nature communications

Article

https://doi.org/10.1038/s41467-024-50644-y

Electrochemical *meta*-C–H sulfonylation of pyridines with nucleophilic sulfinates

Received: 9 April 2024

Accepted: 17 July 2024

Published online: 28 August 2024

Check for updates

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Considering the indispensable significance and utilities of *meta*-substituted pyridines in medicinal, chemical as well as materials science, a direct *meta*-selective C–H functionalization of pyridines is of paramount importance, but such reactions remain limited and highly challenging. In general, established methods for *meta* C–H functionalization of pyridines rely on the utilization of tailored electrophilic reagents to realize the intrinsic polarity match. Herein, we report a complementary electrochemical methodology; diverse nucleophilic sulfinates allow *meta*-sulfonylation of pyridines through a redox-neutral dearomatization-rearomatization strategy by a tandem dearomative cycloaddition/hydrogen-evolution electrooxidative C–H sulfonation of the resulting oxazino-pyridines/acid-promoted rearomatization sequence. Besides, several salient features, including exclusive regiocontrol, remarkable substrate/functional group compatibility, scale-up potential, and facile late-stage modification, have been demonstrated, which further contributes to the practicality and adaptability of this approach.

Pyridines are among the most prevalent functionalities in medicinal and agricultural chemistry, organic synthesis, and materials science[1–7]. Direct C–H functionalization of such heteroarenes can significantly increase step economy for the synthesis and late-stage modification of related complex molecules[8,9]. Pyridine is an intrinsically electron-deficient ring with moderate reactivity toward nucleophilic substitution at *ortho*- and *para* positions and poor reactivity toward electrophilic substitution at *meta*-site. Accordingly, most established protocols for pyridine functionalization occur at *ortho*- or *para* position by virtue of its electronically biased reactivity. These protocols include directed metalation[10,11], Minisci-type radical reactions[12], and nucleophilic addition to *N*-activated pyridinium salts[13,14].

For unbiased pyridines, it is far more challenging to achieve *meta*-selective functionalization[15–19]. Classical electrophilic aromatic substitution has been exploited for pyridine *meta*-nitration and -halogenation[20], but they suffer from harsh conditions as well as low yield and regioselectivity. Milder *meta*-functionalization reactions have also been developed by transition-metal-catalyzed non-directed C–H activation of pyridines[21–25]. Despite extensive investigation and wide synthetic application, these protocols often require elaborate, costly catalytic systems and are limited to substituted pyridine substrates. For unsubstituted pyridine, other regioisomers and even additional functionalization are usually observed as undesirable side reactions, which creates further difficulties in product purification.

To address these issues, a highly attractive temporary dearomatization strategy has recently emerged as an efficient and powerful tool for *meta*-selective C–H functionalization of pyridines[19]. This strategy converts initial pyridines into electron-rich dearomatized intermediates by a dearomatization process. The intermediates contain (di)enamine moieties and thus render the carbon in β-position to the nitrogen atom most nucleophilic. This dearomative activation mode contributes to the potent reactivity of substrates with different electrophiles, followed by subsequent rearomatization to deliver the target product. For instance, the groups of Oestreich[26] and of Wang[27–31]

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realized *meta*-selective silylation, alkylation, allylation, tri/di-fluoromethylthiolation as well as cyanation through 1,4-dihyropyridines via catalyzed reductive dearomatization. To enhance the aerobic and redox stability of dearomatized pyridine intermediates, very recently two redox-neutral dearomatization methods have been developed. Along these lines, *N*-triflated azatriene intermediates obtained by a modified Zincke reaction were initially exploited by Paton et al.[32–34] for pyridine *meta*-halogenation and later by Greaney et al.[35] for arylation. Meanwhile, Studer et al. independently accomplished halogenation and trifluoromethylation reactions via oxazino-pyridines obtained by dearomative cycloaddition[36–38]. However, all these methods focused on the utilization of electrophilic reagents for pyridine *meta*-functionalization (Fig. 1a). Using a nucleophilic partner to fulfill such transformations still remains unexplored, presumably due to the inherent polarity mismatch, although it is attractive since most reagents natively exist as their nucleophilic forms[39].

