A General Nitrene Transfer to Sulfides Enabled by Visible-Light-Mediated Triplet Energy Transfer to Sulfonyl Azides

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ABSTRACT: Sulfilimines and their derivatives have garnered considerable interest in both synthetic and medicinal chemistry. Photochemical nitrene transfer to sulfides is known as a conventional synthetic approach to sulfilimines. However, the existing methods have a limited substrate scope stemming from the incompatibility of singlet nitrene intermediates with nucleophilic functional groups. Herein, we report a general nitrene transfer for the synthesis of *N*-sulfonyl sulfilimines enabled by visible-light-mediated energy transfer to sulfonyl azides, uncovering the neglected reactivity of triplet nitrenes with sulfides. The unprecedented mechanism involving single electron transfer enabled broad functional group tolerance, water compatibility, and amenability to use for the late-stage functionalization of drugs.

Sulfilimines, which can be viewed as the aza-analogs of sulfoxides, play a variety of functional roles in biology and chemistry. Nature employs sulfilimines as cross-links between methionine and hydroxylysine residues in collagen IV networks (Figure 1).[1] Sulfilimine motifs are also found in bioactive compounds such as TPh A, an inhibitor of the nuclear protein pirin.[2] Sulfilimines can be oxidized to generate sulfoximines, which have received significant attention as a new toolbox in medicinal chemistry and are found in various drug candidates, such as the ATR inhibitor ceralasertib.[3] In organic chemistry, sulfilimines can serve as valuable precursors or reagents for the synthesis of nitrogen-containing molecules.[4] Recently, Ritter demonstrated a novel transformation of alkenes into *N*-heterocycles via a radical-polar crossover annulation enabled by tailored sulfilimines acting as bifunctional *N*-radical precursors.[4i]

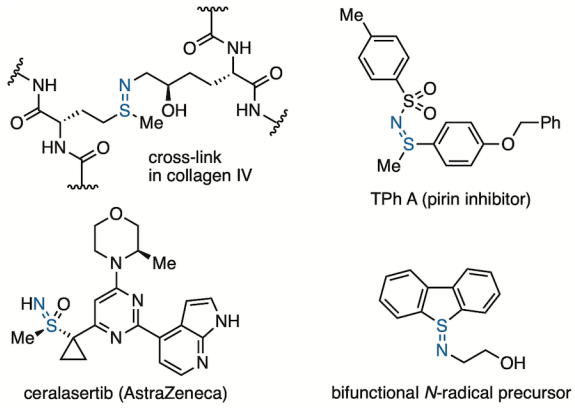


Figure 1. Examples of sulfilimines and their oxidized derivatives.

The conventional synthetic approach to sulfilimines entails the imination of readily available sulfides through nitrene transfer or, alternatively, the substitution of *in situ* generated halosulfonium intermediates with nitrogen nucleophiles (Figure 2A, left).[5,6] However, this strategy is often plagued by a limited substrate scope that arises from the oxidizing conditions. Recently, a novel strategy based on alternative disconnections for the preparation of sulfilimines emerged,[7] involving the formation of a C–S bond between a sulfenamide and a carbon electrophile (Figure 2A, right). This approach offers access to sulfilimines under milder reaction conditions but additional synthetic steps are required to prepare the pre-functionalized substrates. Thus, there is a need to develop iminations of sulfide feedstocks that provide a wider substrate scope, to enable rapid access to complex and functionalized sulfilimines.

