COMMUNICATION

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Selective hydrogen isotope exchange on sulfonamides, sulfilimides and sulfoximines by electrochemically generated bases†

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We present a mild, metal-free electrochemical method to selectively add deuterium to the position α of the sulfur atom in sulfonamides, sulfilimides, and sulfoximines using a simple two-electrode setup under galvanostatic conditions. Our method is based on readily available NMR solvent DMSO-d_6 as the deuterium source and reusable glassy carbon electrodes. A low current density ensures functional group tolerance and enables selective incorporation of deuterium into pharmaceutically relevant moieties. With deuterium incorporation up to 97% the method stands out as a new possibility to label molecules electrochemically without the use of toxic and expensive transition-metal catalysts.

Introduction

Isotopic labelling of molecules is a powerful tool in life sciences and a well-known technique in chemistry.[1–6] The hydrogen isotope deuterium has a prominent role in isotopic chemistry.[7–12] Moreover, during the last decade the labelling of drug candidates with deuterium has been used to create improved pharmacological properties.[13–15] With deutetrabenazine as the first deuterated drug to be approved by the Food and Drug Administration (FDA) in 2017, showing enhanced metabolic stability, a new era in drug development was activated.[15,16] Lately, deuruxolitinib was also approved by the FDA, with this drug possessing not only better metabolic features but also possessing enhanced inhibition of the respective kinase, which further displays the emerging opportunities related to stable isotope labelling of drug candidates with deuterium.[17,18] Electrosynthesis as a technique has undergone

a renaissance over the last two decades.[19–26] Using electrochemistry as a method in chemical reactions is widely shown to open the possibilities to avoid, for example, transition and rare metals, and toxic or expensive reagents. Additionally, electrochemistry is reported to be an inherently safe method.[23,27,28] Exploiting chemical modifications regarding the pharmacological properties of a potential drug candidate by deuteration requires selective incorporation into the molecule. Several approaches for selective hydrogen isotope exchange (HIE) reactions have been established.[11,14,29–31] Although there are HIE reaction techniques known using acid or base catalysis,[12,32–41] transition-metal catalysis[42–50] is often employed. Sulfur-containing molecules represent a class of substances with broad application in drug research and chemical synthesis.[51–54] Initially developed as antibiotics,[55–57] scaffolds with a sulfonamide functionality are nowadays found in, for example, anti-cancer agents,[58–60] or in treatments for Alzheimer's disease[61–63] or migraine.[64–66] Additionally, sulfoximines have emerged as a highly promising functional group with growing significance in academia as well as in the pharmaceutical and agrochemical industry.[67–69] Sulfilimides are widely utilized in organic chemistry.[70–72] Furthermore, they can serve as key synthetic intermediates forming the respective tetravalent sulfur species.[73–75] However, the ease of oxidation presents challenges in the HIE reaction of these molecules. Some reports of HIE with sulfur-containing molecules have already been reported (see Fig. 1). Chen demonstrated HIE of sulfones and sulfoxides by applying the base barium oxide (BaO) and deuterium water (D_2O),[12] whereas Hevia reported recently the labelling of activated positions in molecules, including in position α to sulfoxide and dithiane units, by using sodium hexamethyldisilazane (NaHMDS) in DMSO-d_6.[76] Recently, Sawama described the α-deuteration of thioethers by using photochemistry.[77] Kerr established a method using an Ir(I) catalyst for the deuterium incorporation at the methyl functionality of sulfoximines.[31] Nevertheless, we were motivated to find a general electrochemical method without the use of transition-metals for a widespread scope of sulfur containing molecules.

