

## RESEARCH ARTICLE

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# Electrochemical strategies for *N*-alkylation and *N*-acylation of NH-sulfoximines via the decarboxylation and deoxygenation of carboxylic acids†

Xiaoman Li,<sup>a</sup> Jiawei Huang,<sup>a</sup> Ji-Xing Zhao,<sup>a,c</sup> Liang Xu,<sup>id</sup> <sup>a</sup> Ping Liu,<sup>id</sup> <sup>\*a</sup>  
Jichang Liu<sup>id</sup> <sup>\*a,b</sup> and Yu Wei<sup>id</sup> <sup>\*a</sup>

The functionalization of NH-sulfoximines to construct N–C bonds from common carboxylic acids remains underdeveloped. Herein, electrochemical strategies were utilized to enable the chemoselective decarboxylation or deoxygenation of carboxylic acids for the synthesis of *N*-alkyl and *N*-acyl sulfoximines. The advantages of these methods include mild reaction conditions, no electrode sacrifice, no external oxidants or metal catalysts, and easy scalability to gram-scale production. Furthermore, 67 diverse sulfoximine derivatives, particularly those incorporating motifs from amino acids and drug molecules, were obtained.

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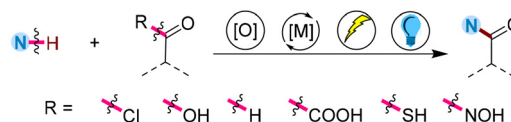
## Introduction

Sulfoximines, the mono-aza analogues of sulfones, are obtained by substituting one oxygen atom of sulfoxides with a nitrogen atom.<sup>1</sup> Due to their chiral sulfur center and coordination ability with metal ions, sulfoximines were initially used primarily as chiral auxiliaries or ligands in asymmetric reactions and catalysis.<sup>2–8</sup> More recently, sulfoximines have garnered increasing attention for their potential applications in the fields of agrochemicals<sup>9,10</sup> and medicinal chemistry.<sup>11–15</sup> Therefore, the synthesis and modification of sulfoximines have witnessed rapid progress.

Unlike sulfones, the presence of a nitrogen atom in sulfoximines can provide more potential for derivatization *via* the modification of *N*-substituents, thus resulting in structures with finely tuned chemical and physical properties.<sup>16–25</sup> Recently, the structural diversification of NH-sulfoximines through efficient *N*-functionalization has garnered significant interest to construct an array of N–C and N–X (X = Br, S, P, etc.) bonds.<sup>26–39</sup> Among these, considerable efforts have been dedicated to converting N–

H to N–C, due to the substantial impact of such modifications on the properties of sulfoximines, such as solubility, H-bonding capability, and metabolic stability.<sup>14,40,41</sup>

Several examples have been reported to achieve this conversion through the dehydrogenative coupling of N–H bonds between sulfoximines and (halogenated) alkanes,<sup>31,42–47</sup> as well as the difunctionalization of alkenes<sup>48–55</sup> to synthesize *N*-alkylated sulfoximines under metal-catalyzed (copper, iron), photocatalytic or electrochemical conditions (Scheme 1a). As

(a) Different methods for *N*-alkylation of sulfoximines(b) Different methods for *N*-acylation of sulfoximines(c) This work: A method for controllable selectivity of *N*-acylation or *N*-alkylation of sulfoximines**Scheme 1** Approaches for the *N*-alkylation and *N*-acylation of sulfoximines.

<sup>a</sup>School of Chemistry and Chemical Engineering/State Key Laboratory Incubation Base for Green Processing of Chemical Engineering, Shihezi University, Shihezi, China. E-mail: yuweichem@shzu.edu.cn, liujc@ecust.edu.cn, liuping1979112@aliyun.com

<sup>b</sup>School of Chemical Engineering, East China University of Science and Technology, 200237 Shanghai, People's Republic of China

<sup>c</sup>Analysis and Testing Center, Shihezi University, Xinjiang 832003, China