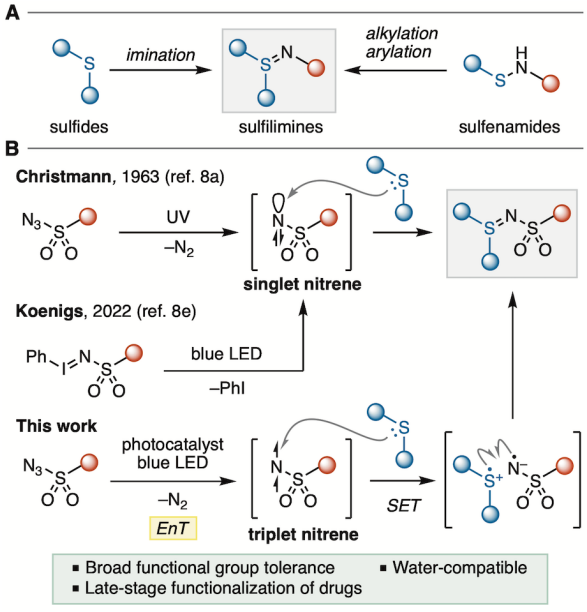
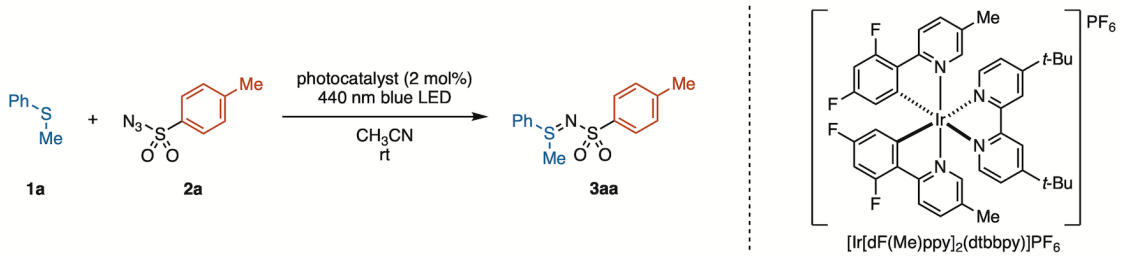


Figure 2. (A) General synthetic strategies for sulfilimines. (B) Sulfilimine synthesis via photochemical nitrene transfer.

Although photochemical methods are known as an attractive approach to circumventing elevated temperatures to generate nitrenes, substrate limitation remains an unsolved problem in

Table 1. Optimization of Reaction Conditions



entry	photocatalyst	E_T (kcal/mol)[a]	$E_{1/2}(Ir^{IV}/*Ir^{III})$[a]	$E_{1/2}(*Ir^{III}/Ir^{II})$[a]	yield **3aa** (%)[b]
1	$[Ir(dtbbpy)(ppy)_2]PF_6$	49.2	–0.96	+0.66	48
2	$Ir(ppy)_3$	55.2	–1.73	+0.31	6
3	$[Ir(dFppy)_2(dtbbpy)]PF_6$	55.4	–0.93	+1.14	88 (86)
4	$[Ir[dF(Me)ppy]_2(dtbbpy)]PF_6$	60.2	–0.92	+0.97	90 (91)
5	$[Ir[dF(CF_3)ppy]_2(bpy)]PF_6$	60.4	–1.00	+1.32	ND
6	none	–	–	–	ND
7	same as entry 4 (Reaction was performed **in the dark**)				ND

Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), photocatalyst (2 mol%), CH_3CN (2 mL), 440 nm Kessil LED, under N_2, rt, 15 h. Structures of the photocatalysts are shown in Figure S2. [a]Literature values.[14] Half-wave potentials ($E_{1/2}$) are given versus saturated calomel electrode (SCE). [b]Yields as determined by ^1H NMR of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are provided in the parentheses. ND: not detected.

the synthesis of sulfilimines via photochemical nitrene transfer.[8] For a classical example, Christman demonstrated that aryl sulfonyl azides irradiated with ultraviolet (UV) light with an excess amount of dimethyl sulfide yielded the corresponding sulfilimines in conjunction with the loss of nitrogen (Figure 2B, top).[8a] However, this reaction lacks substrate generality posed by deleterious UV irradiation and the incompatibility of electrophilic singlet nitrenes possessing an empty orbital with nucleophilic functional groups, as evidenced by the formation of adducts of the nitrenes with solvents such as methanol and pyridine.[8b] Recently, Koenigs developed lower-energy visible-light-mediated iminations using iminoiodinanes as nitrene precursors (Figure 2B, middle).[8e] Computational studies suggested that singlet nitrenes as the reactive intermediates undergo nucleophilic attack of sulfides, whereas the reactions with alkenes occur through intersystem crossing (ISC) from singlet to triplet nitrenes.[10]

