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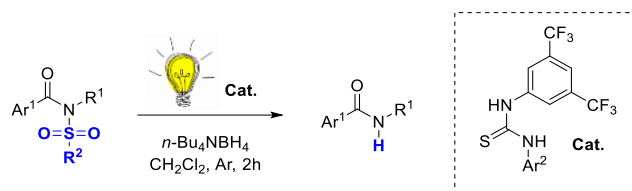
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# Light-driven reductive cleavage of sulfonamides promoted by thiourea organophotosensitizers

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Supporting Information Placeholder



**ABSTRACT:** We have developed a practical method to perform the reductive photocleavage of sulfonamides using thioureas as organophotocatalysts. This transformation, which tolerates a variety of substrates, occurs under mild reaction conditions in the presence of tetrabutylammonium borohydride as a reducing agent. Experimental and theoretical mechanistic investigations complete the study, shedding light on the nature of the active species involved in the photocatalytic process.

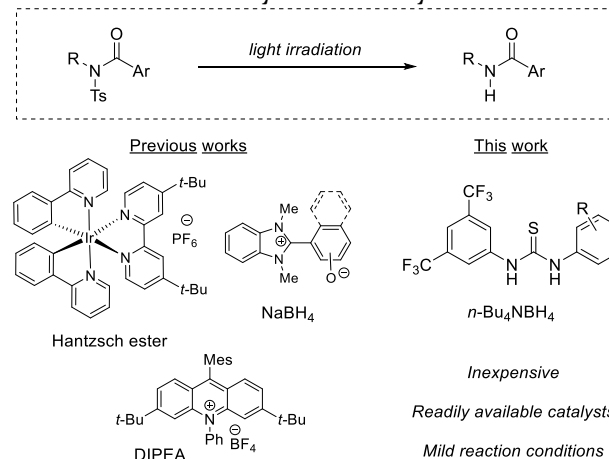
## Introduction

Sulfonamides can be considered as useful amine protecting groups due to their advantageous properties including ease of introduction, general inertia to acids, bases, electrophiles, or mild reducing agents, and stability under oxidizing conditions.<sup>1</sup> In addition, some of these derivatives, incorporating for example benzenesulfonyl or *p*-toluenesulfonyl moieties, can easily crystallize, a characteristic that may simplify products purification.<sup>1</sup> As of today, the main drawback limiting the potential widespread use of sulfonamides in organic synthesis is the difficult cleavage of these functions, which can require quite harsh reaction conditions.<sup>1-17</sup> Indeed, classical deprotection of *N*-sulfonyl protected compounds usually involve treatments with strong acids, bases or reducing agents such as HBr,<sup>2-4</sup> NaOH or KOH in MeOH,<sup>5,6</sup> or sodium naphthalene.<sup>7</sup> Electrochemical methods have also been described over the years,<sup>8-11</sup> together with different procedures relying on Sml<sub>2</sub>-promoted electron transfer cleavage.<sup>12-17</sup>

Recently, the advent of photocatalysis has opened up new possibilities for performing light-driven desulfonylation reactions under milder conditions. However, most of the processes described up to now require stoichiometric amounts of various reagents.<sup>18</sup> Only few catalytic approaches have proven to be successful to date.<sup>19-21</sup> These include the use of transition metal photocatalysts in combination with Hantzsch esters (Scheme 1),<sup>19</sup> benzimidazolium aryloxy betaines in the presence of hydride donors (Scheme 1),<sup>20</sup> or extremely potent acridine radical photoreductants (Scheme 1).<sup>21</sup> Herein, we describe a convenient

and practical alternative to these methods, which encompasses the employment of expensive or hard-to-prepare photocatalysts. Our approach exploits the scarcely investigated organophotocatalytic activity of thioureas (Scheme 1) and allows the efficient cleavage of N-S bonds under mild reaction conditions.

## Scheme 1. Photocatalytic desulfonylation reactions



Thioureas have been extensively employed in organocatalysis to promote a variety of transformations.<sup>22-24</sup> Only recently, however, the ability of these molecules to act as photocatalysts has been reported in the literature. In fact, Schreiner's catalyst has proven capable of promoting the formation of acetals under light irradiation.<sup>25</sup> Thioureas have also played the role of photosensitizers in light-ena-

bled [2+2] or [4+2] cycloadditions.<sup>26</sup> Taking into consideration these interesting examples, we envisaged the possibility to employ such molecules to promote different light-driven reactions. Herein, we describe the use of these compounds to achieve the reductive photocleavage of sulfonamides.

