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Decarboxylative sulfinamidation of *N*-sulfinylamines with carboxylic acids *via* a photochemical iron-mediated ligand-to-metal charge transfer process†

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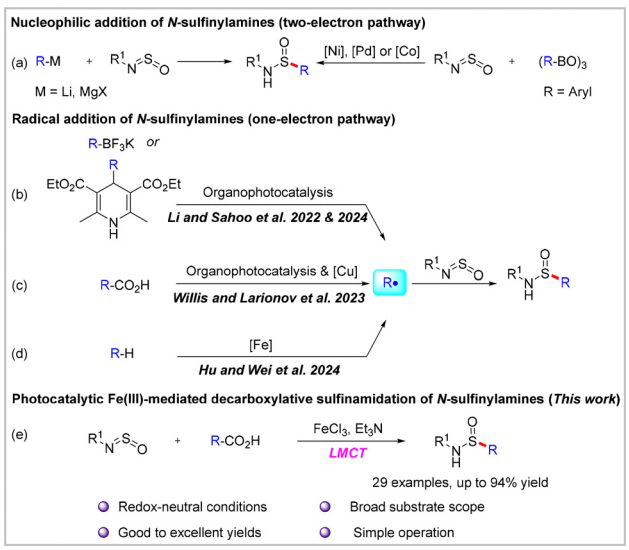
Sulfinamides are valuable four-valent sulfur compounds in medicinal chemistry, yet methods relying on simple and readily available feedstocks are scarce. Herein, a novel and efficient strategy was developed to facilitate the direct decarboxylative sulfinamidation of carboxylic acids *via* a photoinduced iron-mediated ligand-to-metal charge-transfer process. Notably, this protocol exemplifies an environmentally benign approach to the synthesis of a range of structurally diverse sulfinamides with an excellent functional group compatibility, thereby rendering it suitable for the late-stage modification of bioactive molecules.

The sulfinamide motif is widely recognized as one of the most important motifs in organic synthesis.[1] The four-valent sulfinyl group has been demonstrated to facilitate the unification of a comprehensive organosulfur chemical library containing all of the predominant sulfur functional groups, including sulfonamides,[2] sulfoximines,[3] sulfonimidamide esters,[4] and sulfonimidoyl halides.[5] Moreover, the prevalence of this group is widely found in pharmaceutical compounds (and related compounds) that have been previously approved by the United States Food and Drug Association.[6] In addition, enantiopure sulfonamides and their derivatives have been extensively used as chiral auxiliaries,[7] ligands,[8] and organocatalysts[9] in asymmetric synthesis. Given their pivotal functions in organic synthesis, a considerable corpus of creative strategies has been dedicated to their preparation. Conventional access to sulfonamides primarily involves the two-electron nucleophilic substitution of amines with unstable sulfinyl chlorides, which in turn are derived from sulfinic acids and sulfinate salts in the presence of oxalyl chloride or thionyl chloride.[10] Recent studies have demonstrated that the addition of organometallic reagents to *N*-sulfinylamines represents an efficient manner for the synthesis of sulfonamides and related organosulfur derivatives (Scheme 1a).[11] Notwithstanding the ingenious methodologies that have been developed, the application of one-electron routes to sulfinamides remains in its infancy.

Photocatalysis has recently emerged as a reliable tool for the chemical community, facilitating the generation of carbon-centered intermediates, wherein coupling with *N*-sulfinyl amines has been employed to prepare sulfinamides *via* one-electron processes under mild conditions. In the course of the synthesis of alkyl sulfonamides, 1,4-Dihydropyridines (DHPs)[12] or potassium trifluoro(organo)borates[13] (as nucleophilic alkyl radical precursors) were employed in combination with



Scheme 1 Previous strategies for the synthesis of sulfinamides and our design.

