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Electrochemical Oxidation

# Electrochemical Benzylic C–H Sulfation beyond the *O*-Sulfonation Limitation

*Wei Sheng, Huanhuan Peng, Ben Gao, Chunlan Song, and Jiakun Li**

**Abstract:** Direct C–H sulfation represents a valuable transformation for the synthesis of organosulfates. However, it has been challenging to achieve owing to the presence of multiple C–H bonds with comparable strengths and steric environments. Current methods for producing organosulfates primarily rely on *O*-sulfonation, which limits their applicability to hydroxyl-containing compounds. Herein, we report a practical and cost-efficient method for the electrochemical sulfation of benzylic C–H bonds. This reaction avoids the need for strong oxidants, demonstrating broad substrate scope, excellent chemoselectivity, and site selectivity. The orthogonal reactivity of this protocol is particularly evident in the transformation of alcohol substrates.

The development of late-stage functionalization (LSF) methods, particularly C–H functionalization, has opened new avenues for retrosynthetic disconnections and has led to improvements in resource economy.[1–9] The LSF approach leverages specific C–H bonds for diversification, allowing for the introduction of various substituents without the need of lengthy and tedious de novo synthesis for each target compound. Despite significant progress, LSF strategies are still in their nascent stages, facing challenges related to high functional-group tolerance, chemo-selectivity and, preferably, site-selectivity.[1–3] Additionally, a critical consideration in strategy design is the identification of groups amenable to LSF introduction. Although the incorporation of larger groups, such as (hetero)aryl moieties, may significantly alter a drug's properties and potentially compromise its biological activity, smaller groups like fluoro, methyl, or hydroxyl can beneficially modulate properties such as binding affinity, solubility, drug metabolism, and bioconjugation.[4–6]

Organosulfates ($-OSO_3^-$) are ubiquitous in nature, occurring in polysaccharides, proteins, steroids, and drug metabolites.[10–12] The introduction of negatively charged sulfate groups onto target molecules markedly modifies their physicochemical properties, including water solubility, conformational changes, and electrostatic and hydrogen bonding interactions.[11] This modification has been implicated in regulating a variety of biological and disease processes, such as molecular recognition, immune regulation, detoxification, pathogen evasion, and cancer metastasis.[13–19] Given the significance of benzylic sulfates in natural products, drug metabolites and surfactants, as well as their roles as versatile directing groups in regioselective functionalization (Figure 1a), [20–26] it is therefore essential to develop efficient methods for the selective sulfation of benzylic C–H bonds without the need for de novo synthesis (Figure 1b). However, current methods, whether enzymatic or chemical, primarily restrict the production of organosulfates to *O*-sulfonation and limit the substrates containing OH groups.[27–30] In phase I metabolism, cytochrome P450 enzymes catalyze the oxygenation of benzylic C–H bonds, and the resulting