## Results and discussion

We began our investigations by synthesizing various thioureas (**3a-g**, Table 1) *via* the condensation of commercially available anilines **1a-f** with isothiocyanates **2a-c**. This well-known one step reaction proceeded smoothly to form the expected compounds in 95% to quantitative yields (Table 1). Following a similar procedure, a urea derivative (**3h**, Table 1) was also prepared in 98% yield by reacting aniline with 3,5-bis(trifluoromethyl)phenyl isocyanate.

**Table 1. Synthesis of the thiourea photocatalysts**

Product	Ar <sup>1</sup>	Ar <sup>2</sup>	X	Yield (%)
<b>3a</b>			S	97
<b>3b</b>			S	95
<b>3c</b>			S	99
<b>3d</b>			S	99
<b>3e</b>			S	99
<b>3f</b>	Ph		S	99
<b>3g</b>	Ph	Ph	S	95
<b>3h</b>	Ph		O	98

We next set out to study the ability of catalysts **3a-h** to promote the photocleavage of N–S bonds under mild reducing conditions. To this end, we synthesized an *N*-sulfonylated model compound (**4a**, Table 2) starting from benzylamine and following a two-step procedure which involves first a tosylation and then a benzoylation reaction.<sup>20</sup> Having the model substrate in hand, we turned our attention to the optimization of the reaction conditions. We first tested the photodesulfonylation under light irradiation at 350 nm in the presence of catalyst **3a** (15 mol%) with NaBH<sub>4</sub> as the reducing agent and DMSO as the solvent.<sup>27</sup> Under these conditions, the formation of the expected product **5a** could be detected by proton NMR of the crude reaction mixture,

but the reaction reached only 46% conversion after irradiation for 2 h (Table 2, entry 1). A longer reaction time was required to achieve total conversion (18h, Table 2, entry 2). Different reducing agents, namely NaBH(OAc)<sub>3</sub> and *n*-Bu<sub>4</sub>NBH<sub>4</sub>, were also tested but moderate conversions were again attained in 2 h (Table 2, entries 3 and 4). We next screened different solvents, and we were pleased to observe that the reaction proceeded smoothly in CH<sub>2</sub>Cl<sub>2</sub> (DCM) when using *n*-Bu<sub>4</sub>NBH<sub>4</sub> as the reducing agent. In this case, total conversion could be reached after irradiating at 350 nm for short reaction times (2h, Table 2, entry 5). Note that in chlorinated solvents such as CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub> only the thiourea catalysts can absorb light at this wavelength (for more details, see the supporting information). A lower catalytic loading (5 mol%) could be employed to promote the deprotection of **4a**, without any loss in efficiency (Table 2, entry 6). Other reducing agents (*i.e.* NaBH<sub>4</sub> or NaBH(OAc)<sub>3</sub>) failed to react in DCM due to their known poor solubility in this common organic solvent.

**Table 2. Optimization of the reaction conditions**

Entry	Cat. (mol %)	Solvent	[H]	t (h)	Conv. (%) <sup>[c]</sup>
1 <sup>[a]</sup>	<b>3a</b> (15)	DMSO	NaBH <sub>4</sub>	2	46
2 <sup>[a]</sup>	<b>3a</b> (15)	DMSO	NaBH <sub>4</sub>	18	>99
3 <sup>[a]</sup>	<b>3a</b> (15)	DMSO	NaBH(OAc) <sub>3</sub>	2	32
4 <sup>[a]</sup>	<b>3a</b> (15)	DMSO	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	44
5 <sup>[a]</sup>	<b>3a</b> (15)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
6 <sup>[a]</sup>	<b>3a</b> (5)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
7 <sup>[a]</sup>	<b>3a</b> (5)	DCM	HE	2	/
8 <sup>[a]</sup>	<b>3a</b> (5)	DCM	TTMSS	2	/
9 <sup>[a]</sup>	/	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	/
10 <sup>[a]</sup>	<b>3a</b> (15)	DCM	/	2	/
11 <sup>[b]</sup>	<b>3a</b> (15)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	/
12 <sup>[a]</sup>	<b>3b</b> (5)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
13 <sup>[a]</sup>	<b>3c</b> (5)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
14 <sup>[a]</sup>	<b>3d</b> (5)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
15 <sup>[a]</sup>	<b>3e</b> (5)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
16 <sup>[a]</sup>	<b>3f</b> (15)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	>99
17 <sup>[a]</sup>	<b>3g</b> (15)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	/
18 <sup>[a]</sup>	<b>3h</b> (15)	DCM	<i>n</i> -Bu <sub>4</sub> NBH <sub>4</sub>	2	/

<sup>[a]</sup> Reaction performed in a Rayonet photochemical reactor equipped with 350 nm lamps (T = 29 °C, c = 0.05 M). <sup>[b]</sup> Reaction performed in dark (T = 25 °C, c = 0.05 M). <sup>[c]</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture.

