN = 1:1.

Willis and co-workers considered this species as nucleophile in their studies (Scheme 2).[6] The formation of an amine–SO_2 complex is well described in the literature.[43] However, complexes of triethylamine or DIPEA with SO_2 are relatively unstable.[31,44] Furthermore, the presence of HFIP could weaken the S–N interaction, so that DIPEA takes the role as base in this reaction also leading to deprotonation of HFIP, which is considered as additional supporting electrolyte[45] and protonation probably also minimizes competitive oxidation of DIPEA. In general, sterically hindered amine substrates with weaker S–N interaction, such as dibenzylamine or 2,2,6,6-tetramethylpiperidine, did not perform well in this reaction. We conclude that only amines with stronger dative bonds to SO_2 are eligible for this protocol.

The proposed mechanism of the electrochemical sulfonamide synthesis proceeds via initial anodic oxidation of the arene substrate to form the radical cation intermediate (Scheme 7). Subsequent nucleophilic attack of the amidosulfinate, followed by a second oxidation step, provides the sulfonamide. As cathodic reaction, SO_2 reduction was identified in our previous work.[28] Therefore, undivided cells are ineligible due to anodic reoxidation of the reduced SO_2 species resulting in significant lower overall current efficiency.

Additionally, cyclic voltammetry studies were executed in order to support the proposal of the reaction mechanism (Scheme 8). The oxidation potentials of 1,4-dimethoxybenzene (1.05 V) and 1,2,3-trimethoxybenzene (1.13 V) indicate the initial anodic oxidation of the arene substrate when comparing to the amidosulfinate species (black graph), which determines the electrochemical potential window. The increased oxidation potential of **6** (1.26 V) in comparison to 1,4-dimethoxybenzene is in accordance with the electron-withdrawing sulfonamide substituent.

In conclusion, we have developed the first single-step dehydrogenative synthesis of sulfonamides from non-pre-functionalized electron-rich (hetero)arenes, SO_2, and amines. Highlights of this reaction are the use of inexpensive electricity as "green" oxidant, as well as no necessity of any additional supporting electrolyte. In situ formed amidosulfinates perform a dual role as nucleophile and electrolyte. The direct use of SO_2 from a stock solution increases the atom economy of this reaction in comparison to expensive SO_2 surrogates such as DABSO. Regarding the mechanism of the reaction, direct anodic oxidation of the (hetero)arene is proposed to initiate the reaction based on the CV data. In total, 36 different products were isolated, showing the full potential of this novel reaction. Importantly, fluoro, chloro, bromo, and iodo substituents are tolerated providing complementarity to transition metal-catalyzed reactions. Scalability of the reaction has been demonstrated by a 13-fold scale-up.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: electrochemistry · green chemistry · oxidation · radical reactions · sulfonamides

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