We hypothesized that the substrate limitations associated with photochemical sulfilimine synthesis could be overcome by replacing the singlet nitrene intermediates with triplet nitrenes characterized by two unpaired electrons on the nitrogen atom (Figure 2B, bottom). Triplet nitrenes were expected to be less susceptible to undesired nucleophilic attacks owing to the absence of an empty orbital. The diradical nature could induce the reactivity toward sulfides through a single electron transfer (SET) process. Recombination of the resulting radical ion pair would lead to the formation of sulfilimines. Inspired by Christman's pioneering work (Figure 2B, top) and a recent surge in visible-light-mediated triplet energy transfer (EnT),[11] it was envisaged that triplet nitrenes could be accessed via EnT to readily available and bench-stable sulfonyl azides.[12,13] Herein, we report the successful realization of the visible-light-mediated synthesis of sulfilimines via triplet nitrenes, which have been neglected as potential reactive species for sulfide iminations. We demonstrate that the SET-based distinct mechanism enables broad functional group tolerance, water compatibility, and amenability to late-stage functionalization of drugs.

We began our investigations by testing reaction conditions using thioanisole (**1a**) and tosyl azide (**2a**) in the presence of a photocatalyst in CH_3CN under irradiation of a 440 nm blue LED (Table 1). Employing $[Ir(dtbbpy)(ppy)_2]PF_6$ provided sulfilimine **3aa** in 48% NMR yield (entry 1). Subsequently, photocatalysts having higher triplet energy (E_T) were evaluated. The use of $Ir(ppy)_3$ significantly reduced the yield, presumably due to the decomposition of **2a** ($E_{1/2}^{red}$ = –1.22 V vs SCE in CH_3CN)[12a] by SET from the highly reducing photocatalyst ($E_{1/2}^{red}[Ir^{IV}/*Ir^{III}]$ = –1.73 V) (entry 2). In agreement with this hypothesis, employing less-reducing $[Ir(dFppy)_2(dtbbpy)]PF_6$ drastically increased the yield of **3aa** to 88% (entry 3). Use of $[Ir[dF(Me)ppy]_2(dtbbpy)]PF_6$ possessing higher E_T led to a marginal improvement in the yield (entry 4). In sharp contrast, the use of $[Ir[dF(CF_3)ppy]_2(bpy)]PF_6$ did not afford **3aa**, presumably because the single electron oxidation of **1a** (+1.34 V vs SCE in CH_3CN)[15] was preferred over the EnT process due to the higher oxidizing nature ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.32 V) (entry 5). Control experiments showed that both a photocatalyst and light irradiation were indispensable to the reaction (entries 6 and 7). Hence, the judicious choice of photocatalysts, considering E_T as well as redox properties, was a key to the success due to the modest redox activities of both sulfide **1a** and sulfonyl azide **2a**.

With the optimized reaction condition in hand, we next investigated the scope of sulfonyl azides using **1a** as a model substrate (Figure 3A). Unsubstituted benzene sulfonyl azide afforded sulfilimine **3ab** in 83% yield. Both electron-donating and -withdrawing functionalities on the benzene ring were tolerated, including methoxy (**3ac**), trifluoromethyl (**3ad**), nitrile (**3ae**), amide (**3af** and **3ag**), ester (**3ah**, **3ak**, and **3al**), bromo (**3ai** and **3am**), and alkyl (**3aj**). Naphthalene (**3an**) and heteroaryl sulfonyl azides containing pyridine (**3ao**), imidazole (**3ap**), and thiophene (**3aq**) moieties also provided the desired products in