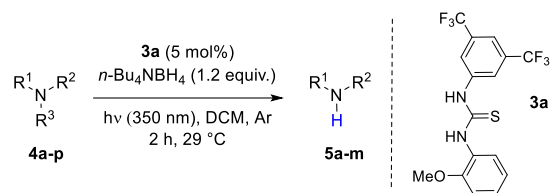
In the presence of different hydrogen atom donors such as the Hantzsch ester (HE) or tris(trimethylsilyl)silane

(TTMSS) no conversion was detected after 2 h (Table 2, entries 7 and 8). Control reactions were then performed and proved the utility of all reaction partners as compound **4a** did not undergo the photodeprotection in the absence of the catalyst or the hydride source (Table 2, entries 7 and 8). Light irradiation was also essential for the reaction to work, as no product **5a** was formed in the dark (Table 2, entry 9). The ability of catalysts **3b-h** to promote the photocleavage was investigated next (Table 2, entries 10–16). Most of the synthesized thioureas resulted to be efficient photocatalysts in this transformation, also a higher catalytic loading (15 mol%) was required to achieve complete conversion in the presence of catalyst **3f** (Table 2, entry 14). However, the presence of at least one strong electron-withdrawing aromatic moiety on the compounds, and in particular the 3,5-bis(trifluoromethyl)phenyl group, turned out to be important to ensure a good catalytic activity. Indeed, no conversion of sulfonamide **4a** into the corresponding product **5a** was observed in the presence of thiourea **3g**, showing two phenyl substituents (Table 2, entry 15). Urea **3h** also failed to promote the photodeprotection (Table 2, entry 16). These results are probably due to the inferior ability of compound **3h** to absorb light at 350 nm (see the SI for more details), whereas the absence of the electron-withdrawing fluorinated moiety on thiourea **3g** presumably influences the excited states nature and/or hydrogen bonding capability of this catalyst (<sup>1</sup>H NMR studies support this last hypothesis, see the SI for more details). The optimized detosylation of **4a** (Table 2, entry 6) could be performed on the millimolar scale without any loss in efficiency. A longer reaction time (4 h) was nonetheless required to reach complete conversion.

The scope of the photodeprotection was then investigated using thiourea **3a** (5 mol %) as the catalyst (Table 3). Different sulfonyl groups (Ts, SO<sub>2</sub>Ph, SO<sub>2</sub>Mes) could be easily cleaved under the optimized reaction conditions to afford the deprotected products **5a** in excellent yields (Table 3, entries 1–3). A mesyl group was also successfully cleaved to afford product **5a** in 77% yield (Table 3, entry 4). Various substituents were tolerated on the starting materials, including differently substituted (hetero)aromatic groups and alkyl chains (Table 3, entries 5–12). However, the presence of an aroyl moiety on the substrates was required for the reaction to work (Table 3, entries 1–14). Boc- or Me-substituted sulfonamides indeed proved to be unreactive, as only the starting material was recovered after the reaction (Table 3, entries 15 and 16). Secondary tosylamides did not undergo the photodesulfonylation under these conditions (Table 3, entries 18 and 19). Moreover, decomposition of the starting material was observed in the presence of an acetyl moiety (Table 3, entry 17). Note that, starting from precursors **4a-d** and **4f**, quantitative yields of products **5a**, and **5c** could be obtained by increasing the catalytic charge to 15 mol%. Based on these observations, we anticipated the possibility to achieve the chemoselective cleavage of differently substituted sulfonamides. We therefore synthesized compound **4p**, incorporating two diverse tosylamide moieties. This substrate underwent the reductive cleavage

smoothly to deliver the mono-deprotected product **5m** in 81% yield (Scheme 2a).