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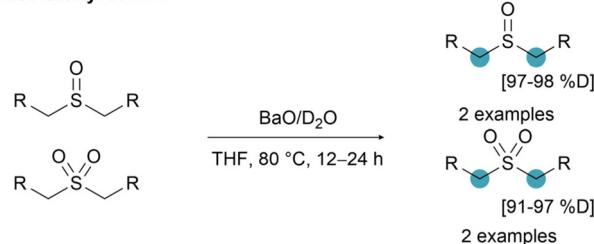
Base-catalyzed HIE

Ir-catalyzed HIE
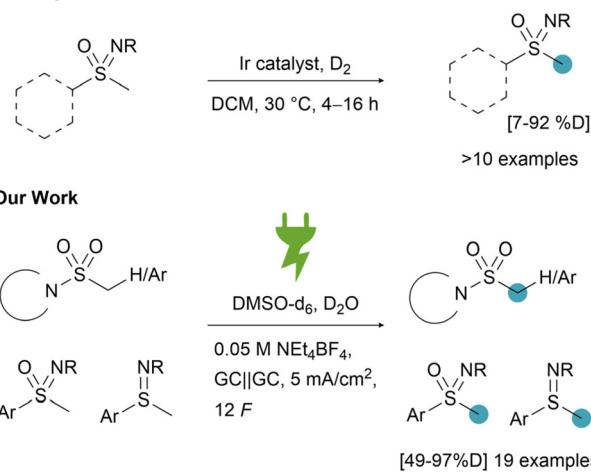
Our Work

Fig. 1 Previous work on base-catalysed hydrogen isotope exchange (HIE) reaction on sulfur-involving compounds,[12] by using transition-metal catalysis[31] and our electrochemical method to deuterate sulfonamides, sulfilimides and sulfoximines.

Table 1 Deuterium incorporation into **1** with our method and achieved deuterium incorporation with deviations in the reaction conditions

Entry	Deviation from optimised conditions	Deuterium incorporation (%D)
1	None	96
2[a]	DMAc-h_9 (instead of DMSO-d_6), D$_2$O (200 eq.)	81
3[a]	DMF-h_7 (instead of DMSO-d_6), D$_2$O (200 eq.), 4 F	60
4[a]	DMSO-h_6, D$_2$O (200 eq.)	58
5[a]	D$_2$O (no DMSO-d_6, 5 mL)	—
6[a]	No D$_2$O	90
7[a]	Addition of 1 vol% MeOD-d_4	95
8[b]	Graphite electrodes	94
9[b]	Graphite foil electrodes	7
10[b]	Graphite felt electrodes	93
11[a]	Recycled DMSO-d_6	77
12[a]	Stirring at doubled speed	39
13[a]	No electricity	—

Reaction conditions unless indicated otherwise: 0.25 mmol **1**, 0.25 mmol Et$_4$NBF$_4$ in 5 mL DMSO-d_6 and 50 μL D$_2$O as the solvent and deuterium source. Electrochemical reactions were performed using glassy carbon electrodes as anode and cathode, 5 mA cm^{-2}, 12 F. After confirmation of the position of deuterium incorporation via ^{1}H NMR the incorporation was determined via UPLC-MS in accordance with the ^{1}H NMR data. [a] 0.1 M NEt$_4$BF$_4$ used. [b] In the experiments corrosion of the cathode was visible (see Fig. S2†).

Results and discussion

Optimisation of the deuterium incorporation into sulfonamide 1

The screening and optimisation experiments were conducted in 5 mL glass cells, allowing a quick electrochemical study.[78–80] Electrochemical studies demonstrated that the position α to the sulfur atom in a simple sulfonamide (**1**) can be activated and subsequently deuterated during electrolysis, using D$_2$O (200 eq.) as the deuterium source. This process occurs in a non-deuterated polar solvent such as dimethyl-acetamide (DMAc-h_9, 81%D, Table 1, entry 2), dimethyl-formamide (DMF-h_7, 60%D, Table 1, entry 3), or dimethyl-sulfoxide (DMSO-h_6, 58%D, Table 1 entry 4). Interestingly, HIE reactions in D$_2$O alone did not show any deuteration (Table 1, entry 5). After screening different polar aprotic solvents, DMSO-h_6 was chosen as the solvent due to its reduced toxicity compared to the other solvents and availability from biogenic origin (Kraft pulping process).[81,82] However, reactions in non-deuterated DMSO-h_6 provided suboptimal results, likely due to partial deuteration of the solvent. Consequently, we opted to switch to the readily available and cost-effective deuterated solvent DMSO-d_6. We initially evaluated electrochemical parameters, including current density and the amount of applied charge (Fig. 2A). As the current density was increased (ranging

