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Synthesis of Vinyl and 1,3-Dienyl Sulfones Enabled by Photochemical Excitation of Halogen-Bonding Complexes

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Abstract. The photochemical catalyst-free radical-based synthesis of vinyl and 1,3-dienyl sulfones is disclosed. Mechanistic investigations support that the transformations rely on a visible-light-promoted activation of a halogen-bonding complex, which is formed between an alkenyl (or 1,3-dienyl) bromide and a sodium sulfinate salt. The reactions exhibit a wide functional group tolerance (compatible with heteroatoms, electron-withdrawing and electron-donating groups), finding application in the

structural modification of biologically relevant molecules. Eventually, a continuous flow protocol was developed to upscale these transformations.

Keywords: Photochemistry; Halogen-Bonding; Radical disconnection; Vinyl sulfone; Visible light.

Introduction

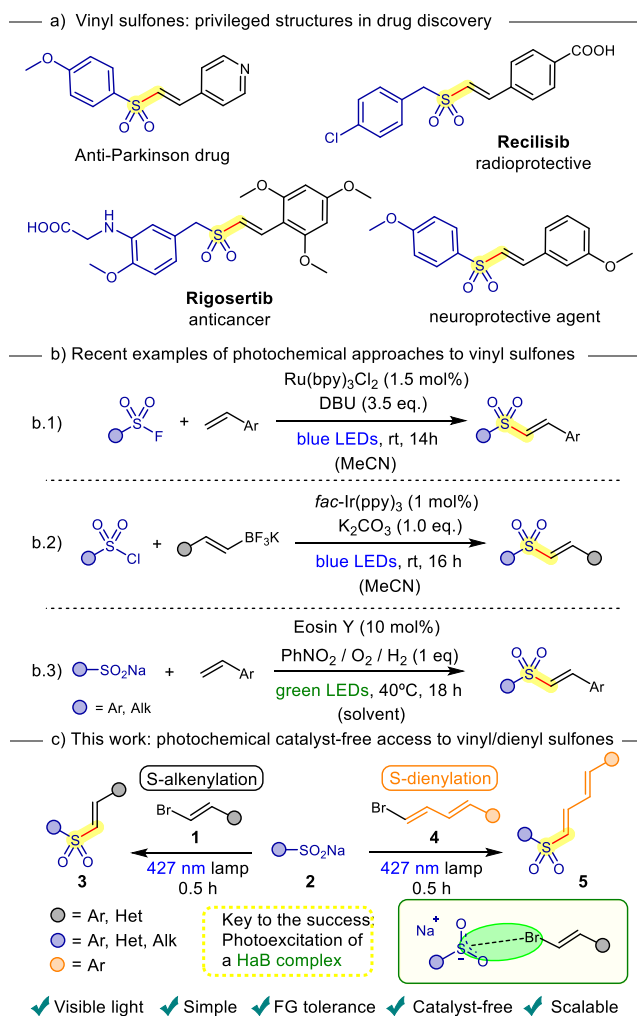
The development of novel methods for the construction of C–S bonds stands as a forefront area of research in modern organic synthesis.^[1] Within this framework, photochemical approaches which leverage visible light as their driving force enable unprecedented activation modes that provide a more efficient pathway to sulfur-containing molecules compared to traditional methodologies, making them particularly appealing.^[2]

Vinyl sulfones are considered privileged structures in drug discovery, and their synthesis has been studied by different research groups for many years due to their interesting biological properties (Scheme 1, a).^[3] However, traditional methodologies that focus to forge this kind of compounds normally require high temperatures, long reaction times, the use of stoichiometric oxidants or the employment of complex catalysts.^[4] In this regard, in recent years different research groups have developed innovative photochemical methodologies which provide an alternative, simplified access to sulfone-containing molecules.^[5] In particular, synthetic strategies which rely on a visible-light-driven excitation of photocatalysts stand as the most recent synthetic strategies for the synthesis of this kind of compounds (Scheme 1, b). In this context, the research group of Gao recently reported an elegant photoredox methodology for the preparation of vinyl sulfones starting from styrenes and sulfonimidoyl fluorides, based on the combination of a ruthenium-based

