DECLARATION OF INTERESTS

The authors declare no competing interests.

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Sulfonylation enabled through the photoactivation of EDA complexes

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In this issue of *Chem Catalysis*, Molander and co-workers report the visible-light photoactivation of electron donor-acceptor (EDA) complexes formed between thianthrenium and sodium sulfinate derivatives to generate sulfone-containing compounds in moderate to good yields. This approach can be used for late-stage functionalization and enables the retention of halide handles.

The sulfone moiety represents one of the most important scaffolds in organic chemistry with derivatives that have found applications in, among others, material science, agrochemicals, and pharmaceuticals. Hence, it is not surprising that several synthetic routes have been developed over the years to gain access to these scaffolds. The most common strategies for the synthesis of sulfone-containing compounds include the oxidation of the corresponding sulfides or sulfoxides,[1] Friedel-Crafts-type sulfonylation of arenes, alkylation of sulfinate salts, addition reactions to alkenes and alkynes or by decarboxysulfonylation.[2,3] Among these, the direct oxidation of sulfides is the most commonly used pathway to obtain sulfones. Unfortunately, this method usually requires harsh reaction conditions (excess oxidizing agent, high temperatures, or long reaction times to achieve the complete conversion of the intermediate sulfoxide to the sulfone), which can limit the functional group tolerance and substrate scope and be of environmental concern.[4] To circumvent these limitations, light-mediated transformations (via the broadly defined "photoredox catalysis" approach) have emerged and serve as alternatives to access sulfones under milder conditions. A portion of these reactions are based on photoinduced sulfur dioxide insertion using metabisulfite salts ($Na_2S_2O_5$ or $K_2S_2O_5$) or SO_2 gas surrogates such as DABSO (1,4-Diazabicyclo [2.2.2]octane bis(sulfur dioxide) adduct).[5] However, these reactions require the use of exogenous photocatalysts such as the prototypical $[Ru(bpy)_3]^{2+}$, $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$, or Rhodamine 6G. Alternatively, (hetero)aryl sulfone derivatives can be obtained via Ni/photoredox dual catalysis, as reported for example in the C_{sp^2}–SO_2R coupling using sulfinate salts.[6] Still, the scope of this approach was unfortunately limited to the C_{sp^2}–SO_2R

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coupling and was not extendable to the C_{sp}^3–SO_2R coupling.

In recent years, new, versatile, and sustainable strategies based on electron donor-acceptor (EDA) complex photoactivation have emerged to perform C–S bond formation.[7] This EDA approach relies on the association of an electron donor and an electron acceptor to generate a new, colored molecular structure in the ground state that can be photo-activated by visible light to yield a radical ion pair. Subsequently, this intermediate can go through an irreversible homolytic fragmentation to generate high-energy radical species that undergo radical-radical coupling transformations. The ability to use visible light to activate colorless substances in the absence of exogeneous photocatalysts makes this method a very powerful synthetic tool to generate carbon- and heteroatom-based radicals under very mild conditions. In this context, photoinduced sulfonylation reactions have been reported, typically proceeding via UV light irradiation or by using blue light emitting diode (LED) with a Hantzsch ester as terminal photoreductant.[8,9] This approach, however, usually employs C–X bond activation, ruling out any possibility of using substrates bearing multiple halides, and hence severely limiting the potential for further functionalization via cross-coupling reactions, for example.

The approach presented by Molander and co-workers in this issue of *Chem Catalysis* offers a sophisticated alternative to the usually harsh conditions used in the synthesis of sulfone-containing compounds, while allowing the complete retention of the bromide handle.[10] To do so, a series of aryl thianthrenium salts and sodium sulfinate compounds were used to form EDA complexes *in situ* via, in this case, electrostatic interactions between the positively charged thianthrenium derivatives and the negatively charged sulfinate compounds. The sulfinate salts did not absorb visible light, while most of the thianthrenium derivatives absorbed visible light only moderately. However, the formation of these EDA complexes allowed to double the amount of light absorbed at wavelengths between 390 and 470 nm. It was found that aprotic polar solvents, such as DMSO and DMF, were suitable solvents, as they increased the solubility of all components while still allowing the formation of EDA complexes.