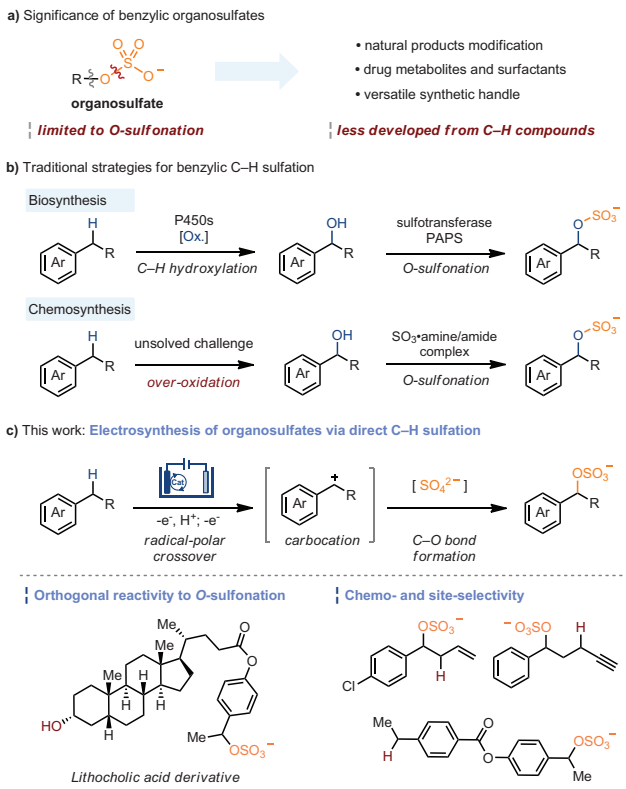


***Figure 1.*** Strategies for benzylic C–H sulfation.

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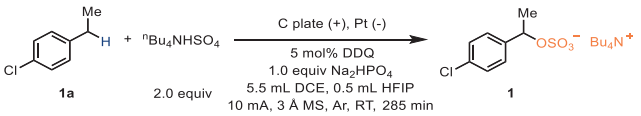
benzylic alcohols are then subjected to *O*-sulfonation in phase II metabolism by sulfotransferase.[23–26,31–34] In this process, a sulfuryl group ($SO_3$) is transferred from a donor molecule, typically 3′-phosphoadenosine-5′-phosphosulfate (PAPS), to target molecules, facilitating sulfate conjugation.[35,36] The direct synthesis of benzylic alcohol by chemical C─H oxidation is a challenging transformation due to the inherent susceptibility toward oxidation of the resultant alcohols to ketones.[37–41] Consequently, the current approach for manufacturing benzylic alcohols involves stepwise protocols with esters as intermediates to prevent over-oxidation.[42–46] Even when benzylic alcohol is obtained, its *O*-sulfonation is generally not straightforward and often requires custom-tailored trioxide-amine/amide complex reagents.[23–26] Furthermore, the preparation of these $SO_3$ motifs typically involves laborious multistep sequences that require corrosive $SO_3$ reagents and stoichiometric excess of base.[47,48] Notably, a method for radical benzylic C─H sulfation by persulfates has been reported.[49] However, the strong oxidative capacity of persulfates may hinder their further application, and does not provide clear advantages that are not otherwise readily accessible through *O*-sulfonation.[50] Considering the accessibility of persulfate from electrooxidation of sulfate,[51] it may be feasible to develop an electrooxidative C─H sulfation method under simple and mild conditions, ideally demonstrating distinct reactivity compared to *O*-sulfonation.

Organic electrochemistry has greatly expanded the organic chemist's toolbox to address challenging redox reactions.[52–59] Electrochemical oxidation, in particular, provides an efficient method for generating benzylic cations from benzylic C─H bonds through sequential electron-transfer, proton-transfer, and second electron-transfer steps (ET/PT/ET).[60–70] Although these reactive intermediates can be captured by nucleophiles to yield functionalized benzylic products, the coupling of benzylic cation with sulfate anion ($SO_4^{2-}$) to form organosulfate via C─O bond formation remains unexplored. This is largely attributed to the low nucleophilicity of the sulfate ($H_2SO_4$, p*K*a: -3), which restricts the construction of C─$OSO_3^-$ bonds through nucleophilic substitution reactions.[71–73] In addtion, the lability of benzylic sulfates to acid and temperature increases the synthetic difficulty to the sulfation.[49,74,75]

We have been interested in the synthesis of organosulfates through C─O bond formation, and have successfully achieved the *O*-sulfonation using dialkyl sulfates under tetrabutylammonium bisulfate ($^nBu_4NHSO_4$) activation.[76,77] We propose that the $^nBu_4N$ cation not only enhances the stability of the sulfate product but also improves the nucleophilicity of bisulfate. Herein, we report an efficient and practical electrochemical benzylic C─H sulfation with tetrabutylammonium bisulfate as a nucleophile (Figure 1c). This direct C─H sulfation demonstrates several advantages: 1) orthogonal reactivity with *O*-sulfonation, enabling the direct sulfation of feedstock chemicals containing hydroxyl groups without resorting to complicated protection group strategies; 2) high chemo- and site-selectivity in substrates with multiple potential sulfation sites, including various benzylic and allylic positions, as well as those adjacent to heteroatoms; and 3) broad scope and excellent scalability.