To overcome the above-mentioned shortcomings and in continuation of our interest in electrochemical C–H functionalization[40,41], we envisioned that an electrochemical method for realizing *meta*-C–H sulfonation of pyridines with nucleophilic sulfinates should be feasible for the direct construction of the *meta*-sulfonyl pyridine framework, a privileged core motif in many bioactive compounds such as intepirdine[42], alvelestat[43], G007-LK[44], as well as oxazosulfyl[45] (Fig. 1c), via capture of the generated oxazino-pyridine species by a sulfonyl radical. However, several key issues need to be considered for ensuring the target reaction as follows: a) because of their inherent electron-rich properties, both sulfinates and oxazino-pyridines might be competitively oxidized at the anode, b) the sulfonyl radicals, even if anodically generated by a single electron oxidation of sulfinates, must be swift enough to react with the dearomatized pyridines to avoid undesired potential pathways, such as overoxidation and desulfination, especially for aliphatic sulfonates, and c) although sulfonyl radicals have been mostly documented as electrophilic[46], their polarity match with oxazino-pyridines yet remains elusive. Here we report, how we addressed these concerns to successfully verify the above hypothesis. To the best of our knowledge, there has been no example of nucleophilic partners for pyridine *meta*-C–H bond functionalization under metal- and oxidant-free conditions. In addition, the resulting *meta*-sulfonyl pyridine products could serve as a fundamental synthetic platform for subsequent diversified transformations[47–54].

Results

Reaction development

Our proof-of-concept work was commenced by testing the reaction of bench-stable oxazino-pyridine **1a'** with commercial sodium benzenesulfinate ($PhSO_2Na$, **2a**) as a nucleophile under electrochemical conditions. Extensive optimization revealed that the best results were obtained if a solution of **1a'**, **2a**, and $^nBu_4NBF_4$ in a mixed solvent system of methanol and cyclopentyl methyl ether (CPME) was electrolyzed in an undivided cell equipped with graphite felt (GF) anode and platinum plate (Pt) cathode with a constant current of 5 mA for 1.5 h at room temperature. Subsequent treatment with aqueous acid at 60 °C gave the desired *meta*-sulfonated pyridine **3** with an overall yield of 73% (entry 2, Table 1). In the absence of the sulfinate, the oxazino-pyridine was fully decomposed under the electrolytic conditions (entry 1). This clearly illustrates the potential competitive oxidation of the dearomatized pyridine at the anode and thus demonstrates how challenging a selective reaction was. Mixtures of alcohols and ethers are most effective, in particular a 3:1 volume ratio of MeOH and CPME (entries 3–6). No desired product was observed in the absence of MeOH, which may have dual roles: a) improving the solubility of sulfinate salt; the use of only CPME results in incomplete dissolution; b) functioning as a proton shuttle, supported by the detection of molecular dihydrogen through headspace gas chromatography (GC) analysis (see Supplementary Fig. 14). Several electrode combinations, for example, (+)C|Pt(−) and (+)GF|GF(−) were further examined (entries 7 and 8), and the best result was obtained with (+)GF|Pt(−). Other sulfinate salts, such as $PhSO_2Li$, $PhSO_2K$, $PhSO_2Cs$, and $PhSO_2N^nBu_4$ as well as $PhSO_2NHNH_2$ were also effective, albeit in lower yields (entries 9 and 10). The reactivity difference of these sulfinate salts might be

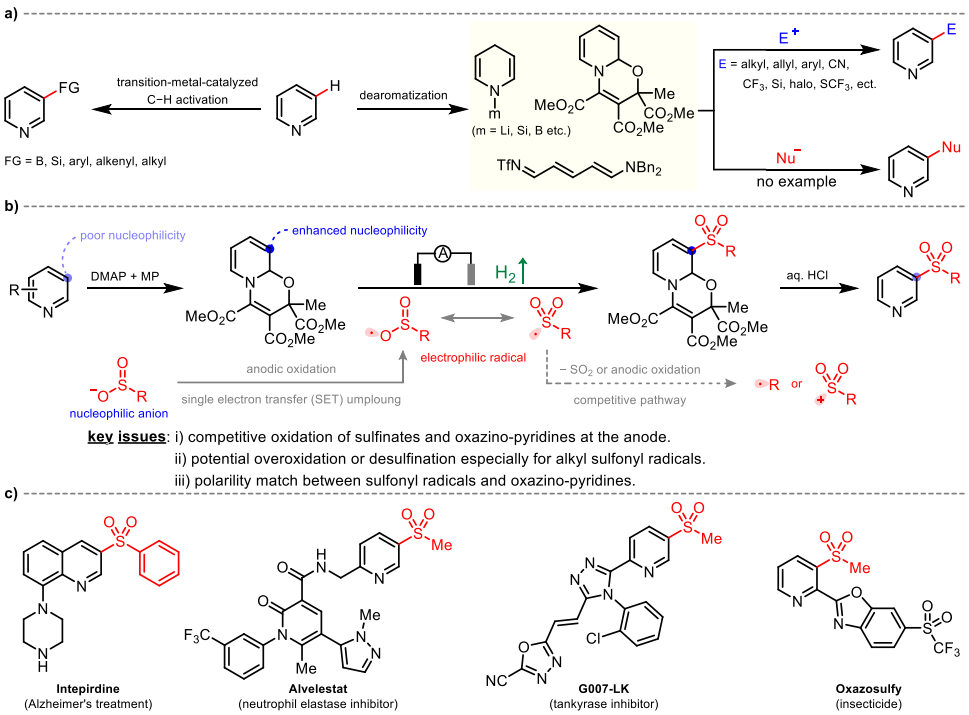
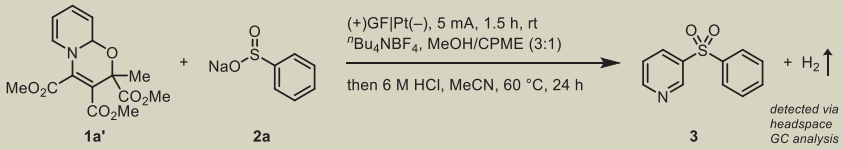