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for *N*-acylation of NH-sulfoximines (Scheme 1b), it has been traditionally achieved using pre-activated coupling partners, such as acyl chlorides.<sup>56</sup> Efficient carboxyl activation agents (such as DCC or EDC) and boron catalysts like boric acid or 1,3-dioxane-2,4,6-triborane (DATB) also facilitate the formation of *N*-acyl sulfoximines from carboxylic acids.<sup>56–58</sup> However, these methods inevitably produce excess and undesired chemical waste and require high temperatures. By utilizing external chemical oxidants or transition metal catalysts, NH-sulfoximines can undergo oxidative cross-coupling reactions with aldehydes,<sup>59</sup> methyl aromatics,<sup>60</sup> and  $\alpha$ -keto acids<sup>61</sup> to afford *N*-acylated sulfoximines. Additionally, several photochemical and electrochemical methods have also been developed to enable the formation of *N*-acylation products with thioacids,<sup>62</sup> hydroxamic acids<sup>63</sup> and  $\alpha$ -keto acids,<sup>64</sup> respectively.

Despite the fruitful results, a general protocol for N–C(alkyl) construction from NH-sulfoximines and common carboxylic acids, which are usually stable, inexpensive, and widely available in bioactive molecules like amino acids, has not been disclosed. This seemed strange since recent advancements in the derivatization of either sulfoximines or carboxylic acids have been substantial, separately.<sup>25,65–71</sup>

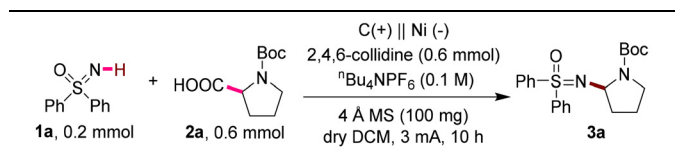
Due to the continuing interest of our group<sup>35,36,48</sup> in the N–H functionalization of sulfoximines and the ongoing development of electrochemical synthesis strategies,<sup>72–75</sup> it was questioned whether the construction of N–C(alkyl) was feasible using sulfoximines and carboxylic acids. Theoretically, the selective decarboxylation and deoxygenation of carboxylic acids would afford *N*-alkylation and *N*-acylation products of sulfoximines, respectively, thus providing a diverse range of sulfoximine derivatives with potential applications.

Herein, the corresponding results were disclosed to showcase the feasibility of this strategy for the first time. Under electrochemical conditions without sacrificial electrodes, chemical oxidants, or metal catalysts, the *N*-alkylation of NH-sulfoximines with carboxylic acids was achieved. Meanwhile, by adding triphenylphosphines to the electrochemical system, *N*-acylation products were obtained with chemoselectivity (Scheme 1c).

## Results and discussion

Initially, *S,S*-diaryl sulfoximine **1a** and *N*-Boc-D-proline **2a** were chosen as model substrates to screen the reaction conditions for the envisioned electrochemical decarboxylative *N*-alkylation reaction. After extensive experimentation to screen an array of variables systematically, including current, electrode, and electrolyte, the best result was obtained by conducting the electrolysis at room temperature and a constant current of 3.0 mA in an undivided cell equipped with a graphite anode and a nickel cathode in dry dichloromethane containing <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub> as a supporting electrolyte, with 2,4,6-collidine as a non-oxidizable base and 4 Å molecular sieves as dehydrating agents. Under these conditions, the desired product **3a** was obtained in 90% isolated yield (Table 1, entry