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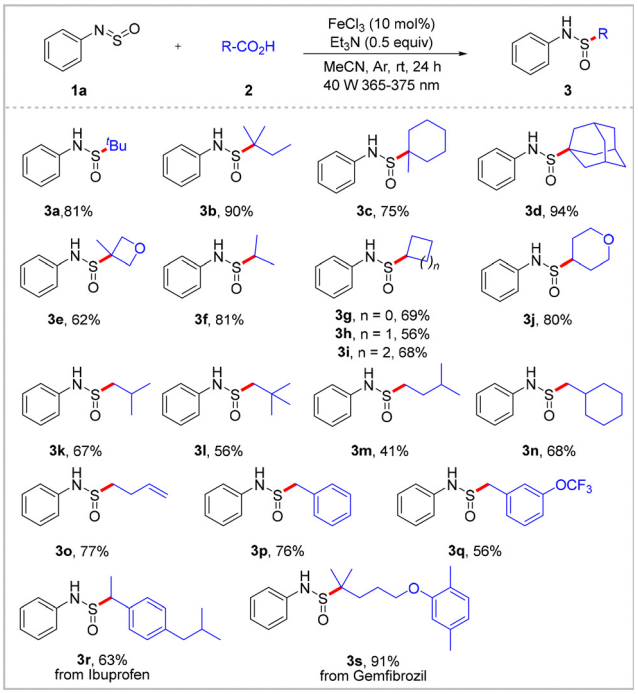
N-sulfinylamines (as electrophiles) in the presence of organic photosensitizers (Scheme 1b). Subsequently, Willis[14] and Larionov[15] independently described the use of decarboxylative sulfinamidation reactions to access sulfinamides using readily available carboxylic acids as alkyl radical sources (Scheme 1c). More recently, Hu *et al.* reported the direct C(sp^3)–H bond sulfinamidation of simple hydrocarbons and *N*-sulfinylamine *via* a photochemical iron-mediated ligand-to-metal charge-transfer process (Scheme 1d).[16] Despite these achievements, the development of green and efficient synthesis strategies still holds great opportunities.

Carboxylic acids are structurally diverse compounds from nature, organisms and synthesis.[17] Owing to their abundant, stable, and non-toxic properties, along with their widespread availability, carboxylic acids are regarded as optimal structural units for the assembly of intricate molecular frameworks through a one-electron process.[18] Nevertheless, the direct conversion of carboxylic acids to other functional groups remains challenging due to the high oxidation potentials and reactivities of carboxylic acids, which prevent the decarboxylative radical generation protocol that is common in catalytic reactions. Iron-mediated ligand-to-metal charge transfer (LMCT), an electronic transition from the filled orbital of a ligand to the vacant orbit of a metal center, has recently emerged as a powerful strategy for the efficient generation of alkyl radicals from carboxylic acids. Notably, this approach has enabled the direct conversion of carboxylic acids into a variety of functionalities *via* an open–shell mechanism.[19] In the context of our sustained research interest in the decarboxylative functionalization of carboxylic acids *via* one-electron processes,[20] the work presented herein describes our most recent findings concerning the direct decarboxylative transformation of aliphatic carboxylic acids to generate sulfonamides *via* an iron-mediated LMCT process (Scheme 1e).

Initially, sulfinylamine **1a** and pivalic acid **2a** were employed as model substrates for the preparation of sulfinamide **3a** (see ESI,† Tables S1–S5). To our delight, **3a** was obtained in a 22% isolated yield in the presence of 10 mol% $FeCl_3$ as the photocatalyst, along with K_2CO_3 as the base in acetonitrile (MeCN), under irradiation with a 40 W violet light-emitting diode (LED, 365–375 nm) at room temperature (Table S1, entry 1, ESI†). Subsequently, a range of iron salts were tested, and it was established that $FeBr_3$ exhibited a considerable catalytic activity. Conversely, $Fe_2(SO_4)_3$, $Fe(OTf)_3$, and $FeSO_4$ proved ineffective within the parameters of this protocol (Table S1, entries 2–7, ESI†). Switching the reaction solvent to CH_2Cl_2, tetrahydrofuran (THF), dimethylformamide (DMF), or dimethyl sulfoxide (DMSO) led to reduced product yields (Table S2, ESI†). Different bases were also investigated, including Na_2CO_3, Na_3PO_4, Et_3N, and pyridine, with an enhanced yield of 69% being achieved using Et_3N as the base (Table S3, entries 1–8, ESI†). Notably, the yield was further increased to 81% when the Et_3N dosage was reduced to 0.5 equivalents (Table S3, entry 9, ESI†). In addition, light sources with different wavelengths were examined to replace the violet LED, with blue and white LEDs yielding the corresponding product **3a** in yields of 18 and 74%,