Fig. 1 | Background and motivation of pyridine *meta*-C–H functionalization. **a** Current methods for *meta*-selective C–H functionalization of pyridines. **b** This study: Proposed electrochemical *meta*-C–H sulfonation of pyridine with nucleophilic sulfinates. **c** Representative bioactive molecules featuring *meta*-sulfonated pyridines. Tf triflate, Bn benzyl, DMAP dimethyl acetylenedicarboxylate, MP methyl pyruvate, SET single electron transfer.

https://doi.org/10.1038/s41467-024-50644-y

Table 1 | Representative reaction optimization[a]



Entry	Variation from the optimal conditions	Yield of 3 (%)
1	Without **2a**	**1a'** decomp.
2	None	73
3	MeOH/MeCN (3:1) as solvent	60
4	MeOH/THF (3:1) as solvent	69
5	MeOH as solvent	68
6	CPME as solvent	<1
7	(+)C|Pt(–) as electrode	58
8	(+)GF|GF(–) as electrode	52
9	$PhSO_2Li$, $PhSO_2K$, $PhSO_2Cs$, or $PhSO_2N^nBu_4$ instead of $PhSO_2Na$	55, 64, 63, 66
10	$PhSO_2NHNH_2$ instead of $PhSO_2Na$	40
11	$PhSO_2H$ (3 equiv.) + Na_2CO_3 (1.5 equiv.) instead of $PhSO_2Na$	24
12	3 mA	22
13	7 mA	37
14	Under air	46
15	No electrolyte	45
16	No electricity	<1
17	BQ, $K_2S_2O_8$, or I_2 (2 equiv.) instead of electricity	<1, <1, 8
18	Ag_2CO_3, $Cu(OAc)_2$ or $Mn(OAc)_3{\cdot}2H_2O$ (2 equiv.) instead of electricity	<1, 15, 20

CPME cyclopentyl methyl ether, *THF* tetrahydrofuran, *C* graphite phate, *BQ* 1,4-benzoquinone.
[a]Conditions: **1a'** (0.15 mmol), **2a** (0.45 mmol), $^nBu_4NBF_4$ (0.15 mmol), MeOH/CPME (3:1, 2 mL), undivided cell with graphite felt (GF) anode (10 mm × 20 mm × 2 mm) and platinum plate (Pt) cathode (10 mm × 20 mm × 0.3 mm), constant current of 5 mA (ca. 1.9 $F{\cdot}mol^{-1}$), room temperature (25 °C), 1.5 h, under N_2; then hydrolysis with 6 mol/L HCl (5 mL) in MeCN at 60 °C for 24 h. Isolated yields.

rationalized by the interplays among the cathode electrode, electrolyte, the cation of sulfinates, and methanol solvent (related to hydrogen evolution), although the detailed mechanism remains unclear at this stage. The in-situ generated $PhSO_2Na$ from $PhSO_2H$ and Na_2CO_3 was much less efficient (entry 11). The current density is also crucial, with 5 mA being optimal. Unsatisfactory yields were obtained by either decreasing or increasing the density, which may be attributed to insufficient formation of the sulfonyl radical or unwanted oxidative degradation of the oxazino-pyridine at the anode, respectively (entries 12 and 13). The reaction yield dropped to 46% under air, likely resulting from the quenching of engaged radicals by molecular oxygen (entry 14). Removal of electrolytes occurred with moderate efficiency (entry 15). Control experiments validated that the electricity is indispensable and even uniquely efficient to spur this net-oxidation reaction; no or much lower efficiency was observed with conventional chemical oxidizing agents such as 1,4-benzoquinone (BQ), $K_2S_2O_8$, I_2, Ag_2CO_3, $Cu(OAc)_2$, and $Mn(OAc)_3{\cdot}2H_2O$ (entries 16–18 and Supplementary Table 1). This electrooxidative reaction has an excellent current efficiency of 78%, thus underlining the sustainability of the overall process.