**Table 1** Optimization of the reaction conditions<sup>a</sup>

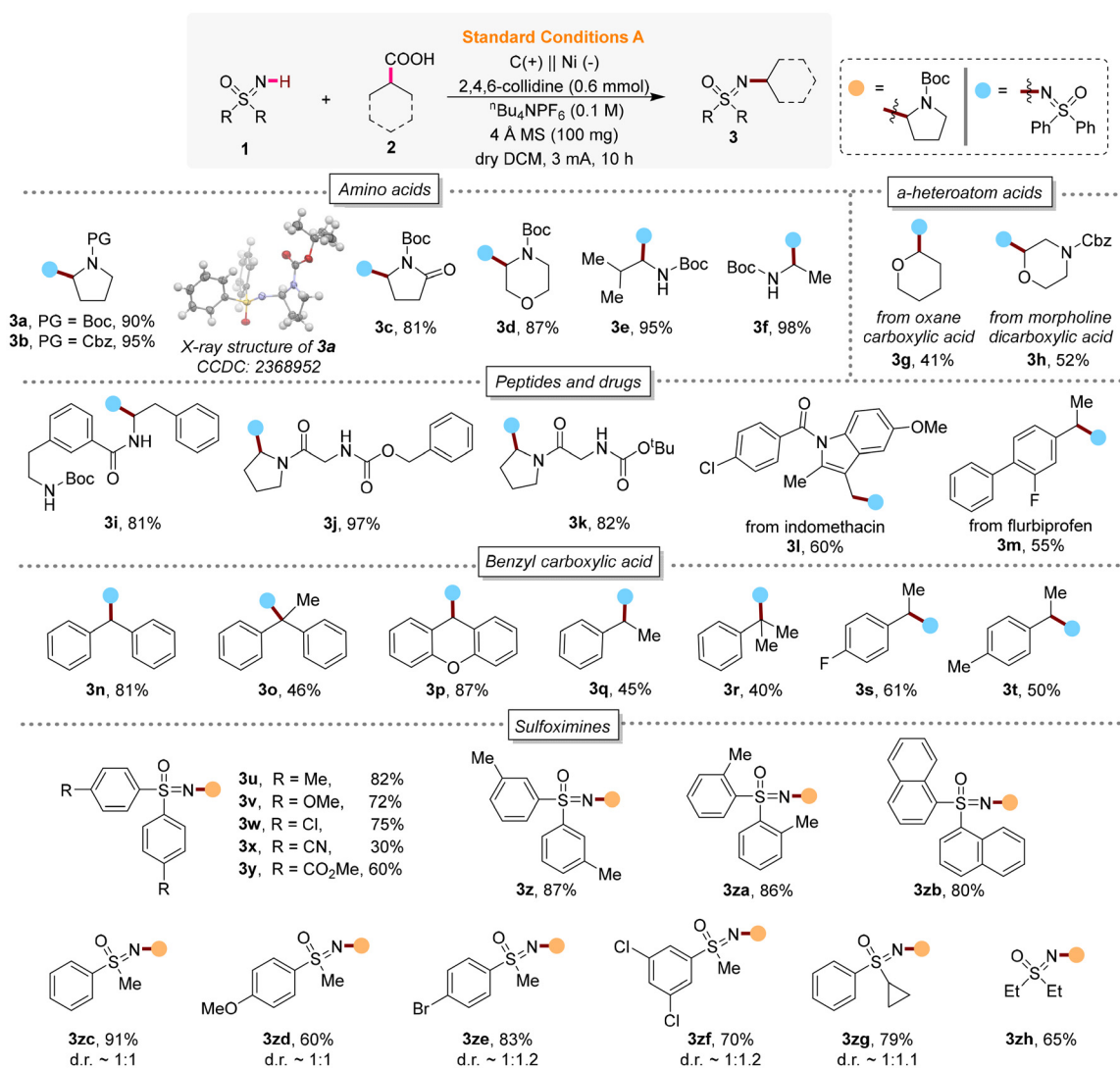


Entry	Variations from the 'standard' conditions	Yield of <b>3a</b> <sup>b</sup> (%)
1	<b>None</b>	<b>90</b>
2	No current	N.R. <sup>c</sup>
3	C/C, Pt/Pt, or C/Pt as the electrode	41, 59, 82
4	MeCN or MeOH as the solvent	63, N.R.
5	<sup>n</sup> Bu <sub>4</sub> NClO <sub>4</sub> or <sup>n</sup> Bu <sub>4</sub> NOAc as the electrolyte	85, 17
6	8 h or 12 h as the reaction time	65, 89
7	2 mA, 5 mA, or 7 mA as the current	51, 64, 65
8	No 2,4,6-collidine	25
9	No 4 Å MS	67

<sup>a</sup> Standard conditions A: **1a** (0.2 mmol), **2a** (0.6 mmol), 2,4,6-collidine (0.6 mmol), <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub> (0.1 M), dry DCM (4.0 mL), 4 Å MS (100 mg), constant current = 3.0 mA under air for 10 hours. <sup>b</sup> Isolated yields. <sup>c</sup> No reaction.