photocatalyst and DBU as a super-base (Scheme 1, b.1).^[6] Also in 2023, He and Guan reported another photoredox strategy for the general synthesis of sulfones (among them, vinyl sulfones), but this time employing sulfonyl chlorides and trifluoroborate salts as the reaction precursors (Scheme 1, b.2).^[7] Regarding the employment of sulfinate salts as coupling partners in photochemical reactions devoted to the formation of vinyl sulfones, König and coworkers reported a photocatalytic strategy relying in the employment of Eosin Y, styrenes and sodium sulfinate (Scheme 1, b.3).^[8] However, these reactions require a stoichiometric amount of an oxidant or reducing agent to enable catalytic turnover.^[8] Although all these transformations represent a significant advance in the field of photochemical synthesis of vinyl sulfones, the use of photocatalysts is unavoidably needed, along with long irradiation times. Finally, when it comes to 1,3-dienyl sulfones **5**, to the best of our knowledge, there are only a few methodologies available for their synthesis,^[9] and no visible-light-driven procedures have been reported so far. Given the interesting biological properties these molecules may feature, it is as well highly desirable to develop simple and general procedures for their preparation.

Our research group is pioneer in the development of catalyst-free alkenylation and dienylation reactions enabled by photochemical excitation of halogen-bonding complexes.^[10] The visible-light-driven activation of these complexes has attracted considerable notice in recent times due to its role in generating carbon-centered radicals,^[11] thereby

enabling the occurrence of unique photochemical radical-based organic transformations.^[12] The halogen bond, categorized as a type of weak interaction within σ -hole interactions,^[13] is characterized by a partial $n \rightarrow \sigma^*$ charge-transfer. In this interaction, a non-bonding orbital of a nucleophilic electron donor (HaB acceptor) engages in charge transfer with an antibonding orbital (σ^*) of an electron acceptor—specifically, the corresponding organic halide (HaB donor).^[14] This stabilizing interplay is instrumental in the creation of halogen-bonding complexes, a distinctive subset of EDA (electron donor-acceptor) complexes.^[15]



Scheme 1. Vinyl sulfones: biological relevance, state of the art in their photochemical synthesis and our work. HaB = Halogen Bond.

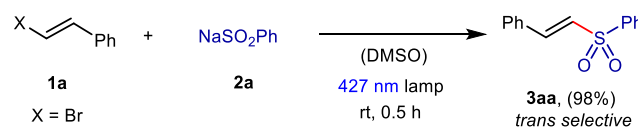
Initiating a photochemical fragmentation of the HaB complex, achieved through reducing the C–halogen bond, leads to the generation of two distinct radical species from the synthetic precursors. These radicals can subsequently undergo direct recombination, culminating in the formation of the desired cross-coupling product. Thus, we saw potential in the employment of alkenyl and dienyl halides as the HaB

donors in the reaction with sulfinate salts (HaB acceptors), which are reagents commonly employed in photocatalytic sulfonylation reactions.^[16]

Results and Discussion

We started looking for optimal reaction conditions taking as a model reaction of β -bromostyrene (**1a**, 0.2 mmol) and sodium phenylsulfinate (**2a**, 0.3 mmol) in DMSO (2 mL), employing a 427 nm Kessil lamp as the irradiation source for only half an hour. Much to our pleasure, under these reaction conditions the desired vinyl sulfone **3aa** was obtained with almost quantitative yield (98%). The reaction was proven to be photochemical, since no conversion was observed in the absence of light (table 1, entry 1). Irradiation for longer times did not lead to decomposition of the vinyl sulfone, revealing its photostability to blue light. Moreover, when DMF was employed as the solvent, a similar yield was observed for the formation of the compound **3aa**, whereas the usage of MeCN, CH_2Cl_2 or THF led to almost no conversion towards the desired product. Notably, the use of alkenyl chlorides or iodides (table 1, entries 8 and 9) resulted in the coupling product with a low yield for the former and a very low yield for the latter. In the first case, this fact may be attributed to the less extensive formation of the halogen-bonding complex, whereas in the second one the decrease in the yield has to do with the inherent photochemical instability of the alkenyl iodide. Finally, the employment of a less energetic blue light source (440 nm lamp) led to a diminished conversion when compared to 427 nm (table 1, entry 10), whereas a more powerful light source (390 nm lamp) shut down the reaction due to a competing photochemical excitation of **1a**, causing its E/Z isomerization, and preventing the selective excitation of the HaB complex.