Under the optimal electrochemical conditions, a broad range of sodium sulfinates reacted with various pyridines with perfect regioselectivity to afford *meta*-sulfonated products in moderate to good yields (Fig. 2). In all these examples, no double *meta*-sulfonation was detected. Scope with respect to the sulfinate components was tested with the simplest, unbiased pyridine as an acceptor. The established protocol is widely applicable to both electron-rich and electron-deficient aromatic sulfinates, bearing substituents in the *ortho*, *meta*, or *para* position. A wealth of common functional groups is compatible, including ether (**6**), fluoro (**8**), amide (**7, 16**), ester (**15**), keto (**14**), trifluoromethyl (**17**), and trifluoromethoxy (**18**). Oxidation-sensitive formyl and amino groups (**13, 22**) and easily reduced nitro groups (**19**) remain intact. Compounds bearing chloro (**9** and **10**), bromo (**11**), and iodo (**12**) groups reacted selectively, showcasing the orthogonality of this electrochemical process to traditional catalytic cross-couplings. Some fused (**20**–**22**) and heterocyclic sulfinates (**23**–**25**) are viable partners, as are alkenyl sulfinates. Furthermore, both primary (**27**–**31**) and secondary alkyl sulfinates (**32** and **33**) were smoothly converted *meta*-sulfonated pyridines without any detectable amount of unwanted desulfinative products, while tertiary series seemed to reach the performance limit of this process presumably due to steric hindrance (**2al** in Supplementary Fig. 10).

The scope regarding pyridine components was then examined (Fig. 2b). A wide series of electronically and sterically varied pyridines underwent *meta*-selective sulfonation in moderate to good yields. Suitable substrates range from the parent pyridine as well as 2-, 3-, 4-monosubstituted to disubstituted pyridines. It is worth noting that oxazino-pyridines bearing a substituent at the α-site delivered the δ-sulfonated product as a single isomer (**36, 37, 53**), which could be rationalized by the steric effect. When two differently substituted pyridines are presented in one molecule, the redox-neutral dearomatization shows high selectivity toward less sterically hindered pyridine, allowing a chemoselective mono-*meta*-functionalization of polypyridine compounds (**45**). Along with pyridines, quinolines (**48**) and isoquinolines (**47**) engaged in this transformation by applying the same activation strategy to prepare the sulfonated heteroarenes with complete *meta*-selectivity, although switching to graphite (C) anode seems required to ensure decent efficiency. By this electrochemical method, 8-chloro-3-(phenylsulfonyl)quinoline (**48**), a key intermediate of the potential Alzheimer's disease drug intepirdine[42], could be facilely synthesized from inexpensive 8-chloroquinoline, instead of