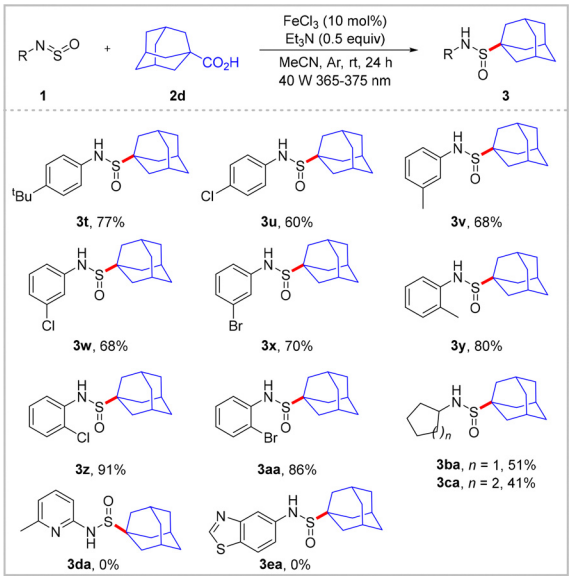


Scheme 2 Substrate scope of carboxylic acids **2**. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $FeCl_3$ (10 mol%), Et_3N (0.5 equiv.), MeCN (2 mL), 40 W violet LED (365–375 nm), Ar, rt, 24 h. Isolated yields.

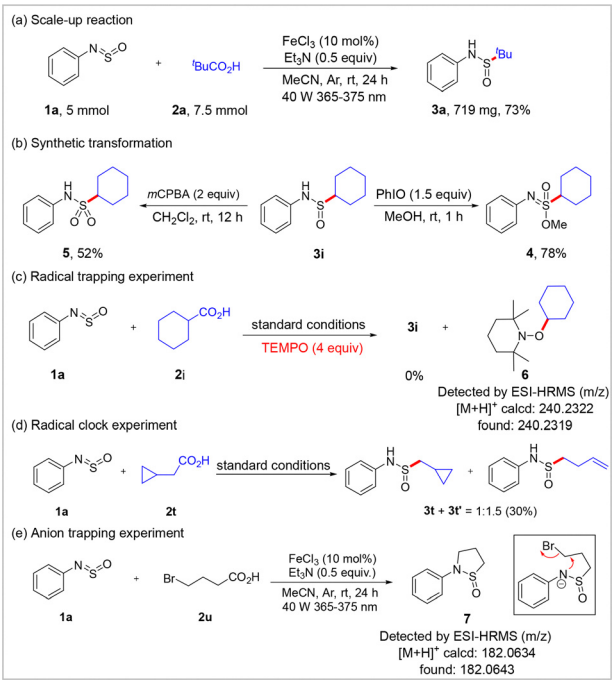
respectively (Table S4, ESI†). Additionally, control experiments revealed that $FeCl_3$, Et_3N, light irradiation, and an argon atmosphere were essential for the successful execution of this transformation (Table S5, ESI†).

With the optimized conditions in hand, various carboxylic acids **2** were treated with sulfinylamine **1a** under the standard conditions to yield the corresponding sulfinamides **3**, as summarized in Scheme 2. A survey of various tertiary carboxylic acids revealed the most suitable reaction coupling partners for this transformation, yielding the corresponding sulfinamides in 62–94% yields (**3b–3e**). This decarboxylative sulfinamidation reaction also proceeded well using an assortment of acyclic and cyclic secondary carboxylic acids, affording products **3f–3j** in good yields (56–81%). Primary carboxylic acids were also suitable for application in this catalytic system, with the desired sulfinamides **3k–3q** being produced in satisfactory yields. These results clearly demonstrate the potential application of the developed method for the subsequent modification of bioactive molecules. More specifically, ibuprofen and gemfibrozil were successfully converted into sulfonamides **3r** and **3s** in an equally straightforward manner under the optimized conditions.

The scope of the *N*-sulfinylamine component was subsequently investigated using 1-adamantanecarboxylic acid **2d** (Scheme 3). It was found that the electronic nature of the phenyl substituent had a negligible effect on reaction yield. However, the position of the substituent had a relatively significant impact on the yield of this transformation, wherein the substrates bearing an *ortho*-substituent gave slightly higher



Scheme 3 Substrate scope of *N*-sulfinylamine **1**. **1** (0.2 mmol), **2d** (0.3 mmol), $FeCl_3$ (10 mol%), Et_3N (0.5 equiv), MeCN (2 mL), 40 W violet LED (365–375 nm), Ar, rt, 24 h. Isolated yields.