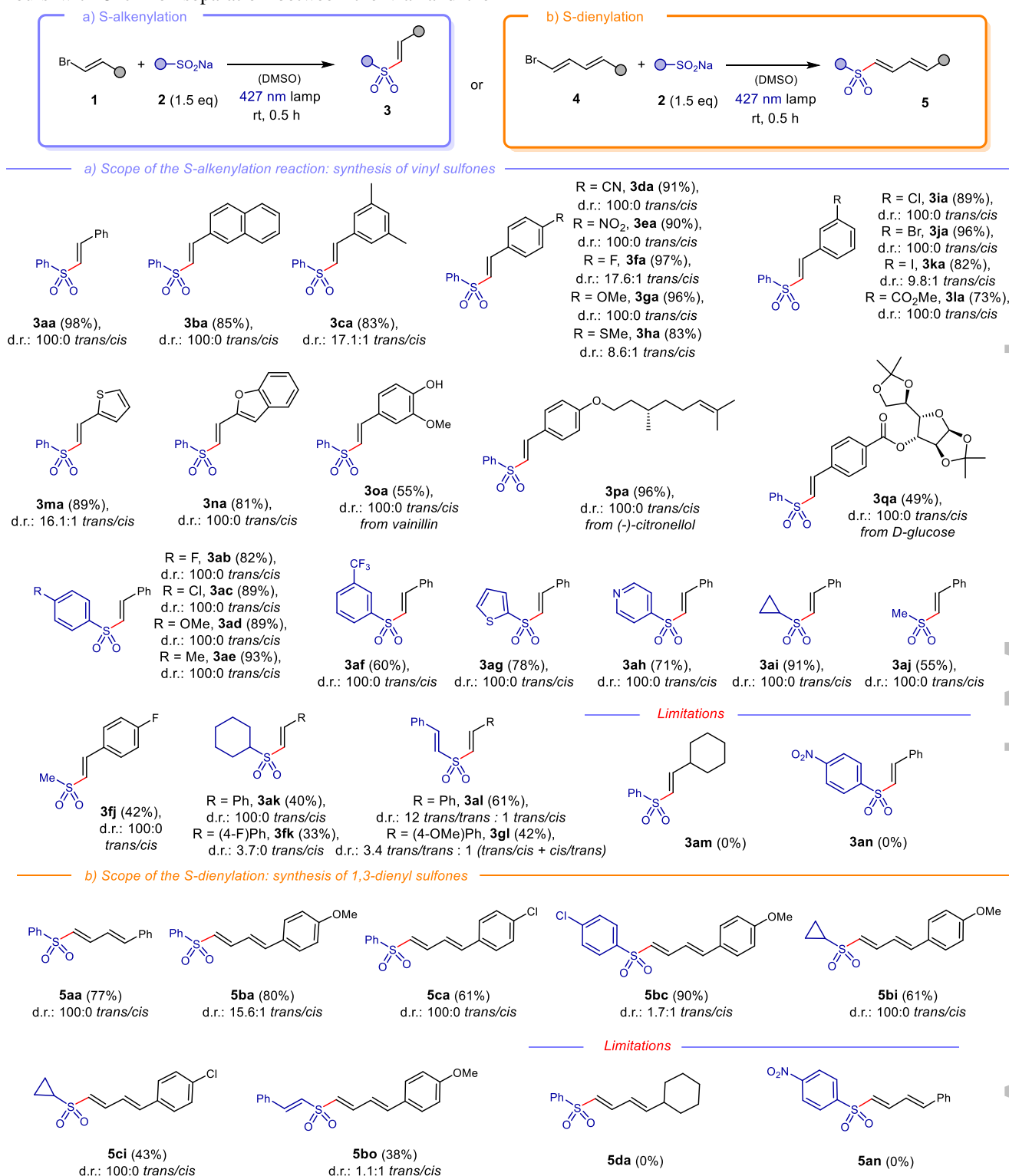
Table 1. Screening of optimized reaction conditions.



| Entry | Deviation from standard conditions | Yield (%) |
|-------|--|----------------|
| 1 | Dark, 16 h | 0 |
| 2 | Ar, 30 min | 81 |
| 3 | 16 h instead of 0.5 h | 98 |
| 4 | DMF instead of DMSO | 95 |
| 5 | MeCN instead of DMSO | 5 |
| 6 | THF instead of DMSO | 2 |
| 7 | CH_2Cl_2 instead of DMSO | 0 |
| 8 | X = Cl | 50 |
| 9 | X = I | 31 |
| 10 | 440 nm lamp instead of 427 nm | 65 |
| 11 | 3 cm of separation vial/lamp | 98 |
| 12 | 8 cm of separation vial/lamp | 89 |
| 13 | 1.1 eq of 2a | 98 |
| 14 | Absence of 2a | 0 ^a |