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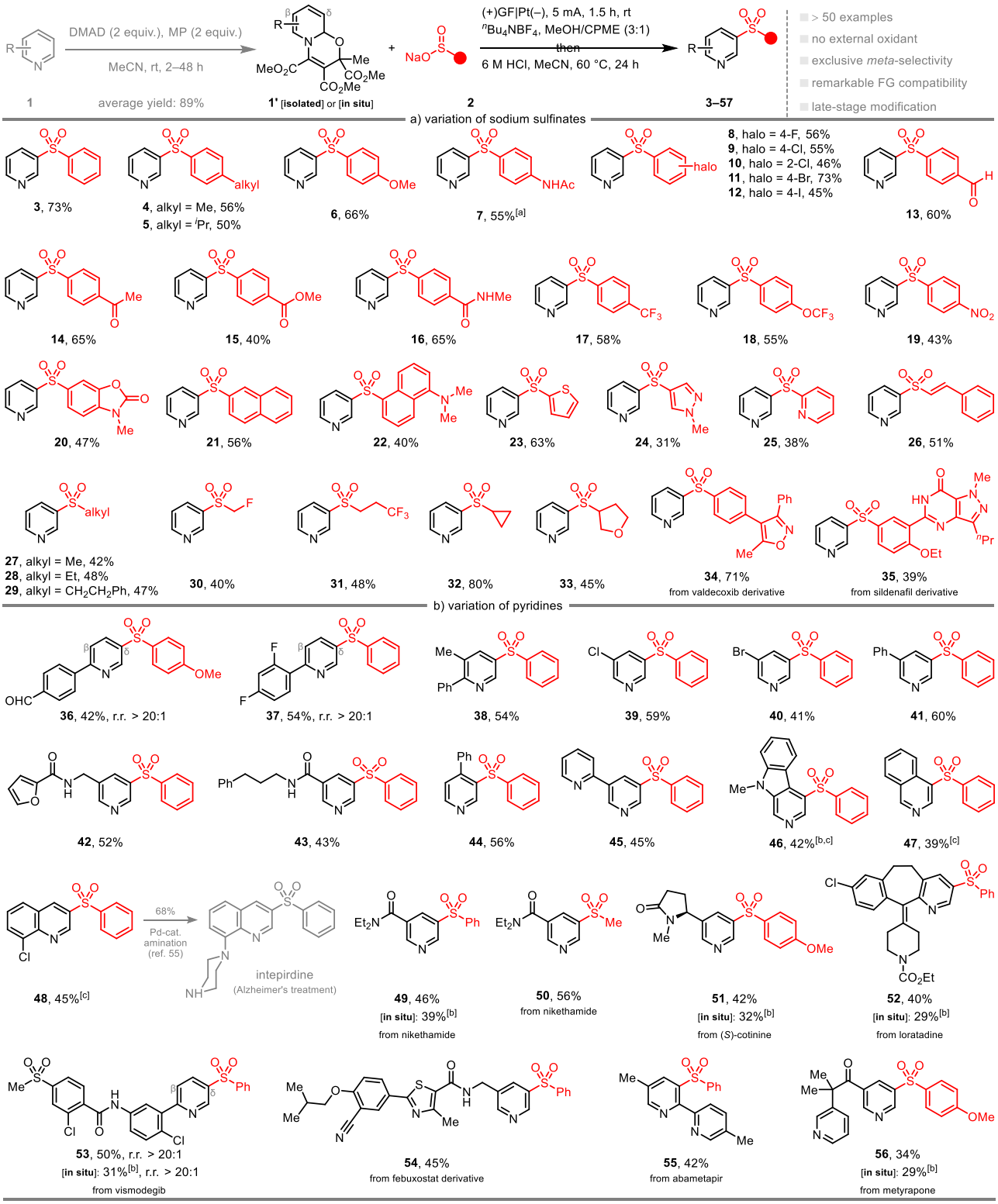

Fig. 2 | Reaction scope of electrochemical *meta*-sulfonation of pyridines. Reaction conditions: **1'** (0.15 mmol), **2** (0.45 mmol), $^{n}Bu_4NBF_4$ (0.15 mmol), MeOH/CPME (3:1, 4 mL), undivided cell with graphite felt (GF) anode (10 mm × 20 mm × 2 mm) and platinum plate (Pt) cathode (10 mm × 20 mm × 0.3 mm), constant current of 5 mA (ca. 1.9 F·mol^{-1}), room temperature (25 °C), 1.5 h, under N_2; then hydrolysis with 6 M HCl in MeCN at 60 °C for 24 h. Unless noted, isolated yields based on oxazino-pyridines. r.r. regioselective ratio of δ:β-reactivity in oxazino-pyridines. [a]The corresponding free NH_2 product (**7-NH$_2$**) was also obtained with 20% yield resulting from acetamide hydrolysis. [b]One-pot procudure from pyridines **1** at 0.15 mmol scale. [c]Graphite plate (C) as an anode.

precedents based on transition-metal-catalyzed cross-couplings of costly 8-fluoro/chloro-3-iodoquinoline[55–57]. The mild electrochemical route also allows for late-stage modification of drug-like molecules such as valdecoxib (**34**), sildenafil (**35**), as well as nikethamide (**40, 41**) and (*S*)-cotinine (**51**), loratadine (**52**), vismodegib (**53**), febuxostat (**54**), abametapir (**55**), and metyrapone derivatives (**56**).

The *meta*-sulfonation reactions described above were performed as a two-pot procedure with the valuable sulfonyl group being