***Table 1:*** Investigation of the reaction conditions.[a)]




| Entry | Variation from standard conditions | Yield of **1**[b)] |
|---|---|---|
| 1 | None | 80% |
| 2 | Graphite rod as anode | 63% |
| 3 | Graphite felt as anode | 48% |
| 4 | Ni foam as cathode | 57% |
| 5 | DCE as the solvent | 33% |
| 6 | DCM as the solvent | 52% |
| 7 | $CHCl_3$ as the solvent | 25% |
| 8 | $^nPr_4NHSO_4$ instead of $^nBu_4NHSO_4$ | 59% |
| 9 | $Et_4NHSO_4$ instead of $^nBu_4NHSO_4$ | 55% |
| 10 | $Me_4NHSO_4$ instead of $^nBu_4NHSO_4$ | 44% |
| 11 | $H_2SO_4$ or $Na_2SO_4$ instead of $^nBu_4NHSO_4$ | <5% |
| 12 | $Et_4NHSO_4$ + $^nBu_4NBF_4$ | 53% |
| 13 | $Na_2SO_4$ + $Et_4NBF_4$ | <5% |
| 14 | Without DDQ | 65% |
| 15 | Without 3 Å MS | 64% |
| 16 | Without $Na_2HPO_4$ | 64% |
| 17 | Without electricity | n.d. |
| 18 | Under air | 66% |

[a)] Standard reaction conditions: graphite plate anode, Pt plate cathode, constant current = 10 mA, **1a** (0.5 mmol), $^nBu_4NHSO_4$ (1.0 mmol), DDQ (0.025 mmol), $Na_2HPO_4$ (0.5 mmol), 3 Å MS (50.0 mg), DCE (5.5 mL), HFIP (0.5 mL), RT, and undivided cell under Ar. [b)] $^1H$ NMR yields were shown. n.d., not detected. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. DCE, 1,2-dichloroethane. DCM, dichloromethane. HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol.

Initial experiments utilized *p*-chloroethylbenzene as the substrate, which is notably more difficult to oxidize (Table 1). Constant-current (10 mA) was conducted in an undivided cell with a carbon anode, a Pt cathode in a mixed solvent of DCE/HFIP. Gratifyingly, the reaction of **1a** with 5 mol% DDQ as a catalyst and $Na_2HPO_4$ as additive in the presence of $^nBu_4NHSO_4$ (2.0 equiv) gave 80% sulfated product **1** (entry 1). Changing the electrodes (entries 2–4) or replacing the mixed solvent with sole ones such as DCE, DCM, or $CHCl_3$ (entries 5–7) was found to decrease the yield of **1**. The use of HFIP could potentially increase the nucleophilicity of $^nBu_4NHSO_4$ and stabilize arene radical cation intermediates.[78] $^nBu_4NHSO_4$ proved to be an optimal sulfating agent (entries 8–13), serving as both sulfate source and enhancing solubility and stability of sulfate product **1** as tetrabutylammonium salt.[79–81] In either the absence of DDQ, molecular sieve or additive (entries 14–16), the transformation proceeded with decreased efficiency. DDQ may facilitate a single electron transfer (SET) process as mediator during electrochemical transfer (Table S13).[82–85] Alternatively, a direct electrooxidation via electron/proton transfer on the anode might also yield the corresponding benzylic sulfates (Figure 3). $Na_2HPO_4$ likely served as a base to the deprotonation of bisulfate, thereby increasing its nucleophilicity. The use of molecular sieves effectively inhibited the formation of oxygenation by-products by preventing water's participation. Notably, the reaction was completely abolished without electricity (entry 17). Finally, 66% yield of product