Preliminary reaction conditions: alkenyl bromide **1** (0.2 mmol) and sodium phenylsulfinate **2** (0.3 mmol) in 2 mL of DMSO, irradiation with a 427 nm lamp (52 W) over 0.5 hours with 5 cm of separation between the vial and the

lamp. Isolated yields after flash chromatography are presented. ^a Full recovery of **1a** was obtained.

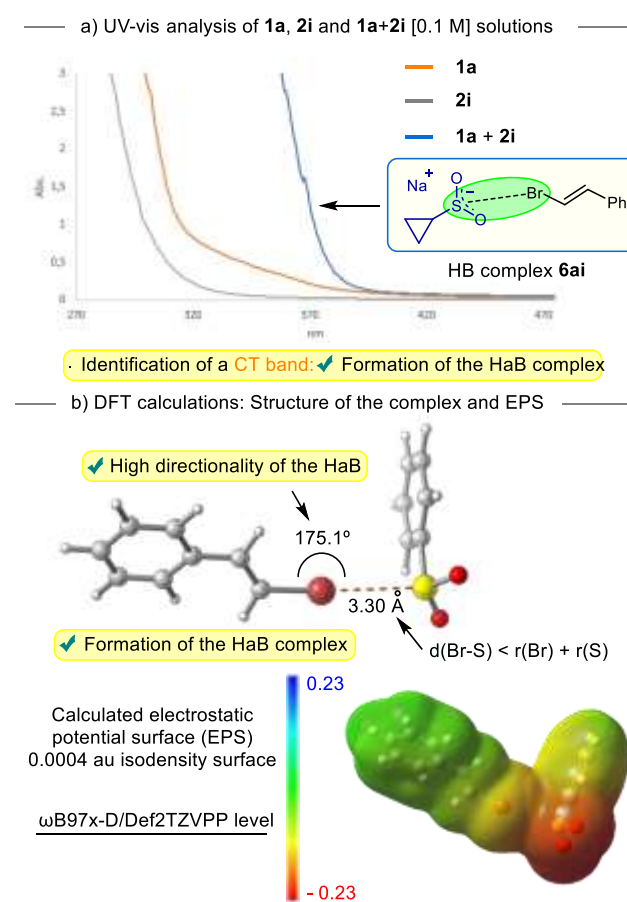


Scheme 2. Scope of the S-alkenylation and dienylation reaction employing sodium sulfonates. Reaction conditions: the alkenyl bromide **1** (0.2 mmol) or dienyl bromide **4** (0.2 mmol) and the corresponding sodium sulfinate **2** (0.3 mmol) were mixed in 2 mL of DMSO and irradiated with a 427 nm lamp (52 W) over 0.5 hours. Isolated yields after flash chromatography are presented.

After establishing the optimal conditions for the photochemical catalyst-free synthesis of vinyl sulfones, we proceeded to assess the compatibility of various alkenyl bromides in their reaction with sodium sulfonates (scheme 2, a). This transformation exhibits significant adaptability, enabling the incorporation of diverse functional groups into the final compounds. For example, different functionalities such as nitrile (**3da**), nitro (**3ea**), halogens (**3fa**, **3ia**, **3ja**, **3ka**), methoxy (**3ga**), thiomethoxy (**3ha**) and ester (**3la**) could be incorporated from the alkenyl bromide. Moreover, the reaction was also found to be compatible with heteroaromatic rings such as thiophene (**3ma**) and benzofuran (**3na**). Neutral aromatic groups such as alkyl-substituted phenyl rings (**3ca**) or 2-naphthyl (**3ba**) were also well-tolerated. Gratifyingly, this reaction found application in the structural modification of molecules derived from biologically relevant scaffolds such as vanillin (**3oa**), (-)-citronellol (**3pa**) and *D*-glucose (**3qa**). Next, different substitutions at the sulfinate fragment were examined. In this regard, it was found that the presence of several functionalities such as halogens (**3ab**, **3ac**), methoxy (**3ad**), methyl (**3ae**) and trifluoromethyl (**3af**) were compatible with the transformation. Once again, different heterocycles such as thiophene (**3ag**) or pyridine (**3ah**) could be accommodated in the final compounds. Remarkably, the synthesis of the divinyl sulfones **3al** and **3gl** could also be accomplished with this synthetic strategy. Alkyl residues such as cyclopropyl (**3ai**), methyl (**3aj**, **3fj**) or cyclohexyl (**3ak**, **3fk**) could also be installed at the vinyl sulfones. Noticeably, alkyl sulfonates have been previously employed as alkyl radical precursors in photochemical transformations with extrusion of SO₂.^[17] The preservation of the SO₂ group in the reactions reported herein might be due to the mild conditions in which the sulfonyl radical is generated,^[8,18] allowing the recombination with the corresponding alkenyl radical to forge the compounds **3**.