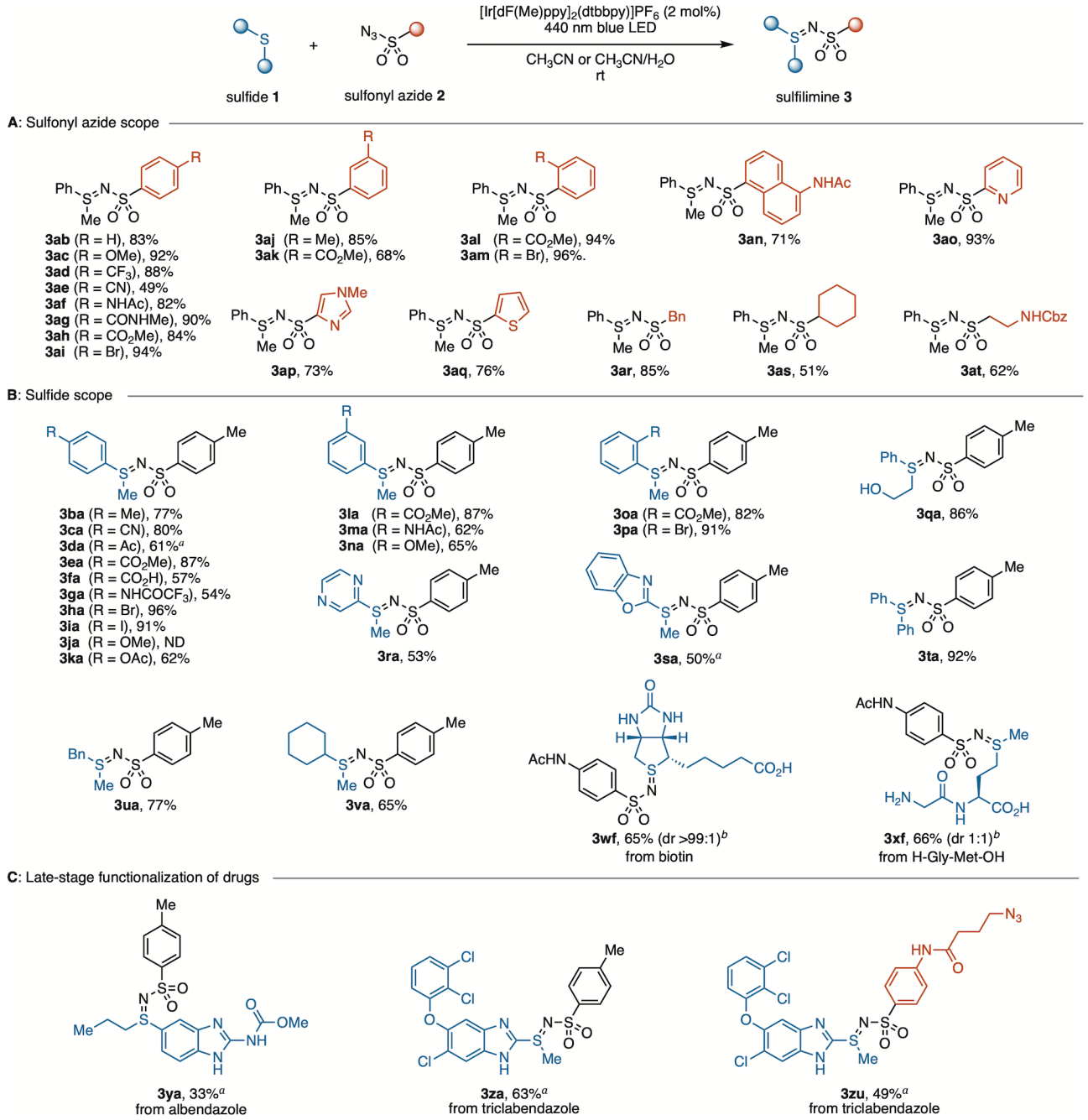


Figure 3. Substrate scope of the *N*-sulfonyl sulfilimine synthesis. Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), [Ir[dF(Me)ppy]$_2$(dtbbpy)]PF$_6$ (2 mol%), CH_3CN (2 mL), 440 nm Kessil LED, under N_2, rt, 15 h. Isolated yields are shown. ND: not detected. [a]24 h instead of 15 h. [b]CH_3CN:H_2O =1:1 instead of CH_3CN.

good to excellent yields. Alkyl sulfonyl azides were also amenable to this transformation (**3ar**–**3at**).

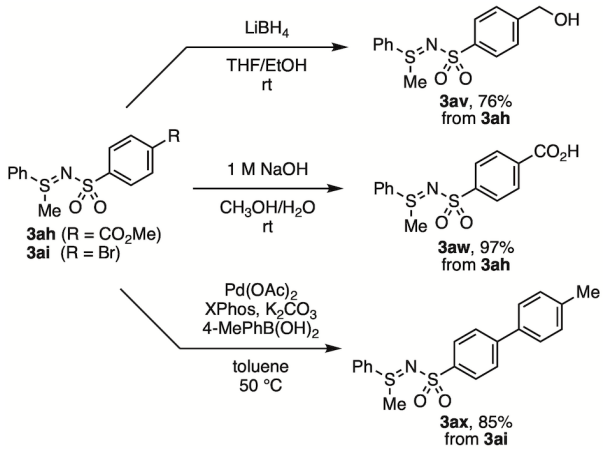
We then proceeded to explore the substrate scope with respect to sulfides (Figure 3B). A wide array of substituents on the S-aryl groups were well tolerated, including alkyl (**3ba**), nitrile (**3ca**), ketone (**3da**), ester (**3ea**, **3ka**, **3la**, and **3oa**), carboxylic acid (**3fa**), amide (**3ga** and **3ma**), bromo (**3ha** and **3pa**), iodo (**3ia**), and methoxy (**3na**). A limitation is the intolerance of the *para*-methoxy substituent, which failed to provide the desired product **3ja** presumably due to oxidative decomposition of the electron-rich starting sulfide. Thus, an electron-withdrawing group was required for the *para*-*O*-substituent, as exemplified by the formation of acetylated **3ka**. It is worth highlighting that **3qa** was obtained in a high yield and with the primary hydroxy group intact. Methylthio groups attached to heteroaromatics such as pyrazine (**3ra**) and benzoxazole (**3sa**) underwent the imination in moderate yields. Diaryl (**3ta**) and dialkyl sulfides (**3ua** and **3va**) were also suitable substrates for this transformation. The versatility and robustness of this synthetic method were