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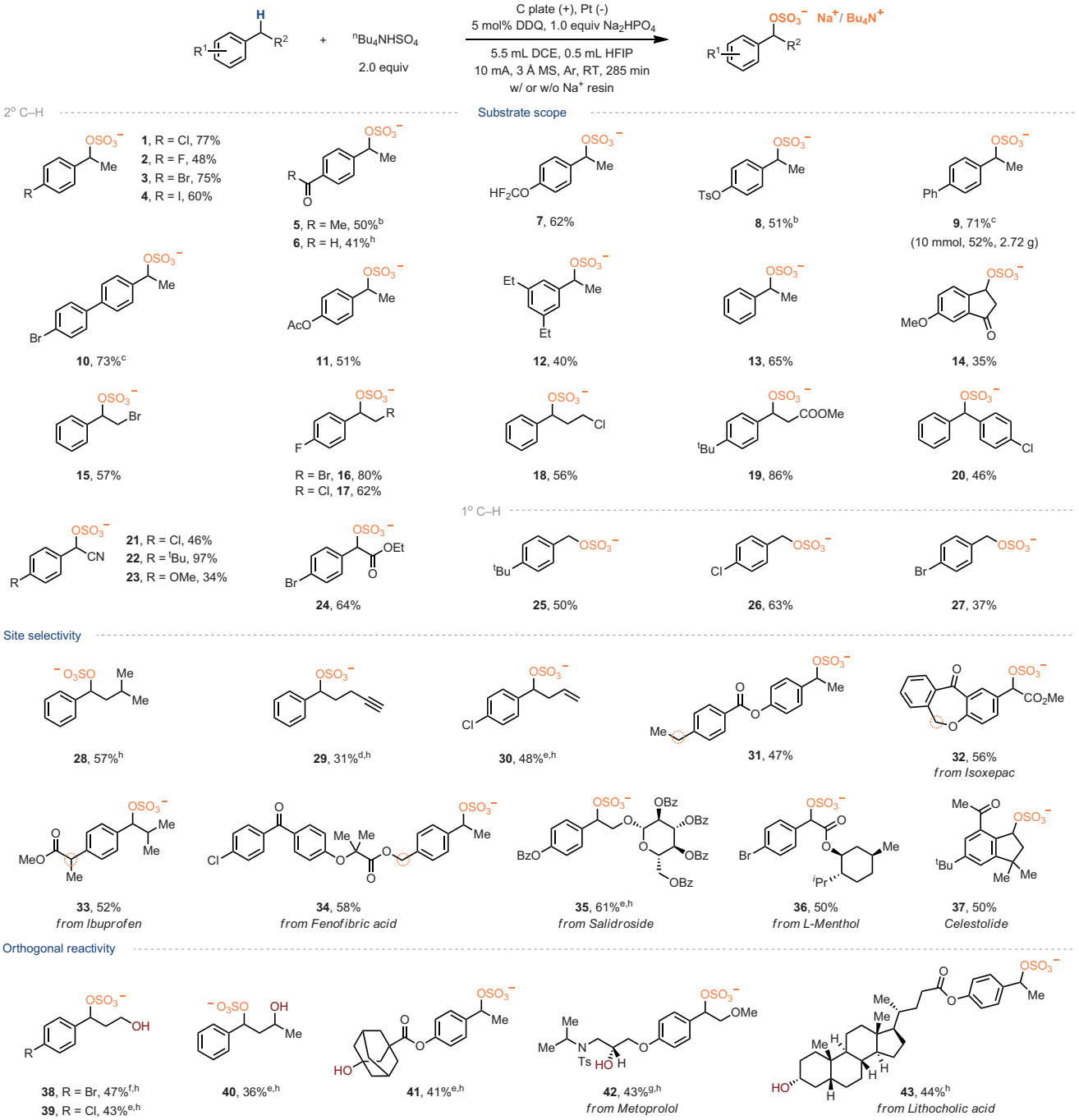
***Table 2:*** Substrate scope for C—H sulfation.[a)]




[a)] Reaction condition: undivided cell, alkylarene (0.5 mmol), $^{n}Bu_4NHSO_4$ (1.0 mmol), DDQ (5 mol%), 3 Å MS (50.0 mg), $Na_2HPO_4$ (0.5 mmol), DCE (5.5 mL), HFIP (0.5 mL), graphite plate as anode, Pt as cathode, 10 mA, 285 min, Ar, and RT. Isolated yield was shown. [b)] C rod (+)/Pt (−), 15 mA, 3.5 h. [c)] C felt (+)/Pt(−). [d)] DCM/HFIP = 5.5/0.5 mL, 4 Å MS. [e)] 4 Å MS. [f)] 10 mA, 161 min. [g)] 0.2 mmol, C felt (+)/Pt (-), 10 mA, 90 min, and 4 Å MS. [h)] $^1$H NMR yields.