After assessing the success of the alkenylation reactions, the analogous dienylation reaction was also explored employing dienyl bromides as coupling partners, seeking the formation of the corresponding 1,3-dienyl sulfones **5** (scheme 2, b). In this context, it was found that different functionalities such as methoxy (**5ba**) and chlorine (**5ca**) could be incorporated from the dienyl bromide, as well as alkyl (**5bi**, **5ci**) and various aromatic groups from the sulfinate fragment (**5aa**, **5bc**). Specially interesting is the dienyl vinyl sulfone **5bo**, which incorporates three different double bonds in the final structure, albeit with no stereoselectivity. As limitations to both of these transformations, it should be noted that alkyl substituted alkenyl and dienyl bromides (**3am**, **5da**)

were non-competent partners in these cross-coupling reactions. This is presumably due to the lack of absorptive properties the HaB complex presents, and therefore its photoexcitation with visible light is not possible. On the other hand, strongly deactivated aryl sulfonates could not be incorporated from the sulfinate residue (**3an**, **5an**). This observation is in accordance with the inherent requirements of the halogen-bond interaction, where the sulfinate in these cases is not nucleophilic enough to promote the formation of the desired HaB complex. Overall, both of the *S*-alkenylation and dienylation reactions exhibit a wide functional group tolerance and excellent *trans* diastereoselectivity, as proven in the scope presented in scheme 2.



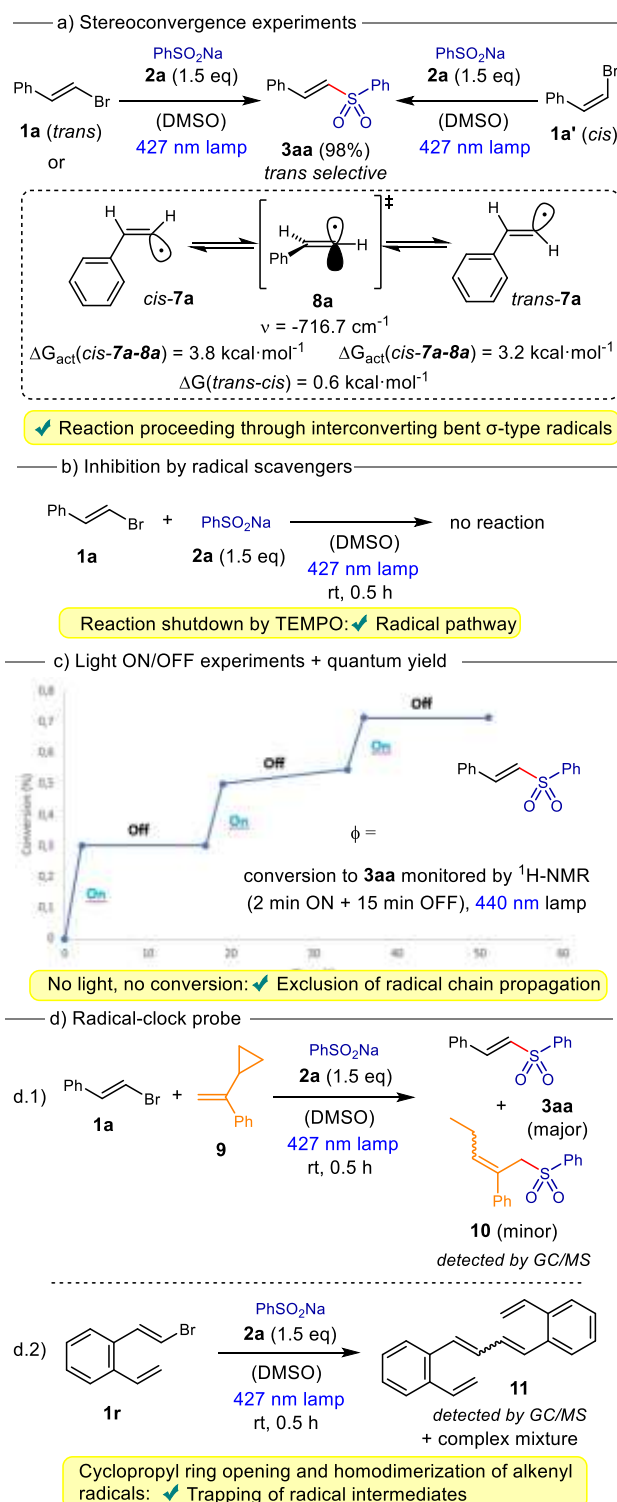
Scheme 3. Set of mechanistic studies aiming at the identification of the structure and nature of the halogen-bonding complexes **6aa** and **6ai**. EPS = Electrostatic Potential Surface.