demonstrated using more functionalized substrates. Biotin was transformed into **3wf** as a single diastereomer at the new S(IV) chiral center, notably in the presence of water as a cosolvent because of the low solubility in organic solvents. In this

case, 4-acetamidobenzenesulfonyl azide (**2f**) was employed based on its higher aqueous solubility. Given the water compatibility and broad functional group tolerance, this reaction was then applied to unprotected dipeptide H-Gly-Met-OH in aqueous CH_3CN, which successfully afforded **3xf** in 66% yield. This result suggests potential future applications involving the chemical modification of methionine residues in more complex peptides and proteins.[16]

To demonstrate the applicability of this method to drug discovery, we also examined the late-stage functionalization of drugs (Figure 3C).[17] Albendazole and trichlabendazole, commercially available benzimidazole-based drugs each containing a sulfide motif at different sites, were reacted with azide **2a**, which successfully provided sulfilimines **3ya** and **3za**, respectively. The introduced functional groups to the sulfur atoms could serve as a platform for gaining additional interactions with the drug targets and modulating the ADME (absorption, distribution, metabolism, and excretion) properties. It is noteworthy that an alkyl azide loaded on a sulfonyl azide via an amide linkage was also tolerated under the reaction conditions, as illustrated by the formation of **3zu**. We believe that our reactions, in combination with azide–alkyne click chemistry, could facilitate the synthesis of hybrid molecules including peptide–drug conjugates (PDC).[18]