**1** was achieved in ambient atmosphere (entry 18), indicating that the reaction is not sensitive to air.

With these optimum conditions, we investigated the generality of the electrochemical-mediated C—H sulfation (Table 2). A range of ethylbenzenes including those with electron-withdrawing groups like halides, acyls, difluoromethoxy, and sulfonate substituents (**1**–**8**), are efficiently tolerated, while electron-donating functionalities such as phenyls, acetoxy, and alkyl afford the desired products (**9**–**12**) with good-to-excellent yields. Indane derivative bearing a carbonyl group reacts selectively at benzylic position to form corresponding sulfate (**14**). Additionally, substrates with sensitive functional groups such as alkylbromides (**15**, **16**), alkylchlorides (**17**, **18**), were not detrimental to the reaction.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$\beta$-sulfate ester **19** was prepared in 86% yield, overriding the propensity for elimination to form an $\alpha,\beta$-sulfate ester, and the sulfation remained operable with diarylmethane (**20**). Notably, the sulfation of benzylic positions adjacent to a cyano group or an ester group provides a straightforward route to $\alpha$-sulfate nitriles (**21**–**23**) and $\alpha$-sulfate ester (**24**), respectively. Additionally, 4-alkyl and 4-halogenated toluenes can also undergo sulfation, resulting in the formation of sulfates **25**–**27**. However, tertiary benzylic C─H compounds were found to be challenging reaction partners because of their low reactivity and the inherent lability of tertiary organosulfates.[86,87] The synthetic utility was successfully scaled up to produce the target product **9** in 52% isolated yield. A sequential exchange of the tetrabutylammonium cation with Na cation delivered sodium organosulfates as natural counterion. Unfortunately, the electrochemical sulfation is currently not applicable to allylic C─H and $\alpha$-heteroatom substituted C─H substrates (Table S5).

The reaction conditions reported in this study are mild, facilitating chemo- and site-selectivity in substrates with multiple potential sites for sulfation. This selectivity is a critical requirement yet a challenge in late-stage functionalization (LSF) reactions. The method demonstrated exclusive sulfation of benzylic C─H bonds compared to their tertiary (**28**), propargylic (**29**), and allylic (**30**) counterparts. The sulfation preferentially occurs at sites with high electron density in substrates containing two benzylic sites, whether they were on the same or on different aryl (**31**–**34**). These findings indicate that selectivity is predominantly influenced by the irreversible deprotonation of the arene radical cations, a process that is governed by the charge distribution on the benzene ring or electron density at benzylic position. No competing site-sulfation and disulfation products were observed, underscoring the electrochemical method's ability to discriminate sites by electron density via precise and tunable electrode potential control. Additionally, over-oxidation (a second oxidation) is slowed down due to the electron-withdrawing effect on the aromatic ring by the $\alpha$-sulfate substituent. This method showcases its synthetic utility for late-stage modification of natural products and drug molecules, including isoxepac (**32**), ibuprofen (**33**), fenofibric acid (**34**), salidroside (**35**), *L*-menthol (**36**), celestolide (**37**), metoprolol (**42**), and lithocholic acid (**43**) derivatives. Importantly, hydroxyl groups (**38**–**43**) are well-tolerated in electrochemical C─H sulfation, exhibiting orthogonal reactivity with *O*-sulfonation. This compatibility would be difficult to achieve through *O*-sulfonation of the alcohol precursor without resorting to complicated protection group strategies. In addition to the instability of benzyl sulfates, which generally leads to a 10% mass loss on column chromatography, the low substrate conversion is the main reason for most substrates (**28**–**37**) with low yields. Meanwhile, for certain substrates, such as **20**, **25**, and **38**, there are 20% side products of benzylic ketones/aldehydes, while hydroxyl oxidation and intermolecular etherification products from HFIP or hydroxyl groups were not observed (Tables S1 and S2).