To substantiate the formation of a halogen-bonding complex during the process, a series of mechanistic studies were conducted. Initially, we examined the UV-Vis profiles of solutions containing individual compounds **1a** and **2i**. Notably, upon combining equimolar quantities of both reaction components in DMSO, a distinct red-shifted charge transfer (CT) band emerged, serving as a clear indicator of the formation of the halogen-bonding complex **6ai** (Scheme 3, a).^[11,19] Further evidence of the presence

of the halogen-bonding complex surfaced through the utilization of $^1\text{H-NMR}$ titration experiments (see the Supplementary Information for detailed procedures).^[11, 19, 20] In this investigation, we systematically observed a notable downfield shift, approaching 1 ppm, in the $^1\text{H-NMR}$ signal of **2a** as we progressively introduced incremental amounts of **1a** while maintaining a constant molar quantity of **2a**. Moreover, we calculated the thermodynamic binding constant between **1a** and **2a**, based on the data obtained in the NMR titration experiments.^[21] An association constant $K = 0.54 \pm 0.06 \text{ M}^{-1}$ was calculated (see SI for details),^[22] which is in accordance with the weak intermolecular interaction due to the formation of a halogen bond between both molecules.^[19,20] Finally, we conducted preliminary computational studies using DFT ($\omega\text{-B97X-D3/Def2TZVPP}$ level) to unveil the nature of the halogen-bonding complex (Scheme 3, b). These investigations led to the identification of a halogen-bonding aggregate involving **1a** and **2a**, confirmed as a local minimum on the potential energy surface. Notably, the halogen bond interaction between the bromine and sulfur atoms exhibited a clearly defined directionality, evident in a dihedral angle of 175.1° within the $\text{C}(\text{sp}^2)\text{-Br-S}$ bonds. This linear geometry, characterized by dihedral angles ranging from 160° to 180° within the HaB complex, aligns with previous findings documented in the literature.^[23] Furthermore, the electrostatic potential surface revealed a positively charged bromine σ -hole zone located nearly at the center of the C-Br axis. Additionally, the distance between the bromine and sulfur atoms within the halogen-bonding complex **6aa** (3.30 Å) was notably shorter than the cumulative Van der Waals radii of these atoms (3.65 Å). This observation strengthens the proposition of an attractive non-covalent interaction binding these atoms, likely attributable to the formation of the halogen bond.

Next, various mechanistic studies were conducted to support the radical nature of the intermediates involved in the transformation (Scheme 4). Based on our previous experience in photochemical HaB-assisted alkenylation reactions, our current hypothesis proposes that the generation of a vinyl radical derived from the alkenyl bromides **1** occurs through a photoinduced electron transfer (PET) at the irradiated halogen-bonding complex.^{[10][24]} To verify this hypothesis, we executed several control experiments. Thus, we conducted two separate reactions originating from the *trans*-configured vinyl bromide **1a** and its corresponding *cis* isomer **1a'** respectively. Noteworthy, the stereochemical information of the alkenyl bromide did not influence the stereoselectivity of the reaction, yielding vinyl sulfone **3aa** with a complete *trans* selectivity irrespective of the stereochemistry of the starting bromide (Scheme 4, a). The stereoconvergence observed might be explained taking into consideration the structure of the vinyl radical. Typically, two distinct structures are conjectured for vinyl radicals: a bent σ -type or a linear π -type.^[25] For β -substituted vinyl radicals, experimental and