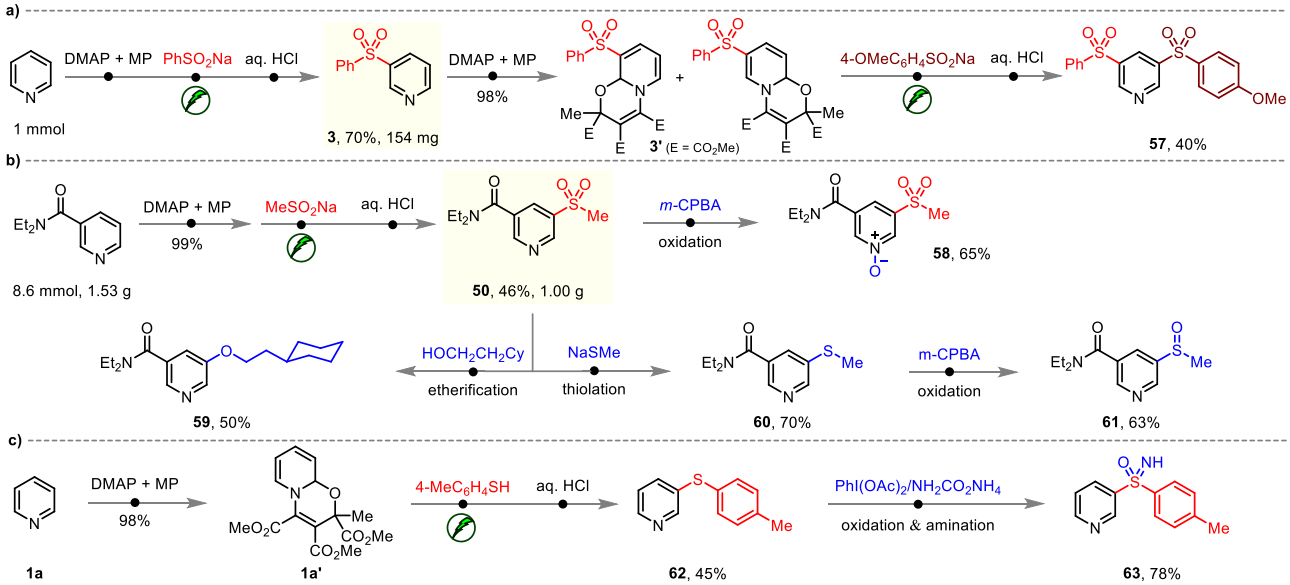

Fig. 3 | Synthetic applications. Isolated yields were reported. **a** Sequential unsymmetric *meta*,*meta'*-disulfonylation of pyridine. **b** Gram-scale synthesis and divergent manipulation of nikethamide. **c** *meta*-Thiolation of pyridine and streamlined derivatization. For detailed reaction conditions, see Supplementary Information.

introduced after dearomatization and isolation of the related oxazino-pyridine intermediates. This provides rapid access to structural analogs, as outlined above. For certain targeted *meta*-sulfonated compounds, we were pleased to find that conducting the entire sequence in one pot is feasible. For instance, one-pot *meta*-sulfonation of pyridine-containing drugs (**49, 51**–**53, 56**) as well as pyridoindoles (**46**) could be achieved with comparable yields.

Both two- and one-pot synthetic procedures could be easily scaled up, as exemplified by the synthesis of *meta*-sulfonated nikethamide **50** and 3-(phenylsulfonyl)pyridine (Fig. 3b), respectively. By taking advantage of the rich chemistry of its pyridyl and sulfonyl moieties, nikethamide-derived compound **50** can serve as a valuable synthetic hub. For instance, its skeletal oxidation led to *N*-oxide analogous **58** in good yield. The introduced sulfonyl handle could be further translated into ether (**59**)[49], thioether (**60**)[54], and sulfoxide (**61**) pharmacophores in one or two steps. Additionally, consecutive C–H bond functionalization of pyridines is appealing to construct polysubstituted pyridines. As illustrated in Fig. 3a, unsymmetric doubly *meta*-sulfonated pyridine **57**, which otherwise is difficult to prepare, was obtained in an overall yield of 27% from pyridine via iterative dearomatization/e-sulfonation/aromatization tandem sequence. Furthermore, the current electrochemical protocol is applied to pyridine *meta*-C–H thiolation with thiophenols, as exemplified by the synthesis of **62**, which can be further converted into sulfoximine **63** through oxidation and amination (Fig. 3c). These outcomes testified its robustness and practicability in medicinal and process chemistry.

To shed light on this electrochemical process, we performed some mechanistic studies. Radical capturing reaction with 1,1-diphenylethylene delivered the adduct **64** in 63% yield, pointing toward the engagement of the sulfonyl radical (Fig. 4a, above). Isolation of the electrochemical process before hydrolysis proved to be an inseparable mixture of β- and δ-sulfonated regioisomers, which clearly indicates the sulfonyl radical addition onto both sites of oxazino-pyridine **1a'**(Fig. 4a, below). In cyclic voltammetry, the oxidative peak of $PhSO_2Na$ was observed at +0.94 V (curve b) while that of oxazino-pyridine **1a'** appeared at +1.72 V (curve c, Fig. 4b). These results clearly reveal the preferential oxidation of sulfinates at the anode over oxazino-pyridines to form sulfonyl radicals. Based on these findings, our proposed mechanism was outlined in Fig. 4c. Initially, a nucleophilic sulfinate undergoes preferential single electron oxidation over an oxazino-pyridine at the anode to form the sulfonyl radical, which is often deemed as electrophilic and thus might be matchable in polarity with the electron-rich oxazino-pyridine intermediate. This radical addition would occur either at the β- or δ-nitrogen site in the dearomatized pyridine **1a'**. The resulting stabilized carbon radical species **I**-β and **I**-δ (which further stabilized by its resonance form **I'**-δ) could further lose an electron at the anode to form iminium-type species **II**-β and **II**-δ, respectively. Deprotonation and subsequent dearomatization uniformly lead to the targeted *meta*-sulfonated product. At the cathode, the dihydrogen byproduct is released.