1). As shown in Table 1, the absence of current resulted in no target product (entry 2), demonstrating its crucial role in the decarboxylative *N*-alkylation process. Among the electrode materials screened, when graphite plates or platinum sheets were used as both cathode and anode, the yield of **3a** greatly decreased. When a graphite plate was used as the anode and a platinum sheet as the cathode, the yield of **3a** decreased slightly (entry 3). With respect to the solvent, the yield of **3a** decreased to 69% when acetonitrile was used; however, no desired transformation occurred when methanol was used as the solvent (entry 4). After that, different electrolytes were screened. The conversion efficiency of <sup>n</sup>Bu<sub>4</sub>NClO<sub>4</sub> was similar to that of <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub>, while the use of <sup>n</sup>Bu<sub>4</sub>NOAc was found to significantly affect the efficiency of the reaction (entry 5). Shortening the reaction time to 8 h was found to be detrimental to the isolated yield, leading to 65% of **3a**, while prolonging it to 12 h did not enhance the yield further (entry 6). Increasing or decreasing the current intensity led to a relatively lower yield (entry 7). The absence of 2,4,6-collidine was detrimental to the yield (25%, entry 8). The addition of 4 Å molecular sieves improved the yield of **3a** (entry 9), probably by suppressing the hydration of the possible carbocation intermediates (for more information on the screening of conditions, see ESI section 3†).

With the optimized conditions in hand, the scope of the reaction was then explored by first varying the carboxylic acid substrates (Scheme 2). Commercially available cyclic *N*-protected  $\alpha$ -amino acids, such as proline, pyroglutamic acid, and six-membered cyclic  $\alpha$ -amino acids, reacted well with *S,S*-diaryl sulfoximine **1a** to give the desired decarboxylation products (**3a–3d**) in 81%–95% yields. Similarly, acyclic amino acid derivatives, including valine (**2e**) and alanine (**2f**), were also suitable substrates for this decarboxylative transformation, yielding products **3e** (95%) and **3f** (98%), respectively. In addition,  $\alpha$ -heteroatom acids such as tetrahydropyran-2-car-



**Scheme 2** Substrate scope of the electrochemical decarboxylation and *N*-alkylation of carboxylic acids and sulfoximines. Standard conditions A: *N*-H sulfoximines (0.2 mmol), carboxylic acids (0.6 mmol), 2,4,6-collidine (0.6 mmol), Bu<sub>4</sub>NPF<sub>6</sub> (0.1 M), dry DCM (4.0 mL), 4 Å MS (100 mg), constant current = 3 mA under air for 10 hours, in an undivided cell.

boxylic acid (**2g**) and *N*-Cbz-2-morpholinecarboxylic acid (**2h**) could be converted to the target products **3g** (41%) and **3h** (52%) with moderate yields. Fortunately, peptides underwent decarboxylation to yield the corresponding products in high yields under optimal conditions (**3i–3k**, 81%–97%). Indomethacin and flurbiprofen, two carboxylic acid-based drug molecules, afforded the corresponding sulfoximine derivatives under these electrochemical conditions (**3l**, 60%; **3m**, 55%). Furthermore, secondary and tertiary benzylic carboxylic acids (**2n–2t**) underwent a direct decarboxylative *N*-alkylation process in this transformation, affording the target products **3n–3t** (40%–87%). However, we did not observe any product formations when using non-benzylic carboxylic acids (benzoic acid, cyclohexanecarboxylic acid and 4-phenylbutyric acid).

We next explored the compatibility of a series of *NH*-sulfoximines with this electrochemical decarboxylative system.