from 2.5 to 50 mA cm^{-2}), deuterium incorporation slightly decreased, while the ^{1}H NMR yield remained constant. The highest deuterium incorporation (75%D) was observed at 2.5 mA cm^{-2}. However, due to a shortened reaction time, we chose to proceed with 5 mA cm^{-2} (73%D). Subsequently, the amount of applied charge was assessed, ranging from 1 to 16 F. Deuterium incorporation increased up to 12 F (90%D). Next, the concentration of the supporting electrolyte NEt$_4$BF$_4$ was studied (Fig. 2B). Using 0.05 M NEt$_4$BF$_4$, corresponding to one equivalent of substrate **1**, did not significantly affect deuterium incorporation compared to the previously used 0.1 M NEt$_4$BF$_4$. Lowering the supporting electrolyte concentration further resulted in slightly lower deuterium incorporation, so 0.05 M NEt$_4$BF$_4$ was selected. Additionally, we discovered, that adding small amounts of D$_2$O and MeOD-d_4 increased deuterium incorporation (Table 1, entries 1 and 7). D$_2$O was chosen as an attractive additive due to the low cost. The effect of D$_2$O concentration was then evaluated. Increasing the amount of D$_2$O from 1 vol% (96%D) to 5–10 vol% (90–91%D) led to a slight decrease in deuterium incorporation, as did reducing the additive concentration to 0.1 vol% (89%D). Various carbon-based electrode materials were tested (Table 1, entries 8–10). While other carbon-based materials such as isostatic graphite (94%D, Table 1, entry 8) or graphite felt (93%D, Table 1, entry 10) performed as good as glassy carbon, cor-