We went on to explore the transformations of the products (Scheme 1). Based on prior derivatizations of the *N*-sulfonyl sulfilimines, including oxidation to sulfoximines[6,19] and desulfonylation[20] followed by C–N bond formations on the resulting free sulfilimines,[7b] we focused on simple transformations that maintained the *N*-sulfonyl sulfilimine moiety intact. The sulfilimine moiety of ester **3ah** was tolerated under reduction with lithium borohydride to primary alcohol **3av** or saponification with 1 M aqueous NaOH to carboxylic acid **3aw**. To demonstrate that bromide **3ai** could lead to further elaborated derivatives, we performed a Suzuki–Miyaura cross-coupling with 4-methylphenyl boronic acid to afford biaryl **3ax**.

Scheme 1. Product derivatizations



We then turned our attention to mechanistic experiments (Figure 4). UV/Vis spectra showed that the photocatalyst was the sole component capable of absorbing visible light (400–600 nm) and that no association of the reactants in the ground state was formed (Figure 4A). Stern–Volmer quenching experiments showed that sulfonyl azide **2a** quenched the luminescence of the photocatalyst more efficiently than sulfide **1a**, which is consistent with an EnT to the sulfonyl azide (Figure 4B). The E_T of sulfonyl azide **2a** was found to be 49.6 kcal/mol by density functional theory (DFT) calculations (Table S4),[21] which was lower than that of the photocatalyst (E_T = 60.2 kcal/mol). Thus, the thermodynamical feasibility of the EnT step was supported. Based on the redox potential of **2a** ($E_{1/2}^{red}$ = –1.22 V),[12a] we postulated that the quenching of the excited photocatalyst ($E_{1/2}^{red}[Ir^{IV}/*Ir^{III}]$ = –0.92 V) was not through a SET pathway. The small Stern–Volmer constant of K_{SV} = 1.0 M^{-1} also indicated that the EnT event competed with the decay of the excited photocatalyst. The activation barrier ($\Delta^{\ddagger}G$) for EnT can be estimated by Marcus theory from the energy difference (ΔG) and the reorganization energy (λ), which is the energetic cost associated with the structural distortion.[22] Structure optimizations of **2a** and its triplet state ^{3}**2a** using DFT suggested that the N–N–N bond angle was bent from 174.8° to 119.5° in association with elongation of the internal N–N bond from 1.24 Å to 1.42 Å upon excitation (Figure 4C). This significant geometrical change meant that **2a** had a higher reorganization energy (calculated as 56.0 kcal/mol, Table S5), accounting for the higher barrier and lower efficiency of the EnT event. Finally, the addition of the radical scavenger TEMPO to the standard reaction of **1a** with **2a** shut down the formation of sulfilimine **3aa** whereas the triplet nitrene was detected as bisTEMPO-adduct **4** by LC/MS analysis (Figure 4D).