The reaction was first optimized using thianthrenium **1a** and sodium sulfinate **2a** in dry and degassed DMSO (Figure 1). Using 390 nm light irradiation, the reaction proceeded with a low yield of 23%. The addition of salts, such as K_2CO_3, Na_2CO_3, K_3PO_4, and Cs_2CO_3, allowed an increase in the yields whereas the use of NaOAc and NH_4OAc had deleterious effects. Optimal conditions were found using 3 equiv of **2a** and 2 equiv of Cs_2CO_3 with an overall concentration of 0.13M of **1a**. This led to a sulfonylation yield of 87%, as determined by gas chromatography, and 78% isolated yield on a 0.5 mmol scale. The cesium cations were proposed to undergo cation exchange with the sodium cations, leading to looser ion-pairs that were more prone to form EDA complexes.

When 456 nm irradiation was used, the yields decreased from 87% to 72%, with the presence of unreacted **1a** still detected after 16 h of reaction. No reaction was observed when 525 nm light was used, and only unreacted **1a** was detected. The fact that the thianthrenium remained unreacted when lower energy irradiation was used speaks toward the high photostability of these derivatives.

The reaction was then extended to a series of sulfinate salts and a series of thianthrenium derivatives (Figure 1). Overall, the thianthrenium-enabled sulfonylation via EDA complex photoactivation using 390 nm irradiation always proceeded with yields that ranged from 11% to 82%. It was shown that the reaction tolerated a wide range of functional groups, from unsubstituted phenyl ring (**3a**), electron-withdrawing (**3b–3f**), and electron-donating (**3g–3j**) groups, as well as several medicinally relevant heterocycles such as quinolinyl- (**3l**), pyridinyl- (**3m**), imidazolyl- (**3n**), and thienyl- (**3aa**) derivatives. Importantly, this EDA approach was not limited to (hetero)aryl sulfinate derivatives, as is the case in photoredox/nickel dual catalysis, but could also be extended to alkyl sulfinates, such as cyclopropyl- (**3o**), cyclohexyl- (**3r**), and methyl- (**3p–3q**) derivatives. The reaction was shown to tolerate a plethora of functional groups, which included ethers (**3s**, **3x**, **3y–3ab**, **3ad**, and **3aj–3ak**), aldehydes (**3s**), esters (**3t**, **3ab**, **3ae**, and **3ag–3ak**), amides (**3u** and **3ac**), and halides (**3years–3aa**, **3ag**, **3ah**, and **3aj**). The complete retention of the bromide handle is a striking result, as these functional groups can serve as the starting point for additional cross-coupling reactions, for example. Finally, the EDA complex approach was further extended to showcase the late-stage functionalization compatibility of biomolecules and pharmaceutically relevant compounds. The corresponding sulfones of lipid-lowering agents gemfibrozil (**3ae**) and fenofibrate (**3ag**) and antifungal bifonazole (**3af**), as well as anti-inflammatory compounds flurbiprofen (**3p** and **3ah**), salicin (**3ai**), and indomethacin (**3aj–3ak**), were obtained with no degradation of the parent molecular structure.

Mechanistically, UV-visible absorption experiments confirmed the ground-state formation of an EDA complex between **1a** and **2a** that was further facilitated by the introduction of Cs_2CO_3. Although speculative, it was proposed that Cs^+ helped in replacing Na^+, leading to looser ion-pairs that were more prone to form EDA complexes. Excitation with 390 and 456 nm light lead to