The high chem- and site-selectivity for sulfation have prompted our investigation into the reaction mechanism (Figure 2). The participation of a benzylic radical has been supported by a radical trapping experiment (Table S15). This benzylic radical may be generated via H atom abstraction (HAA) pathway[88–90] or through a stepwise electron/proton transfer involving arene radical cation intermediates, where the electron and the proton originate from different sites on the substrates.[46,64,65] To differentiate between these potential reaction pathways, we performed a Hammett analysis and an intermolecular kinetic isotope effect (KIE) experiment (Figure 2a,b). The Hammett-slope (−2.0) indicates positive charge bulidup in the rate-determining transition state of the reaction, which is more negative than the usual $\rho$-value of roughly -1 for benzylic radical generation via HAA.[91] Additionally, the intermolecular KIE of 1.8 is lower than typical values ($k_H/k_D \geq 5$) seen for KIE in HAA with oxygen centered radicals.[92,93] The positive charge built up, combined with the observed KIE value, supports a stepwise electron/proton transfer rather than HAA process. The electrochemical sulfation of homobenzylic alcohol **44** and benzyltrimethysilane **50** led to the cleavage of C─Si and C─C bond (Figure 2c).[94–96] These findings provide significant evidence that benzylic C─H cleavage proceeds through an individual electron and proton transfer mechanism via arene radical cation intermediates, such as **47** and **51**. Further anodic oxidation of benzylic radical intermediate to a benzylic cation, followed by nucleophilic attack of bisulfate, can lead to the formation of benzylic sulfates. The electron oxidation of substrates with a pendant amide group in **52a** or hydroxyl group in **53a**, resulted in the formation of the cyclized product of **52b** and **53b**, suggesting the participation of a benzylic carbocation intermediate (Figure 2d). In addition, stoichiometric DDQ chemical oxidation failed to form C─$OSO_3^-$ bond, whereas $^nBu_4NHSO_4$-mediated nucleophilic substitution of benzylic carbocation succeeded (Figure 2e). These results show that DDQ acts as an oxidant to generate benzylic radical but lacks sufficient oxidative capacity to promote subsequent benzylic cation formation in this electrochemical benzylic C─H sulfation.

A proton-coupled electron transfer mechanism (PCET) is unlikely due to the difficulties associated with the oxidative formation of sulfate radical from sulfate ($E^\circ$ = 2.5–3.1 V).[97–100] The previously proposed PCET pathway could potentially explain the broad substrates scope for the unique reactivity of mesyloxyl radicals.[42] Cyclic voltammograms studies revealed that no oxidation peak for $^nBu_4NHSO_4$ was observed (Figure 2f, line c), indicating the absence of sulfate radical formation during our electrocatalytic process.[101]

On the base of the above experimental data, the proposed reaction mechanism is illustrated in Figure 3. The anodic oxidation of alkylarene produces a radical cation intermediate **I**, which subsequently deprotonate to form a benzylic radical **II**. The further oxidation of a benzylic radical on the anode lead to the formation of a benzylic carbocation **III** that then reacts with sulfate anion to yield the desired sulfate products. DDQ likely functions as a redox catalyst to generate a benzylic radical.[82–85] The stepwise electron/proton transfer pathway contributes to the high site selectivity of this electrochemical C─H sulfation, as electron transfer is highly sensitive to electronic properties, enabling the distinction