Discussion

In summary, we have demonstrated a complementary electrochemical method by using diverse nucleophilic sulfinates to empower *meta*-sulfonylation of pyridines through a redox-neutral dearomatization-rearomatization strategy. It so far represents a sole example of using nucleophilic partners to functionalize pyridine *meta*-C–H bond under catalyst-, and oxidant-free conditions. The exclusive regioselectivity, remarkable functional group tolerance, scale-up potential, and late-stage functionalization enhance the robustness and practicability of this electrochemical method. We believe that this work can inspire more method development using nucleophiles to *meta*-selectively functionalize pyridines and their application in synthetic and medical chemistry.

Methods

General procedure for electrochemical *meta*-sulfonation of pyridines

A dry 10 mL undivided cell with a Teflon™-coated stirring bar was charged with dearomatized heteroarenes **1'** (0.15 mmol, 1 equiv.), sodium sulfinates or thiophenol **2** (0.45 mmol, 3 equiv.), $^nBu_4NBF_4$ (49.4 mg, 0.15 mmol, 1.0 equiv.), dry MeOH (3 mL) and CPME (1 mL). The cell was sealed using a screw cap carrying a GF anode (10 mm × 20 mm × 2 mm) and a platinum cathode (10 mm × 20 mm × 0.3 mm). The mixture was subjected to three cycles of vacuum/nitrogen and then electrolyzed at a constant current of 5.0 mA for 1.5 h (cumulated charge: 1.9 F·mol^{-1}) at room temperature. Afterwards, the solvent was removed on a rotary evaporator under reduced pressure followed by the addition of MeCN (2 mL) and 6 M HCl (5 mL). The reaction mixture was stirred at 60 °C under air for 24 h, and then basified with saturated