Various *NH*-diphenylsulfoximines with *ortho*-, *meta*-, or *para*-substituents, such as electron-donating groups (–Me, –OMe) and electron-withdrawing groups (–Cl, –CN, –CO<sub>2</sub>Me), could afford the desired products (**3u–3za**) with yields ranging from 30% to 87%. There was a significant electronic effect among these substrates. Substrates **1x** and **1y**, which have strong electron-withdrawing groups (–CN, –CO<sub>2</sub>Me), only provide target products **3x** and **3y** with yields of 30% and 60%, respectively, under this electrochemical transformation. The conversion efficiency of *NH*-sulfoximines with weak electron-withdrawing groups (–Cl) and electron-donating groups (–Me, –OMe) was similar. When comparing the results of different positional isomers, it had little influence on the yields (**3u**, 82% vs. **3z**, 87% vs. **3za**, 86%). Naphthalene-substituted *NH*-sulfoximine was also a suitable substrate and delivered the target product in 80% yield (**3zb**). In the reactions of *S*-aryl-*S*-methyl sulfoxi-

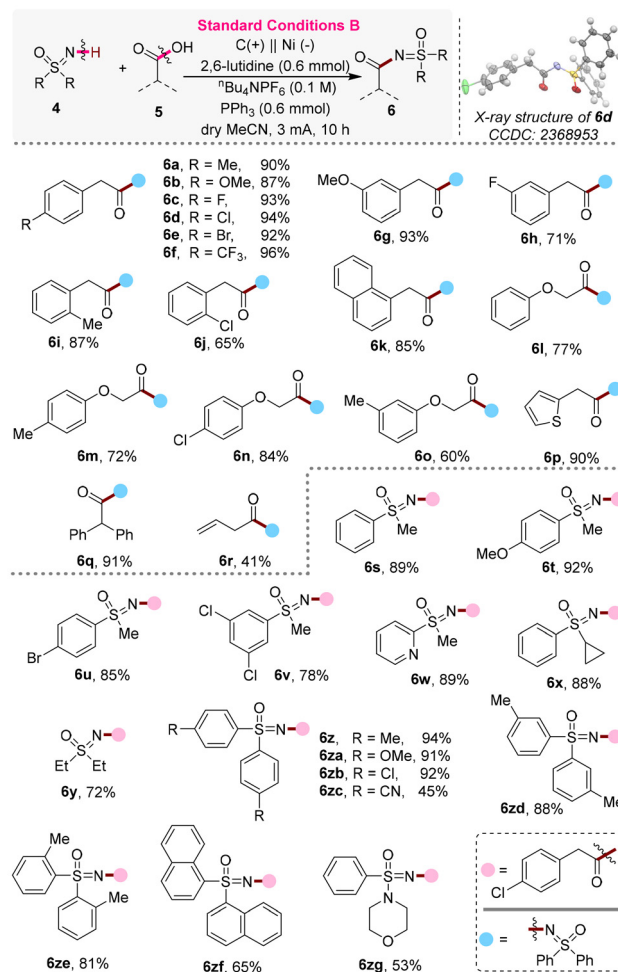
mines, both alkoxy and bromide were well tolerated under the optimal conditions, affording the corresponding products **3zc–3ze** with dr values of approximately 1:1 and yields ranging from 60% to 91%. Moreover, *S*-3,5-dichlorophenyl-*S*-methyl sulfoximines, *S*-aryl-*S*-cyclopropyl sulfoximines and *S,S*-diethyl sulfoximines all transformed to the expected products **3zf** (70%, dr ~1:1.2), **3zg** (79%, dr ~1:1.1) and **3zh** (65%), respectively. These results demonstrated the robustness of this procedure toward the steric and electronic variations of the sulfoximine counterpart.