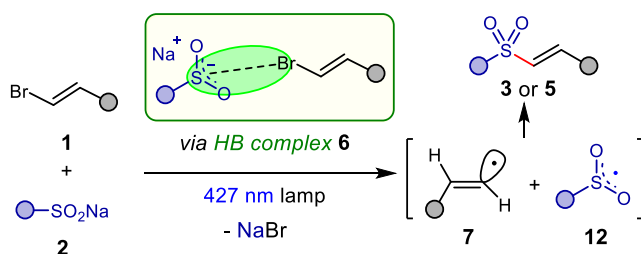
computational studies point to the existence of two interconverting sp^2 bent σ -type structures while the sp linear structure could be the transition structure for this interconversion, instead of a real intermediate.^[26]



Scheme 4. Set of mechanistic experiments carried out to assess the nature of the radical photochemical reaction.

Our own computational calculations are in agreement with this proposal, as we have found that for β -styryl

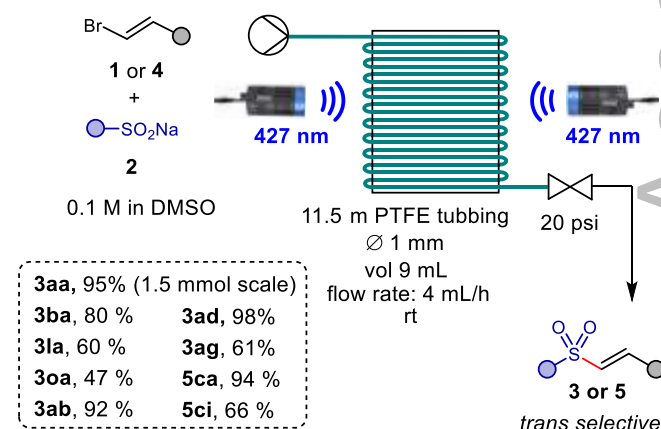
radical (**7a**) the bent σ -type structures (*cis*-**7a**) and (*trans*-**7a**) are minima in the potential energy surface, that might interconvert through the linear π -type structure (**8a**), which has been characterized as saddle point (Scheme 4, a), (see SI for details). Gibbs free energies of activation for the interconversion of 3.8 and 3.2 kcal·mol⁻¹ were obtained respectively. According to this model, the stereoconvergent process should comprise an interconversion rate of the bent σ -type radicals faster than the radical recombination. Moreover, the preference towards the *trans* isomer might be justified considering that the radical recombination on *cis*-**7a** is disfavoured for steric reasons when compared to *trans*-**7a**. Detailed computational studies are underway. In a different experiment, we observed a complete shutdown of the photochemical reaction when adding two equivalents of the radical scavenger TEMPO, what gives additional support to the radical pathway of this transformation (Scheme 4, b). It is known that sulfonylation reactions proceeding through the formation of sulfonyl radicals are inhibited by TEMPO, while if a polar mechanism were operating, the corresponding vinyl sulfone would be formed regardless of the presence of radical scavengers in the reaction media.^[27] Next, light on/off experiments were carried out by monitoring the reaction between the alkenyl bromide **1a** and **2a** to forge the compound **3aa**. It was observed that the reaction proceeds only in the periods in which the light had been turned on (scheme 4, c). Additionally, a high quantum yield but yet below the unit ($\phi = 0.9$) was determined for the transformation (see the SI for a detailed description), which could point at radical chain propagation events, but we believe may be mainly attributed to the high efficiency of these processes.^[28] Considering both of these experiments and also taking into account our previous experience in similar photochemical HaB assisted alkenylation reactions,^[10] we believe that radical chain propagation events are unlikely to take place in this reaction. At the same time, the importance of light for the reaction to proceed was validated. Moreover, radical clock experiments were conducted.^[29] Importantly, these experiments provided a strong support to the radical nature of the reactions, as evidenced by the interception of both the alkenyl and sulfonyl radicals in different transformations which gave rise correspondingly to the compounds **10** and **11** (scheme 4, d).



Scheme 5. Mechanistic proposal.