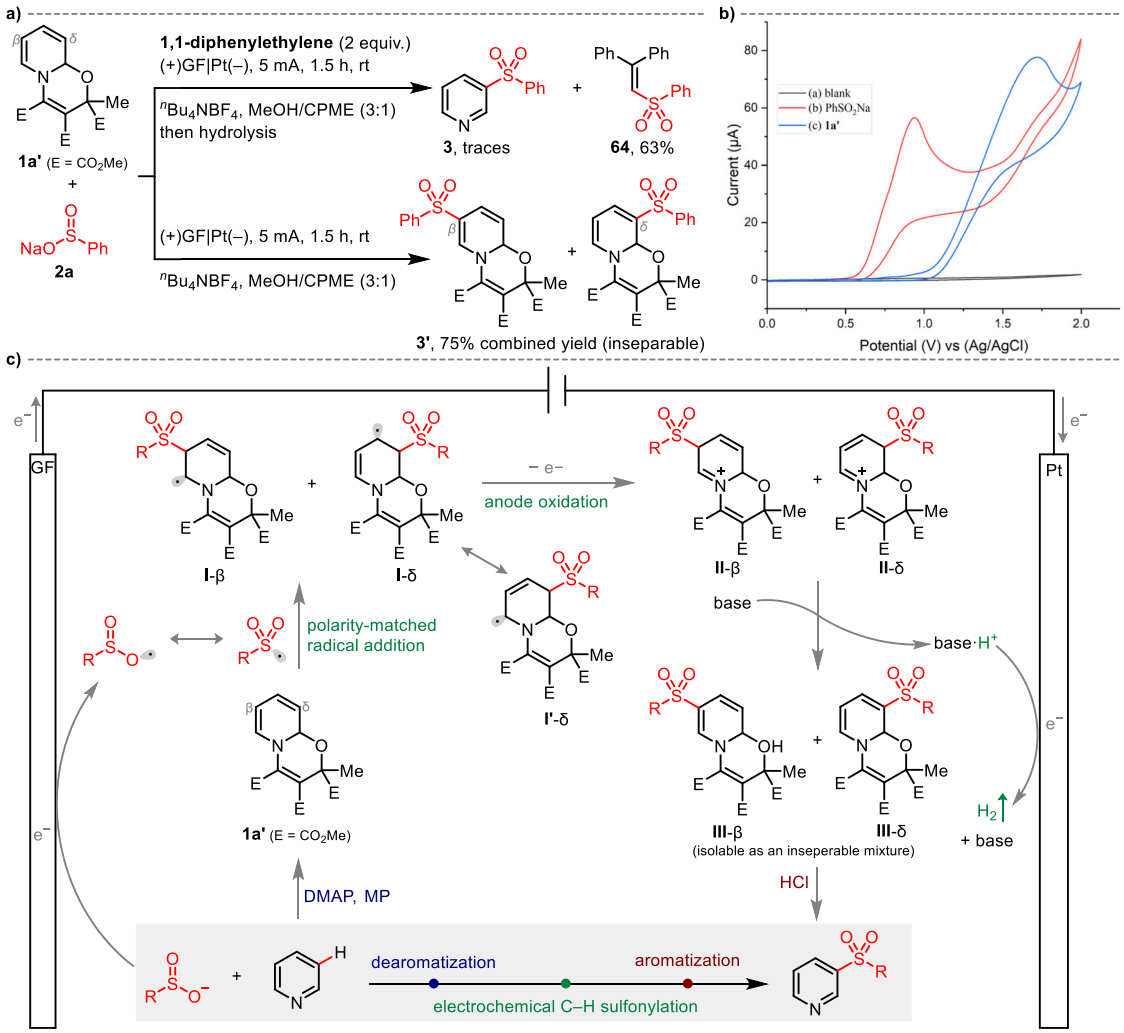

Fig. 4 | Mechanistic insights and plausible pathway. a Radical trapping and intermediate isolation. **b** Cyclic voltammetry. **c** Proposed mechanism.

Na_2CO_3 aqueous solution until pH = 8–9 and extracted with CH_2Cl_2 or EtOAc (5 mL × 3). The combined organic phase was dried over Na_2SO_4 and filtered. The volatiles were removed with a rotary evaporator under reduced pressure and the residue was subjected to flash column chromatography or preparative thin layer chromatography over silica gel to give the corresponding product.

General procedure for one-pot electrochemical *meta*-sulfonation of pyridines

A dry 10 mL glass vessel with a Teflon™-coated stirring bar was charged with heteroarenes **1** (0.15 mmol, 1 equiv.), methyl pyruvate (MP, 30.6 mg, 0.3 mmol, 2 equiv.) and dry acetonitrile (1 mL). The vessel was sealed using a septum and the mixture was subjected to three cycles of vacuum/nitrogen. Dimethyl acetylenedicarboxylate (DMAP, 42.6 mg, 0.3 mmol, 2 equiv.) was then added slowly to the stirred reaction mixture. The reaction mixture was allowed to stir at room temperature for 24 h and directly used for the follow-up electrolysis.

A dry 10 mL undivided cell with a Teflon™-coated stirring bar was charged with sodium sulfinates **2** (0.45 mmol, 3 equiv.), and $^nBu_4NBF_4$ (49.4 mg, 0.15 mmol, 1.0 equiv.). The cell was sealed using a septum carrying a GF anode (10 mm × 20 mm × 2 mm) and a platinum cathode (10 mm × 20 mm × 0.3 mm), and subjected to three cycles of vacuum/nitrogen. Dry MeOH (3 mL) was added to the cell, into which the above-obtained reaction mixture of in situ-generated dearomatized heteroarenes was transferred. The resulting mixture was electrolyzed at a constant current of 5.0 mA for 1.5 h (cumulated charge: 1.9 F·mol^{-1}) at room temperature. Afterwards, the solvent was removed on a rotary evaporator under reduced pressure followed by the addition of MeCN (2 mL) and 6 M HCl (5 mL). The reaction mixture was stirred at 60 °C under air for 24 h, and then basified with saturated Na_2CO_3 aqueous solution until pH = 8–9 and extracted with CH_2Cl_2 or EtOAc (5 mL × 3). The combined organic phase was dried over Na_2SO_4 and filtered. The volatiles were removed with a rotary evaporator under reduced pressure and the residue was subjected to flash column chromatography or preparative thin layer chromatography over silica gel to give the corresponding product.

Data availability

Detailed experimental procedures and characterization data are provided in the Supplementary Information. All data can be requested from the corresponding author.

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Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 22007020 to Z. Zhou, 82273795 to Y. W., 22201051 to Z. Zeng), Science and Technology Program of Guangzhou (Nos. 2023A04J0074 to Z. Zeng), and Plan on Enhancing Scientific Research at GMU (to Z. Zhou) for financial support.

Author contributions

S. Q., M. Y. and M. X. performed the experiments and analysed the data. Z. P. and J. C. repeated some electrochemical reactions. A. S. K. H., W. Y., and Z. Zeng conceived and supervised the project, and wrote the manuscript with insightful discussion and proofreading of S. W., H. G., and Z. Zhou. All authors have given approval to the final version of the manuscript. All authors discussed the results and commented on the article.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-024-50644-y.

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Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.