We observed that carboxylic acids can not only directly decarboxylate to form C–X bonds but can also undergo acylation *via* deoxygenation with the assistance of PPh<sub>3</sub>.<sup>76–79</sup> Subsequently, we investigated the *N*-acylation of sulfoximines with carboxylic acids. Initially, we attempted to use PPh<sub>3</sub> to deoxygenate amino acids (such as **2a**, **2f**) for *N*-acylation, but instead, we obtained decarboxylated products. We then focused on primary carboxylic acids, and after preliminary attempts with phenylacetic acid (**5d**) reacting with sulfoximine, we successfully achieved *N*-acylation. Through a series of optimization conditions (for more information on the screening of conditions, see ESI section 4†), we identified the optimal conditions for PPh<sub>3</sub>-assisted electrochemical deoxygenation *N*-acylation of sulfoximines. After extensive experimentation to screen the current, electrode, electrolyte, *etc.*, the best result was obtained by conducting the electrolysis at room temperature under a constant current of 3.0 mA in an undivided cell equipped with a graphite anode and a nickel cathode in solvent dry acetonitrile containing <sup>18</sup>Bu<sub>4</sub>NPF<sub>6</sub> as the supporting electrolyte, with 2,6-lutidine as a non-oxidizable base. Under these conditions, the desired product **6d** was obtained in 94% isolated yield (standard conditions B).

We subsequently evaluated the substrate scope and functional group compatibility of the *N*-acylation strategy using PPh<sub>3</sub> additives (Scheme 3). Similarly, the scope and tolerance of the reaction were explored initially by varying the carboxylic acids. A range of phenylacetic acids with electron-donating (**6a**, –Me; **6b**, –OMe) or electron-withdrawing (**6c**, –F; **6d**, –Cl; **6e**, –Br; **6f**, –CF<sub>3</sub>) groups located at the *para*-position were effectively converted to the corresponding products (87%–96%).

Comparing the results of positional isomers, there was little influence on the yields (**6a**, 90% *vs.* **6i**, 87%; **6b**, 87% *vs.* **6g**, 93%; **6c**, 93% *vs.* **6h**, 71%; **6d**, 94% *vs.* **6j**, 65%). Naphthylacetic acid was also converted with an 85% yield. Phenoxyacetic acids with various substituents were also transformed into the expected products (**6l–6o**, 60%–84%). Notably, thiopheneacetic acid, diphenylacetic acid, and 4-pentenoic acid also participated in this transformation, with corresponding product yields of 90%, 91%, and 41%, respectively.

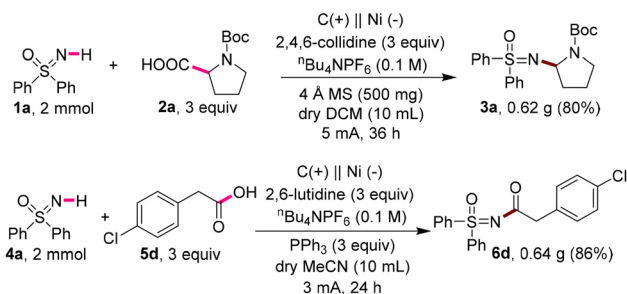
Next, a diverse array of sulfoximines proved to be effective substrates for the construction of the corresponding *N*-acylated compounds. First, *S*-aryl-*S*-methyl sulfoximines were investigated and it was found that *para*-substituted alkoxy and bromide were effectively converted to the corresponding products **6s–6u** with yields ranging from 85% to 92%. Furthermore, *S*-3,5-dichlorophenyl-*S*-methyl sulfoximine,



**Scheme 3** Substrate scope of the electrochemical deoxygenation and *N*-acylation of carboxylic acids and sulfoximines. Standard conditions B: N–H sulfoximines (0.2 mmol), carboxylic acids (0.6 mmol), 2,6-lutidine (0.6 mmol), Bu<sub>4</sub>NPF<sub>6</sub> (0.1 M), PPh<sub>3</sub> (0.6 mmol), dry MeCN (4.0 mL), constant current = 3 mA under air for 10 hours, in an undivided cell.