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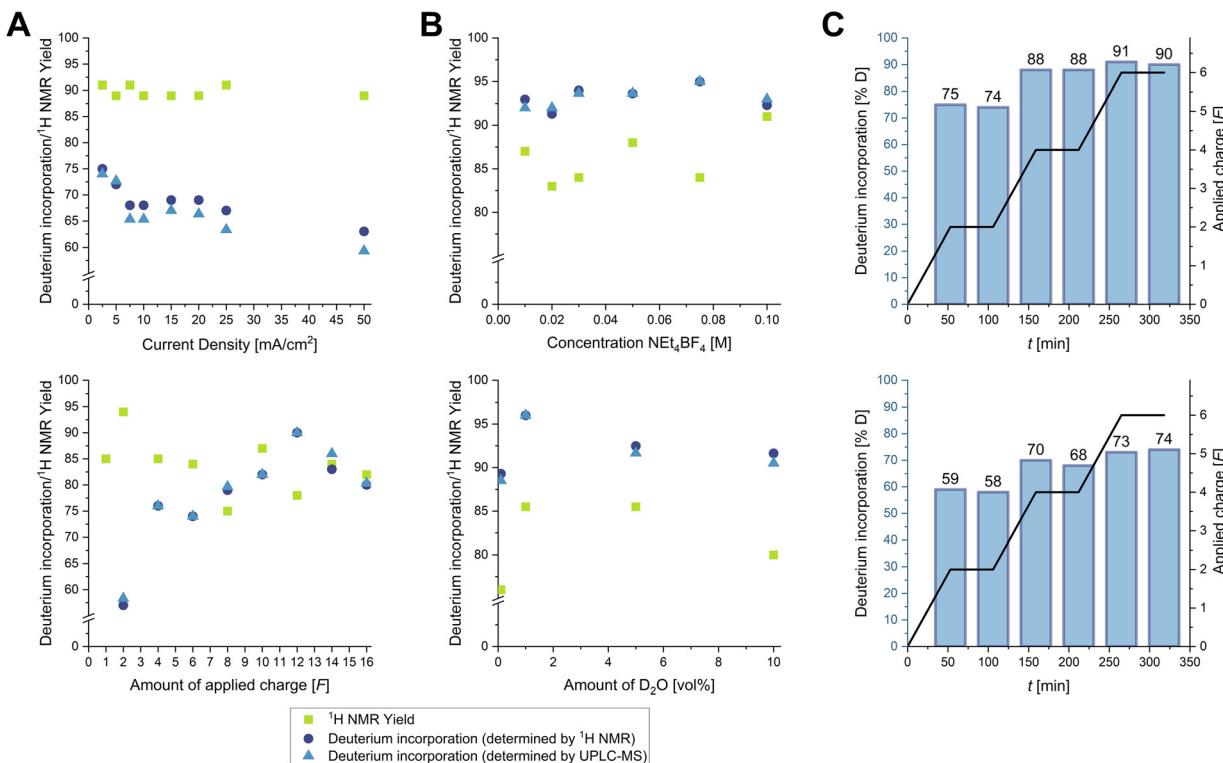
Fig. 2 Optimisation of the reaction parameters. (A) Screening of electrochemical parameters. Current density screening: 0.25 mmol **1**, 0.1 M NEt$_4$BF$_4$, 5 mL DMSO-d_6, 2.5–50 mA cm^{-2}, 4 *F*, glassy carbon as anode and cathode. Amount of applied charge screening: 0.25 mmol **1**, 0.1 M NEt$_4$BF$_4$, 5 mL DMSO-d_6, 5 mA cm^{-2}, 2–14 *F*, glassy carbon as anode and cathode. (B) Screening of electrolyte composition. Screening of supporting electrolyte concentration: 0.25 mmol **1**, 0.01–0.1 M NEt$_4$BF$_4$, 5 mL DMSO-d_6, 50 µL D$_2$O, 5 mA cm^{-2}, 12 *F*, glassy carbon as anode and cathode. Screening of the amount of D$_2$O (additive): 0.25 mmol **1**, 0.05 M NEt$_4$BF$_4$, 5 mL DMSO-d_6, 0.1–10 vol% D$_2$O, 5 mA cm^{-2}, 12 *F*, glassy carbon as anode and cathode. ^{1}H NMR yields determined by using mesitylene (13.7 mg, 0.11 mmol) as an internal standard. (C) On–off-screening of electricity. 0.25 mmol **1**, 0.1 M NEt$_4$BF$_4$ in 5 mL DMAc and 0.9 mL D$_2$O (upper graph) or 5 mL DMSO-d_6 (lower graph), 5 mA cm^{-2}, in total 6 *F* and 150 min of reaction time without electricity in a cycle, glassy carbon as anode and cathode.

rosion of the electrodes was visible after the reaction for isostatic graphite, carbon felt and graphite foil. DMSO-d_6 was shown to be recyclable with a small decrease in deuterium incorporation (77%D, Table 1, entry 11). The optimised reaction parameters for the synthetic scope were established as follows: 12 *F* of applied charge, 5 mA cm^{-2} current density, glassy carbon electrodes, an electrolyte composed of 5 mL DMSO-d_6, 50 µL D$_2$O as an additive, and 0.05 M NEt$_4$BF$_4$ as the supporting electrolyte. For all optimisation and scope experiments, the same set of glassy carbon electrodes were used, cleaned with solvents in between of experiments, demonstrating the excellent reusability of this metal-free electrode material.