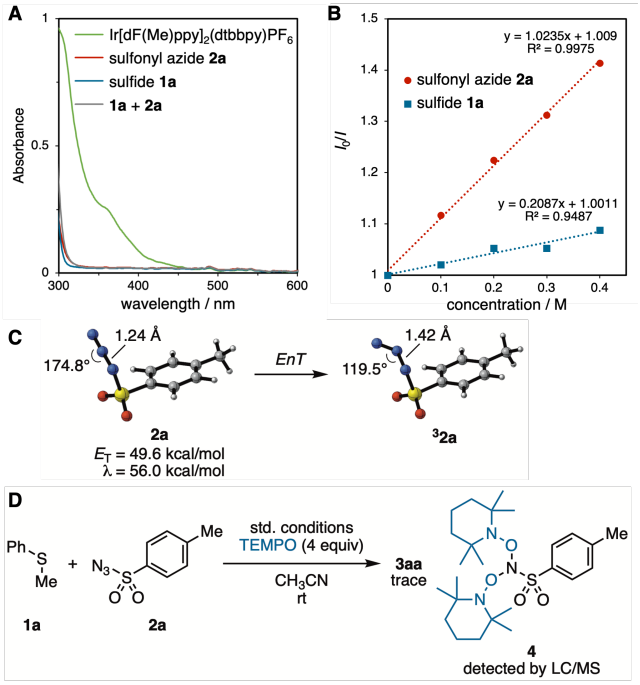


Figure 4. Mechanistic studies. (A) UV/Vis absorption spectra. (B) Stern–Volmer plot for quenching 0.1 mM [Ir[dF(Me)ppy]$_2$(dtbbpy)]PF_6. (C) Optimized structures of tosyl azide (**2a**) and its triplet state ^{3}**2a** by DFT calculations performed at the SMD(CH_3CN)-(U)B3LYP-D3/6-311++G(2d,p)//(U)B3LYP-D3/6-31+G(d) level of theory. (D) Trapping of the triplet nitrene with TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl).

Based on the experimental results, we propose the mechanism shown in Figure 5. Upon irradiation of blue light, the ground state of the iridium photocatalyst is excited to the triplet state (^{3}Ir) through photoexcitation and ISC.[11] EnT from the ^{3}Ir to sulfonyl azide **2** generates its triplet state ^{3}**2**, which decomposes to give triplet nitrene ^{3}**5** with the release of nitrogen gas.[12] SET from sulfide **1** to ^{3}**5** would then afford triplet radical ion pair ^{3}**6**,

leading to the formation of sulfilimine **3** through ISC and radical recombination. The possibility of a singlet nitrene pathway was considered but discounted because reverse ISC from triplet nitrene ^{3}**5** to the less stable singlet nitrene (by 14.6 kcal/mol in the case of tosyl nitrene **5a**)[8e] seemed unlikely.

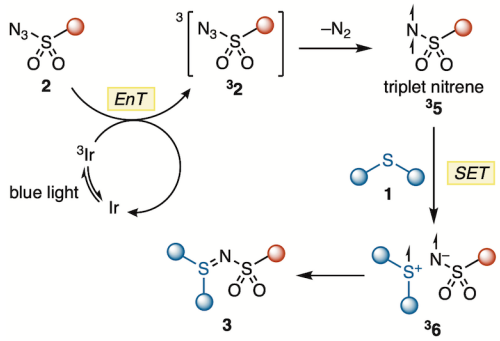


Figure 5. Proposed mechanism.

In summary, we have developed a general nitrene transfer for the synthesis of *N*-sulfonyl sulfilimines enabled by EnT to sulfonyl azides, uncovering the neglected reactivity of triplet nitrenes with sulfides. The unprecedented SET-based mechanism, which is distinct from the conventional nitrene transfer via a singlet nitrene, enabled remarkable functional group tolerance and amenability to use for reactions in aqueous solvent and late-stage functionalization of drugs. We expect this work will expand the synthetic and medicinal utilities of sulfilimines and their derivatives. We are investigating the application of this methodology to the functionalization of peptides and proteins at methionine residues.

ASSOCIATED CONTENT

Supporting Information

Experimental details, computational study, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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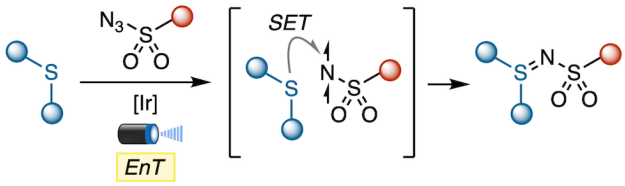

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