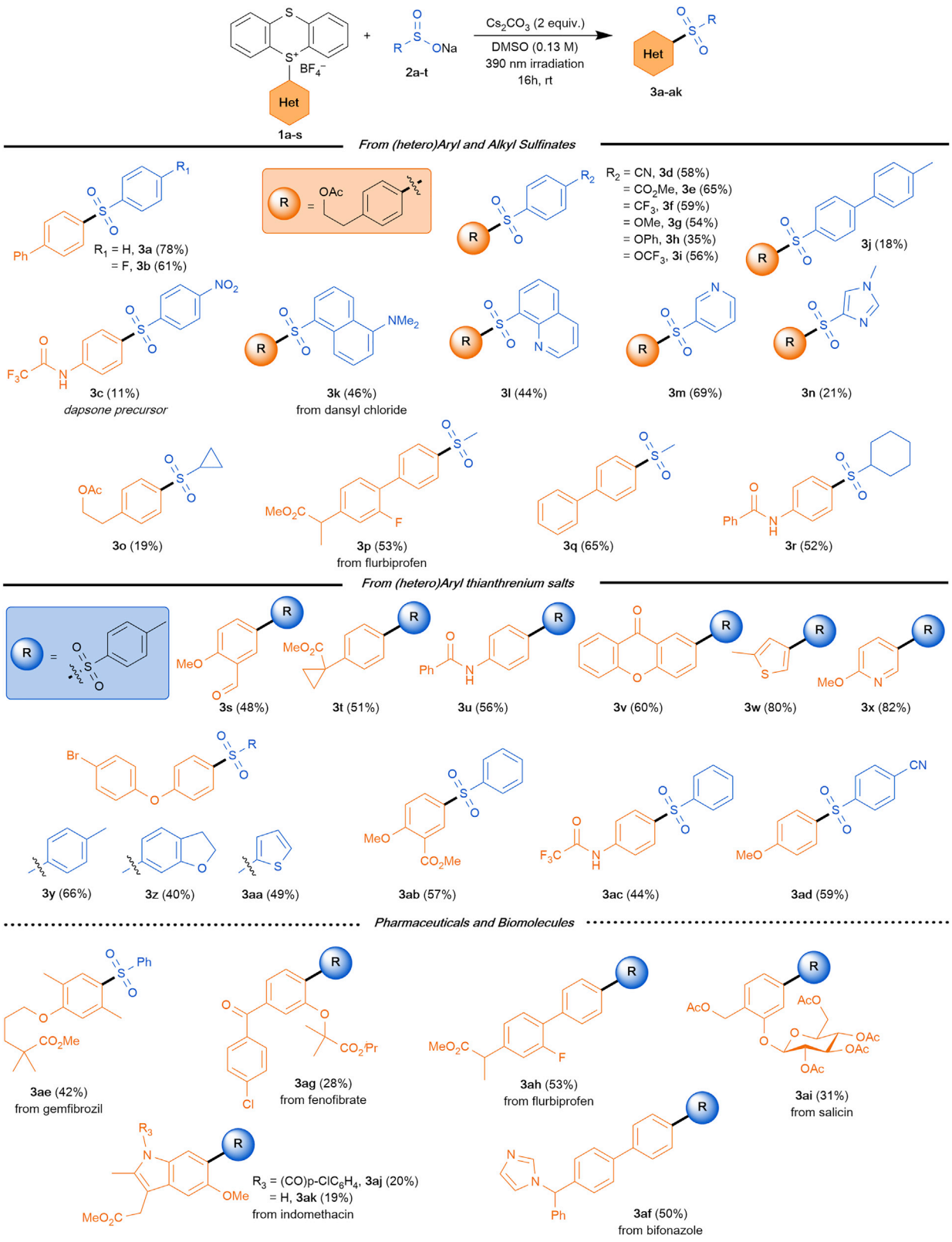

Figure 1. Scope of the thianthrenium-enabled sulfonylation via EDA complex photoactivation

the formation of an excited state that underwent "intra-EDA-complex" electron transfer, generating the singly reduced thianthrenium radical anion and the persistent sulfonyl radical. The subsequent irreversible fragmentation of the thianthrenium radical anion yielded the desired aryl radical and the neutral thianthrene side product. Both the sulfonyl radical and the aryl radical could then generate the desired corresponding sulfone via radical-radical coupling. Radical trapping experiments using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl radical) and 1,1-diphenylethene confirmed that the reaction pathway was proceeding via the formation of radicals.

In conclusion, the study reported by Molander and co-workers represents an important advance in the field of EDA complex reactivity using visible light to trigger a desired reaction. Importantly, the approach reported herein allowed activation of thianthrenium salts in the absence of exogeneous metal complexes or photosensitizers under very mild conditions. The formation of EDA complexes enabled to selectively trigger the photoreaction. Indeed, the thianthrenium derivatives used herein showed very selective reactivity as **1a** was not altered by photolysis upon irradiation at 390 nm in DMSO in the absence of sodium sulfinate salts. The reaction is also highly versatile and tolerates a plethora of functional groups. In addition, it is amenable to late-stage functionalization of biomolecules while also enabling the complete retention of bromide handles. Finally, the neutral thianthrene side products formed in the course of the photoreaction can be recycled and reused for the synthesis of thianthrenium salts, working toward a more circular and atom-economic process. In the future, one can hope to obtain further mechanistic information by steady-state and time-resolved spectroscopies, for example, which could help to develop even more efficient systems based on EDA complex formation.

DECLARATION OF INTERESTS

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