Mechanistical discussions

An aim of our investigation was to gain a deeper understanding of the mechanisms underlying the deuteration reaction by studying **1** through cyclic voltammetry experiments, using DMAc as the solvent and NEt$_4$BF$_4$ as the supporting electrolyte. However, the results showed no electrochemical activity of **1** within the electrochemical window of the electrolyte. Instead, the experiments revealed electrochemical activity attributed solely to the electrolyte in the absence of **1** (see ESI†).

Electrochemical base generation has been studied by several groups.[83–90] Therefore, we used this basis as a starting point for mechanistical investigation of our reaction. Experiments conducted using D$_2$O as the solvent (Table 1, entry 5) showed no deuteration, highlighting the necessity of DMSO, DMAc or DMF for the reaction. We also observed a decreased deuterium incorporation with increased stirring rate (Table 1, entry 12), suggesting that the reaction likely involves a locally generated base species facilitating the deuteration. To further investigate the mechanism, we conducted studies in an on–off setup (Fig. 2C). When 2 *F* of current was applied, **1** underwent deuteration in both the DMAc/D$_2$O (upper graph) and DMSO-d_6 (lower graph) system. After additional stirring for the equivalent time of 2 *F* without any current applied, no further deuterium incorporation was observed. Subsequent experiments involving two additional cycles produced consistent results regarding deuterium incorporation. These findings, showing deuteration only during application of electrical current, emphasise the requirement for electricity in the reaction. Based on this, we propose an electricity-driven, base-catalysed mechanism occurring in the vicinity of the electrode.