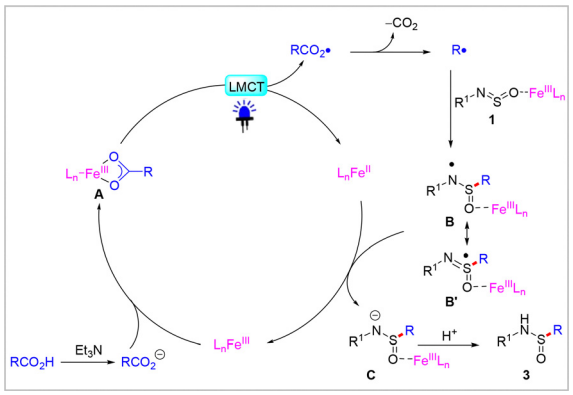


Scheme 4 Synthetic applications and control experiment.

yields than those bearing *para*- and *meta*-substituents (**3t–3aa**). Of particular importance was the tolerance of the reaction toward chloride and bromide groups, which enabled modification of the halogenated position. Additionally, *N*-alkylsulfinylamines were efficiently converted to the corresponding sulfonamides **3ba** and **3ca** in yields of 51 and 41%, respectively. However, heteroary sulfinylamines **1da** and **1ea** proved incompatible with this catalytic system.

To demonstrate the practicality of the developed method, a 5 mmol scale-up experiment was carried out under standard conditions, giving target compound **3a** in 73% yield (Scheme 4a). Subsequently, the obtained sulfinamides were easily converted into valuable S(VI) congeners. More specifically, sulfonimidate ester **4** was conveniently constructed in 78% yield *via* an iodosylbenzene-mediated oxidation/nucleophilic addition cascade using methanol as the nucleophile (Scheme 4b, right).[21] In addition, sulfinamidation product **3i** was efficiently oxidized to sulfonamide **5** in 52% yield using *meta*-chloroperbenzoic acid (*m*CPBA) as the oxidant (Scheme 4b, left). A control experiment was also performed to elucidate the reaction mechanism. More specifically, when 4 equiv. of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) was added to the reaction system under standard conditions, the reaction was completely inhibited, and the corresponding TEMPO-adduct **6** was detected by high-resolution mass spectrometry (HRMS) (Scheme 4c). A radical clock experiment involving **1a** with **2t** yielded in a mixture of non-ring-opened product **3t** and the ring-opened product **3t'** in a 1 : 1.5 ratio (Scheme 4d). Both the radical trapping experiment and the radical clock experiment confirmed that the reaction proceeds *via* a decarboxylation-induced alkyl radical pathway. Cyclic sulfinamide **7** was observed when **1a** reacted with 4-bromobutyric acid **2u**, supporting the generation of a sulfinamide anion intermediate in this reaction (Scheme 4e).

Based on the control experiments and previous reports,[22] a possible mechanism for this transformation was proposed, as shown in Scheme 5. Initially, the in situ-generated carboxylate anions coordinate with Fe(III) cations to form intermediate **A**. This intermediate undergoes intramolecular carboxylate-to-Fe(III) charge transfer process to produce the Fe(II) species and the corresponding carboxylate radical. The reaction is initiated by the release of CO_2 from the carboxylate radical, which subsequently generates a key alkyl radical. Then addition of alkyl radical to Fe(III) coordinated *N*-arylsulfinylamine **1** to form aminosulfinyl radical **B**, where O-binding is proposed in analogy to the prior report with MgX_2.[23] Density functional theory (DFT) computations have also elucidated that $FeCl_3$ acts as a Lewis acid in facilitating nucleophilic attack processes



Scheme 5 Proposed mechanism.

(see ESI,† Fig. S1). Subsequently, the single-electron reduction of aminosulfinyl radical **B** by leads to the generation of the corresponding Fe(III) species and anion **C**. Finally, the protonation of anion **C** provides the desired sulfonamide product **3**.

In conclusion, a novel and direct protocol for the decarboxylative sulfinamidation of carboxylic acids was developed *via* a photoinduced iron-mediated LMCT process. This approach features mild conditions and is a straightforward procedure for the preparation of a range of structurally diverse sulfonamides, demonstrating an excellent functional group compatibility. Furthermore, the obtained sulfonamides were smoothly transformed into valuable sulfur(VI) derivatives including sulfonamides and sulfonimidate esters. It is expected that the versatility of this method will result in its widespread application in the preparation of sulfur-containing derivatives.

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Conflicts of interest

There are no conflicts to declare.

Data availability

All experimental procedures, characterization data and NMR spectra for all new compounds can be found in the ESI.†

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