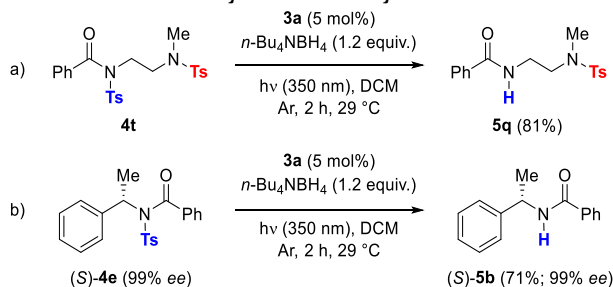
**Table 3. Scope of the photodeprotection**



Entry	SM	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	P <sup>[a]</sup>	% <sup>[b]</sup>
1	<b>4a</b>	Bn	COPh	Ts	<b>5a</b>	76
2	<b>4b</b>	Bn	COPh	SO <sub>2</sub> Ph	<b>5a</b>	73
3	<b>4c</b>	Bn	COPh	SO <sub>2</sub> Mes	<b>5a</b>	78
4	<b>4d</b>	Bn	COPh	Ms	<b>5a</b>	77
5	<b>4e</b>		COPh	Ts	<b>5b</b>	71
6	<b>4f</b>		COPh	Ts	<b>5c</b>	74
7 <sup>[c]</sup>	<b>4g</b>		COPh	Ts	<b>5d</b>	82
8 <sup>[c]</sup>	<b>4h</b>		COPh	Ts	<b>5e</b>	70
9 <sup>[c]</sup>	<b>4i</b>	Me	COPh	Ts	<b>5f</b>	69
10	<b>4j</b>	<i>n</i> -Bu	COPh	Ts	<b>5g</b>	56
11 <sup>[d]</sup>	<b>4k</b>	<i>n</i> -hexyl	COPh	Ts	<b>5h</b>	74
12	<b>4l</b>	allyl	COPh	Ts	<b>5i</b>	27
13 <sup>[c]</sup>	<b>4m</b>	Bn		Ts	<b>5j</b>	60
14 <sup>[c]</sup>	<b>4n</b>	Bn		Ts	<b>5k</b>	44
15	<b>4o</b>	Bn	Boc	Ts	<b>5l</b>	/ <sup>[e]</sup>
16	<b>4p</b>	Bn	Me	Ts	<b>5m</b>	/ <sup>[e]</sup>
17	<b>4q</b>	Bn	COMe	Ts	<b>5n</b>	/ <sup>[f]</sup>
18	<b>4r</b>	Bn	H	Ts	<b>5o</b>	/ <sup>[c]</sup>
19	<b>4s</b>	H	COPh	Ts	<b>5p</b>	/ <sup>[f]</sup>

<sup>[a]</sup> Reaction performed in a Rayonet photochemical reactor equipped with 350 nm lamps (T = 29 °C, c = 0.05 M). <sup>[b]</sup> Isolated yields. <sup>[c]</sup> 15 mol % of catalyst **3a** were employed to promote the transformation. <sup>[d]</sup> The reaction time was 4 h. <sup>[e]</sup> The starting material was recovered after the reaction. <sup>[f]</sup> Decomposition of the starting material was observed.

## Scheme 2. Selectivity of desulfonation reactions

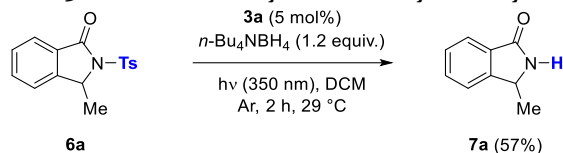


a) Chemoselective cleavage of differently substituted sulfonamides; b) Photodetosylation of an enantiopure sulfonamide.

Base-sensitive stereogenic centers did not racemize under the optimized reaction conditions, as product (S)-**5b** was isolated in 71% yield and 99% *ee* (Scheme 2b).

We next focused our attention on the photodeprotection of cyclic tosylamide **6a**. This compound, which could rapidly be prepared starting from phthalimide (see the experimental part for more details), readily underwent the cleavage reaction under the optimized condition to afford the expected product **7a** in 57% isolated yield (Scheme 3).

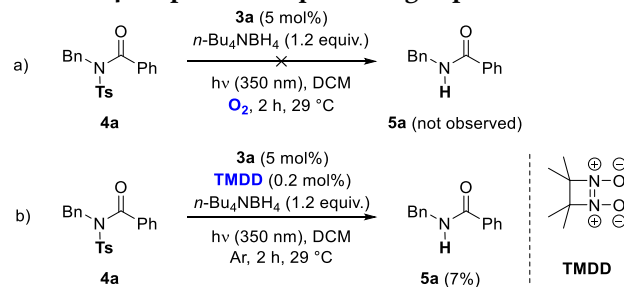
## Scheme 3. Photodesulfonation of a cyclic tosylamide