6528 | *Org. Biomol. Chem.*, 2025, **23**, 6526–6532

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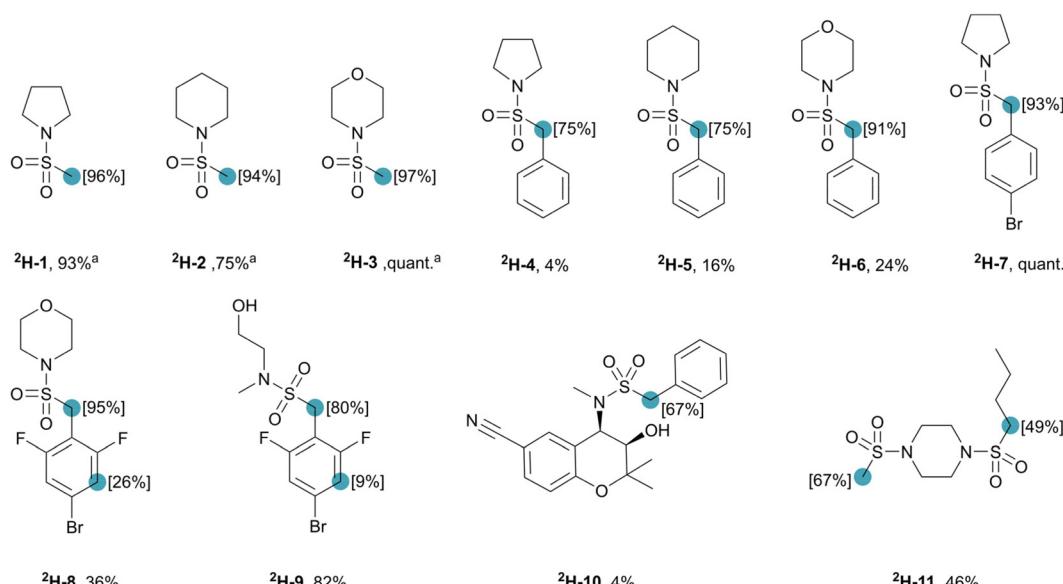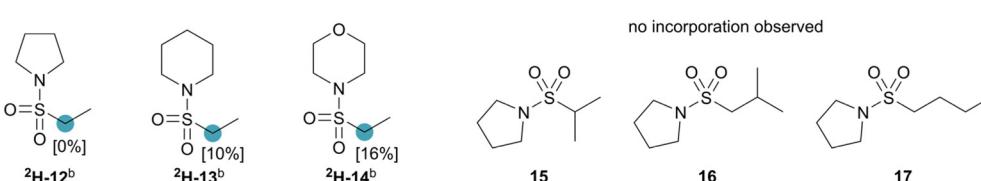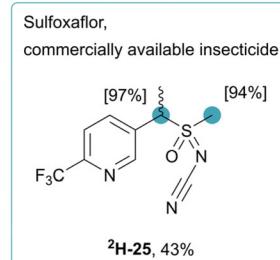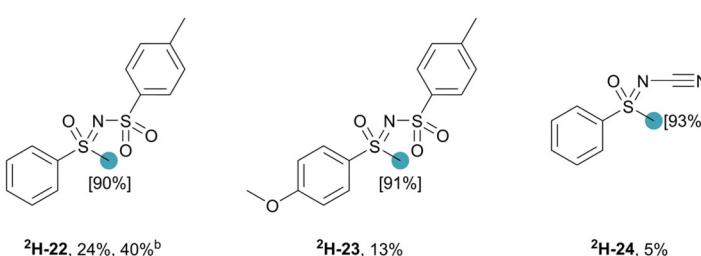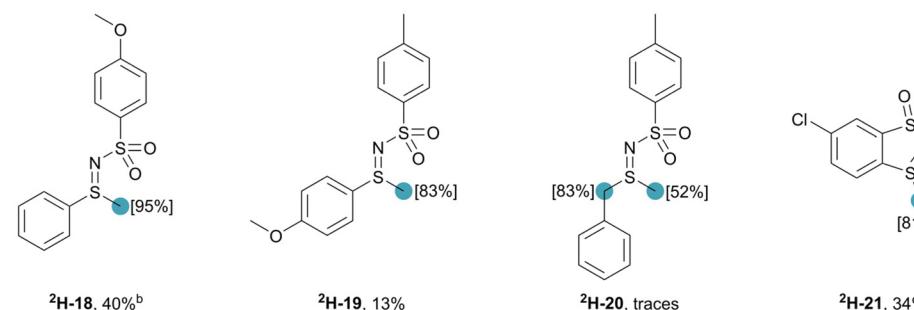
Fig. 3 Scope of the presented HIE method. If not stated otherwise: 0.25 mmol **1–25**, 0.05 M NEt$_4$BF$_4$, 5 mL DMSO-d_6, 50 μL D$_2$O, 5 mA cm^{-2}, 12 F glassy carbon as anode and cathode. ^{a} Yields representing ^{1}H NMR yields using mesitylene (13.7 mg, 0.11 mmol) as an internal standard. ^{b} 4.1 mL DMAc, 0.9 mL D$_2$O used as the solvent and deuterium source.

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Org. Biomol. Chem., 2025, **23**, 6526–6532 | **6529**