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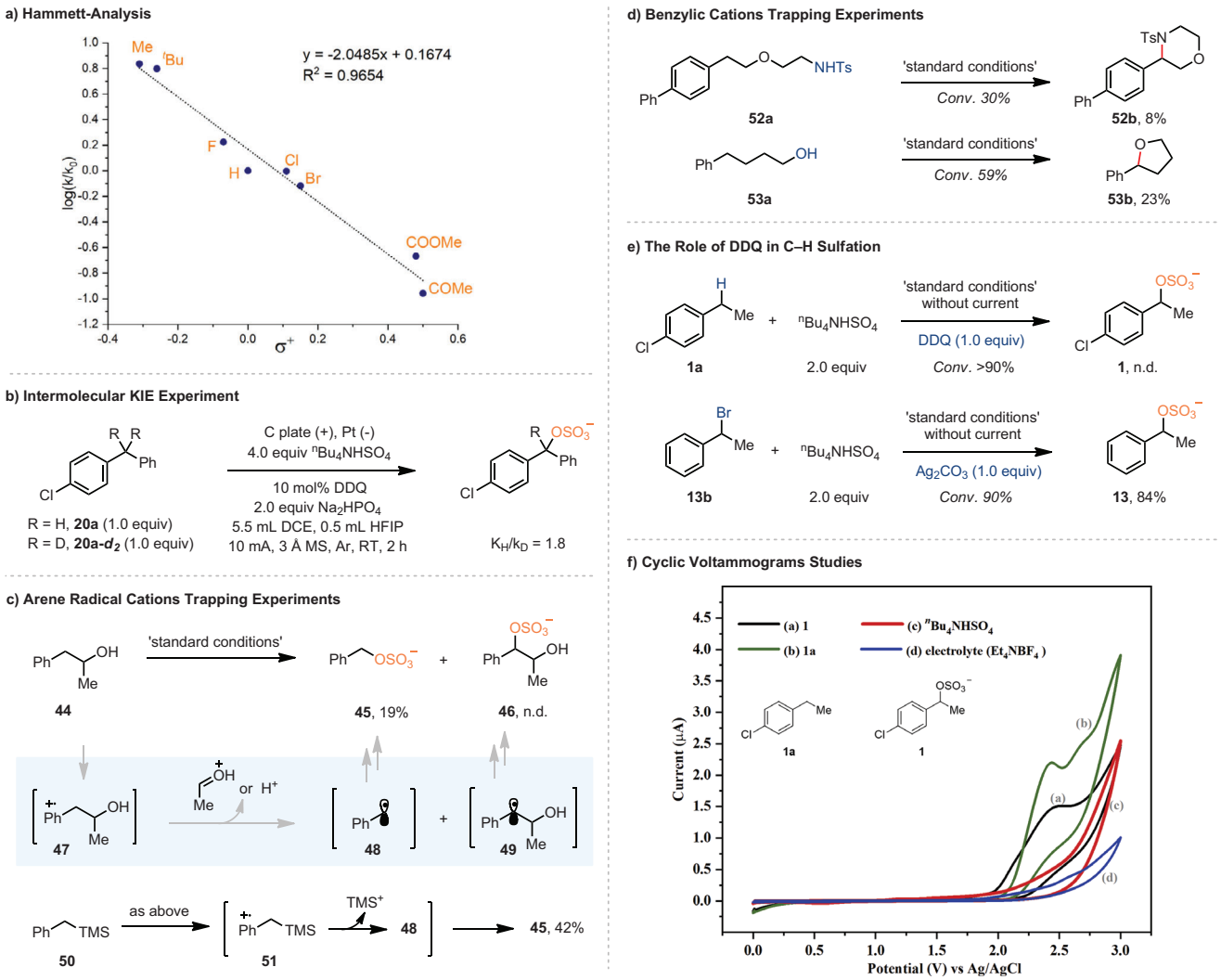


***Figure 2.*** Mechanistic investigations.

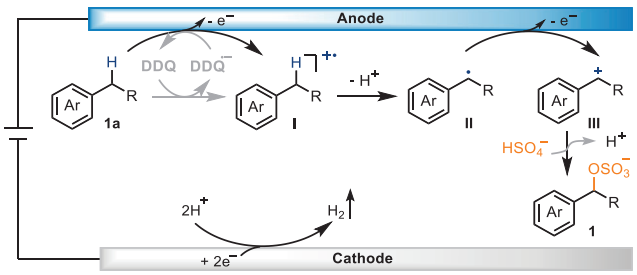


***Figure 3.*** Proposed mechanism.

between C($sp^3$)–H bonds with similar BDE but differing electronic characteristics.

In summary, we have presented a highly efficient and selective electrochemical benzylic C–H sulfation and demonstrated its synthetic utility in late-stage conjugation of natural products and drug molecules. The exclusive functional tolerance of hydroxyl groups is complementary to *O*-sulfonation, offering a rapid approach to make sulfate-conjugates without resorting to complicated protection group strategies. We anticipate that this new strategy would be a useful addition to sulfation toolbox.

## Acknowledgements

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.


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**Keywords:** C—H oxidation · Electrooxidation · Sulfation · *O*-sulfonation


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