In light of all these mechanistic studies, and also based on our previous experience in photochemical halogen-bonding assisted alkenylation reactions,^[10] we propose the mechanism depicted in scheme 5 for the cross-coupling reaction between alkenyl or dienyl bromides and sodium sulfonates **2**. First, the formation of a HaB complex **6** between **1** (or **4**) and **2** is hypothesized, which would be photoexcited with blue light, causing its fragmentation through reduction of the C–Br bond in an intermolecular photoinduced electron transfer (PET) event. This would generate the free vinyl radical **7** and sulfonyl radical **12**, which would experience a radical recombination to forge the final compounds **3** or **5**. Notably, due to the mild generation of sulfonyl radicals **12**, these reactions proceeded in all of the cases with preservation of the SO₂ group, with no desulfonative processes taking place.^[18]

The final segment of our study focused on establishing a continuous flow protocol for scaling up the photochemical transformations. In general, developing light-driven reactions through continuous flow protocols offers several advantages, including rapid scalability, heightened safety, improved reproducibility, and more straightforward control.^[30] To explore the viability of this approach, we initiated a preliminary investigation using a flow reactor constructed from PTFE tubing (refer to the Supplementary Information for details). Our initial protocol involved passing a 0.1 M solution of both reaction components **1** and **2** in DMSO through the flow reactor while subjecting it to a flow rate of 4 mL/h and illumination from two 427 nm lamps (scheme 6). We were pleased to see that our flow protocol provided in general excellent to good reaction yields, and even in some cases, enhanced efficiency when compared to the analogous batch processes (**3ab**, **3ad**, **5ca** and **5ci**).^[31] Moreover, the continuous flow procedure enables the scale-up of the process, as demonstrated in the synthesis of compound **3aa** in a 1.5 mmol scale (with a remarkable 95% isolated yield), overcoming classical limitations inherent to photochemical reactions.



Scheme 6. Continuous flow setup for the upscale of the sulfonylation reactions of alkenyl and 1,3-dienyl bromides.

Conclusion

In conclusion, we have developed a photochemical procedure for the preparation of vinyl and 1,3-dienyl sulfones starting from alkenyl bromides and sulfinate salts. Mechanistic studies support the formation of a HaB complex as the key to the success of these transformations, which light-driven fragmentation makes the reaction proceed through a radical pathway. Additionally, a continuous flow protocol was developed for the scale up of these reactions.

Experimental Section

General procedure A (batch conditions) for the synthesis of compounds **3** and **5**: Vinyl bromide **1** or 1,3-dienyl bromide **4** (0.2 mmol), sulfinate salt **2** (0.3 mmol), and dry DMSO (2 mL) were combined in a 5 mL glass vial. The vial was secured and placed approximately 5 cm in front of the 427 nm Kessil® lamp. Once the lamp and cooling fan were switch on, the reaction mixture was stirred at room temperature for 30 minutes to ensure complete conversion. To stop the reaction, 2 mL of water was introduced. This mixture was then diluted with 5 mL of EtOAc and transferred to a separating funnel. The aqueous phase was extracted three times with 5 mL of EtOAc, while the combined organic phases were washed with 10 mL of brine and dried using Na₂SO₄. The reaction crude was concentrated *in vacuo* and analysed by ¹H-NMR or GC/MS to determine the *trans/cis* ratio. Finally, it underwent flash chromatography (using Hex/EtOAc) to obtain the corresponding sulfone **3** or **5**.

General procedure B (flow conditions) for the synthesis of compounds **3** and **5**: A mixture comprising vinyl bromide **1** or 1,3-dienyl bromide **4** (0.4 mmol) and sulfinate salt **2** (0.6 mmol) in dry DMSO (4 mL) was loaded into a syringe and connected to a high-pressure syringe pump and to a photoreactor. The solution was pumped through the system at a rate of 4 mL/h while both Kessil lamps (two PRL160 427 nm) were activated. As the solution entered the reactor, DMSO was employed to propel the reaction into the collector flask. Subsequently, upon completion of the reaction, 15 mL of water was added to quench it. This mixture was further diluted with 15 mL of EtOAc and transferred into a separation funnel. The aqueous phase underwent three extraction cycles, each involving 15 mL of EtOAc, while the combined organic phases were washed with 20 mL brine and were subsequently dried using Na₂SO₄. The solvents were then removed under reduced pressure, and the crude reaction product underwent purification via flash chromatography using a Hexane/EtOAc mixture, ultimately yielding sulfone **3** or **5**.

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RESEARCH ARTICLE

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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