Scope and limitations

We selected further C–H active compounds to study the scope and limitations of our method. In addition to methyl-sulfonamides with functional modifications in the heterocyclic ring, we also screened benzylsulfonamides with diverse modifications in both the heterocyclic ring and the aryl group. Moreover, sulfilimides and sulfoximines were chosen as substrates due to their significance in the chemical and pharmaceutical industry. Several sulfonamides **1–11** were deuterated with good to excellent deuterium incorporations. The methyl-sulfonamides **1–3** showed deuterium incorporation of >94%D while the benzylsulfonamides **4–10** were deuterated with good to very good deuterium incorporation (67–95%D). Interestingly, the deuterium incorporation increased from pyrrolidine **4** and piperazine **5** (75%D) to morpholine **6** (91%D) indicating the influence of the heterocycle to the reaction. However, the isolated yields of **4–6** need to be improved in the future. For **4** we observed degradation of the compound in the ^{1}H NMR spectrum of the crude reaction mixture. However, comparing these results to monobrominated **7** we observed a higher deuterium incorporation (93%D) while the yield was quantitative by a simple extraction. Polyhalogenated electron-poor aromatics were predominantly deuterated in benzylic positions (**8**: 95%D, **9**: 80%D) beside the aromatic ring (**8**: 26% D, **9**: 9%D) with much lower efficiency. Compound **9** demonstrates that open-chain sulfonamides and free alcohols are compatible with this method, achieving an isolated yield of 82%. In the more complex structure **10** deuterium incorporation of 67%D could be reached while maintaining the stereoinformation. When comparing alkyl functionalities in disulfonamide **11** we observed a deuteration both at the methyl and the butyl moiety, although the deuterium incorporation preferably occurred at the methyl (see ESI†). Interestingly, sulfilimide **20** displayed more deuterium incorporation onto the benzylic position (83%D) than at the methyl moiety (52%D). Furthermore, we expanded the scope to sulfilimides and sulfoximines. Compound **18** showed very good deuterium incorporation (95%D) with moderate isolated yields (40%) using the DMAc/D$_2$O system described in the optimisation. Sulfoximine **22** was tested both for the DMSO-d_6/D$_2$O system as well as for the DMAc/D$_2$O system. Both systems achieved good deuterium incorporation (90%D) while the isolated yield was better in the DMAc/D$_2$O system. Replacement of the tosyl protecting group for a nitrile group (**24**) achieved slightly higher deuterium incorporation (93%D) most likely because of the electron-withdrawing effect of the nitrile. However, a drawback in isolated yield was visible which could be attributed to the electrochemical reaction of the nitrile.[91–93] An electron-donating methoxy functionality at the *para*-position of the aryl group showed no decrease in deuterium incorporation for the respective sulfoximine (**23**, 91% D) and a slight decrease in deuterium incorporation for the sulfilimide (**19**, 83%D). Compound **21**, a benzodithiazol, was also successfully deuterated (81%D). With the commercially available insecticide sulfoxaflor **25** a complex agrochemical was deuterated in high efficiency in both the benzylic position (97%D) and methyl moiety (94%D) while a nitrile and trifluoromethyl moiety were tolerated. Limitations of the method are displayed with **12–17**. Deuterium incorporation into the ethyl functionalities of **12–14** was inferior to the methyl compounds. Other alkyl functionalities even showed no incorporation (**15–17**) (Fig. 3).

Conclusions

A simple and mild electrochemical method to label sulfonamides, sulfilimides and sulfoximines in position α to the sulfur is established. Readily available and inexpensive DMSO-d_6 was used as the source of deuterium and proven to be recyclable. The whole protocol is metal-free avoiding metal contaminations. Noteworthy, DMSO is a side-stream of the Kraft pulping process and therefore of biogenic origin. Employment of reusable glassy carbon electrodes thereby avoiding transition metal catalysts for the HIE reactions is very advantageous in terms of sustainability. The simple and quite common galvanostatic two-electrode setup represents a versatile and practical method for general applications. Mechanistical discussions revealed the electrochemical generation of a base that enables the deuteration and the importance of a polar aprotic solvent such as DMSO, DMAc or DMF.

Author contributions

Carla Marie Stork: Conceptualization (leading), investigation (leading), methodology (leading), supervision (supporting), project administration (supporting), writing – original draft preparation (leading). Elisabeth Glöckler: Investigation (supporting), methodology (supporting). Dr Volker Derdau: Conceptualization (supporting), supervision (supporting) writing – original draft preparation (supporting). Dr Philipp Schnieders: Conceptualization (supporting). Prof. Dr Siegfried R. Waldvogel: Conceptualization (leading), supervision (leading), project administration (leading), funding acquisition (leading), writing – original draft preparation (supporting).

Data availability

The data supporting this article have been included as part of the ESI.† All data therein are detailed and will allow an easy reproduction of the results.

Conflicts of interest

V. D. is employee of Sanofi Germany and may hold stocks and options of the company.

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6530 | *Org. Biomol. Chem.*, 2025, **23**, 6526–6532

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