*S*-pyridyl-*S*-methyl sulfoximine, *S*-aryl-*S*-cyclopropyl sulfoximine and *S,S*-diethyl sulfoximine all reacted efficiently and were transformed to the expected products **6v** (78%), **6w** (89%), **6x** (88%) and **6y** (72%), respectively. As for NH-diphenylsulfoximines, electron-donating groups (–Me, –OMe) and weakly electron-withdrawing groups (–Cl) performed well (81%–94%), while strongly electron-withdrawing groups (**6zc**, –CN) only provided a 45% yield of the target product. Furthermore, the substrates with substituents at the *meta* or *ortho* positions proceeded effectively, affording the desired products in similar yields to those with *para*-substituents (**6z**, 94% *vs.* **6zd**, 88% *vs.* **6ze**, 81%). Additionally, we found that naphthalene-substituted NH-sulfoximine (**6zf**, 65%) and sulfonimidamide (**6zg**, 53%) were well tolerated under the optimal reaction conditions.

To examine the practicability and scalability of the decarboxylative and deoxygenative transformations between sulfoximines and carboxylic acids, 10-fold scaled reactions were conducted by simply amplifying the dosages of every reagent

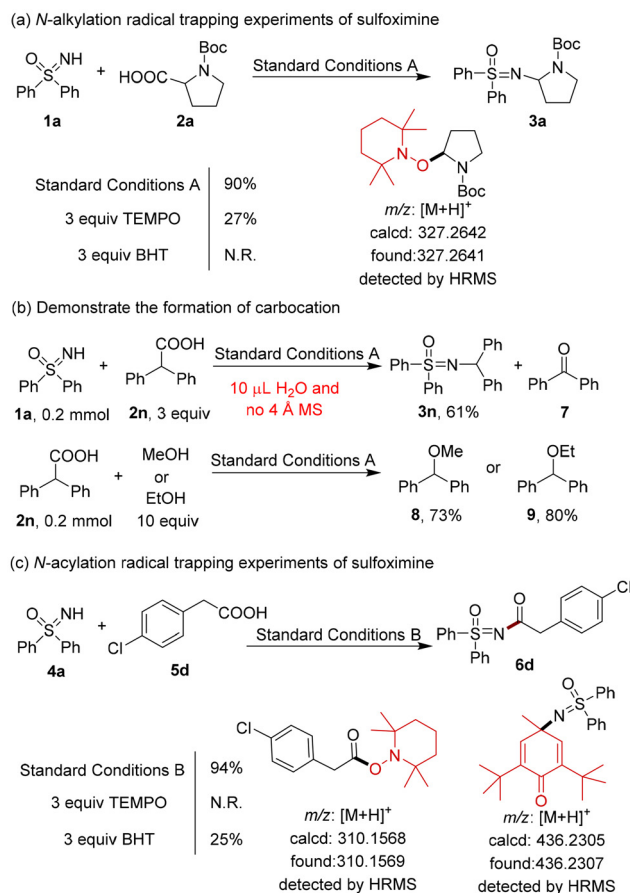


**Scheme 4** Gram-scale synthesis of **3a** and **6d**.

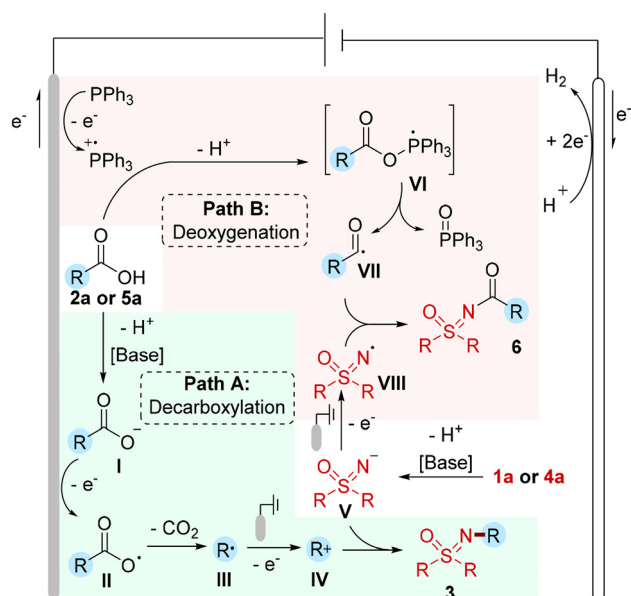
under the optimal conditions, respectively. As shown in Scheme 4, both the decarboxylation and deoxygenation proceeded smoothly, yielding 0.62 g of *N*-alkyl sulfoximine **3a** (80%) and 0.64 g of *N*-acyl sulfoximine **6d** (86%), respectively.

Subsequently, we performed several mechanistic experiments to gain more insight into the reaction process. For the decarboxylative *N*-alkylation reaction, under standard conditions, the addition of 3.0 equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical scavenger, significantly inhibited the formation of **3a**. Alkyl radical trapping products were detected *via* HRMS. The transformation did not proceed when using butylated hydroxytoluene (BHT) as a radical scavenger. This indicated that **2a** was decarboxylated to generate alkyl radicals under electrode oxidation (Scheme 5a). To verify the formation of a carbocation, sulfoximine **1a** and diphenylacetic acid **2n** were reacted under standard conditions with the addition of 10  $\mu$ L of water and without 4 Å molecular sieves. This resulted in a 61% yield of the target product **3n** and diphenyl ketone **7** (Scheme 5b). This implied that diphenylmethyl radicals, after the generation *via* radical decarboxylation, were further oxidized to carbocations, which could then be simultaneously trapped by both sulfoximines and water as nucleophiles. Additionally, methanol and ethanol could also act as nucleophiles to trap carbocation intermediates, yielding (diphenylmethyl) methyl ether (73% yield) and (diphenylmethyl) ethyl ether (80% yield), respectively. These results provided strong evidence for the involvement of carbocation intermediates. For the *N*-acylation of sulfoximines, the use of TEMPO and BHT as radical scavengers also significantly inhibited the formation of the target product. HRMS analysis detected the trapping products of acyl radicals and sulfoximine nitrogen radicals, respectively (Scheme 5c), indicating the possibility that both these radical species were generated and participated in the reaction mechanism.

Based on the above experimental results, we postulated two distinct pathways as shown in Scheme 6. Path A involves the decarboxylative *N*-alkylation process (green square). Under basic conditions, carboxylate anion **I** is initially formed, followed by oxidation at the anode to generate carboxyl radical intermediate **II**. Rapid decarboxylation then forms alkyl radical **III**, which yields carbocation **IV** upon further anodic oxidation. Simultaneously, sulfoximines lose a proton under basic conditions to form sulfoximine anion **V**, which then



**Scheme 5** Mechanistic studies. (a) *N*-Alkylation radical trapping experiments of sulfoximines. (b) Demonstration of carbocation formation. (c) *N*-Acylation radical trapping experiments of sulfoximines.



**Scheme 6** Proposed mechanism.

nucleophilically attacks carbocation **IV** to yield the final product **3**. For *N*-acylation (Scheme 6, path B, pink square), initially, the anodic oxidation of triphenylphosphine generates its cationic radical, which reacts with the carboxylic acid to form a P–O bond, yielding radical intermediate **VI**. Then, **VI** undergoes  $\beta$ -scission to produce acyl radical **VII** and triphenylphosphine oxide. Simultaneously, the single electron transfer (SET) of sulfoximines anion **V** at the anode produces *N*-centered radical **VIII**. Subsequently, *N*-centered radical **VIII** and acyl radical **VII** combined *via* direct radical coupling to yield the desired product **6**.

## Conclusions

In summary, a controllable electrochemical strategy has been developed to achieve *N*-alkylation and *N*-acylation reactions of sulfoximines with readily available carboxylic acids. This method addresses a crucial gap in green synthesis by enabling efficient N–C bond formation at room temperature and without the need for external oxidants, metal catalysts, or sacrificial electrodes. A simple undivided cell setup using commercially available inexpensive electrodes, coupled with easy scalability, highlights the practicality of this reaction. Besides the recoverable phosphine oxide, hydrogen and carbon dioxide are relatively green and clean by-products. This *N*-functionalization of sulfoximines *via* the decarboxylation and deoxygenation of carboxylic acids can deliver a series of products that have not been accessed previously and is expected to broaden the availability and application of sulfoximine derivatives.

## Data availability

All relevant data are available within the manuscript and its ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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