We finally wished to gain some insight into the mechanism of the reaction promoted by thioureas. Taking into account the previously described methods for the photodeprotection of sulfonamides, two different modes of activation could be envisaged, involving either an energy transfer or an electron transfer from the catalyst to the reaction substrates. Based on experimental evidences, the observed photocleavage of sulfonamides was supposed to occur more likely via an energy transfer pathway. Indeed, photocatalytic reactions involving electron transfer processes tend to proceed more smoothly in highly polar solvents in comparison with less polar media. On the contrary, our photodeprotection was found to reach complete conversion more rapidly in DCM rather than DMSO (entries 5 vs 4, Table 2). In addition, considering the redox potentials of catalyst **3a** and substrate **4a** as well as the computed excitation energy associated with **3a**, an electron transfer process appears to be thermodynamically unfavorable (see the SI for more details). Involvement of triplet-excited states in the photodeprotection was highlighted when performing the reaction under an oxygen atmosphere (Scheme 4a), or in the presence of 3,3,4,4-tetramethyl 1,2-diazetidine-1,1-dioxide (TMDD),<sup>28</sup> a well-known triplet-energy quencher (Scheme 4b). The possibility for the photocleavage to occur through a self-sustaining radical process was excluded for the fact that the reaction stops as soon as the light irradiation is turned off.

Based on these results, a plausible mechanism was proposed for this transformation (Scheme 5). The thiourea photosensitizer absorbs light at 350 nm and transfers the energy to the reaction substrate from its triplet-excited state.

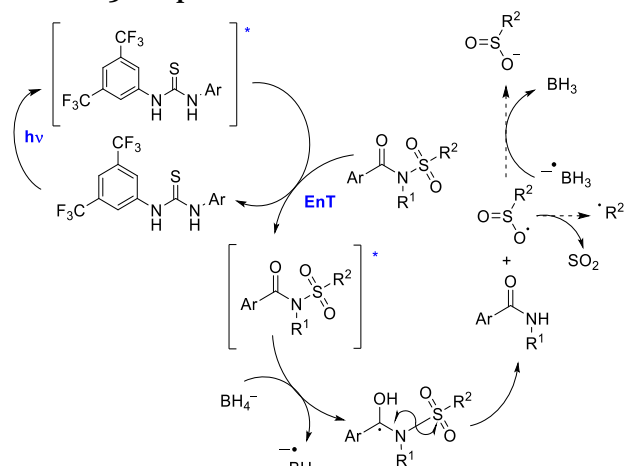
## Scheme 4. Triplet-state quenching experiments



a) Photodetosylation performed under an oxygen atmosphere; b) Photodetosylation performed in the presence of TMDD.

The formation of an EDA complex at this stage was excluded by UV-vis analysis of catalysts **3a** in the presence of increasing quantities of **4a**, while hydrogen-bonding interactions between the two compounds could be detected by proton NMR (see the SI for more details). The excited sulfonamide then reacts with  $\text{BH}_4^-$  to generate a carbon centered ketyl radical.<sup>29</sup> The formation of such reaction intermediate was previously proposed for analogous electrochemical transformations,<sup>12</sup> and is supported by the fact that the reaction does not occur in the absence of a benzoyl moiety on the starting material. This key radical species undergoes an homolytic cleavage of its N-S bond to generate the deprotected amide (after tautomerism), and an aromatic sulphonyl radical than can evolve by either desulfonation and/or reaction with  $\text{BH}_3^{\cdot-}$ .<sup>30</sup>

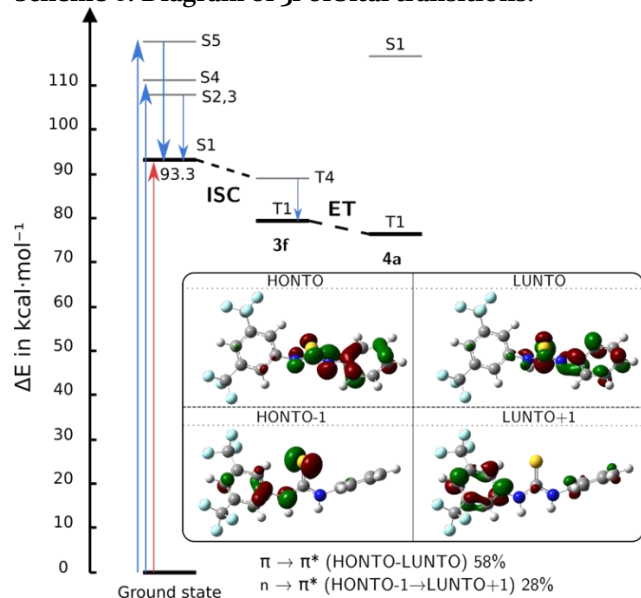
## Scheme 5. Proposed mechanism



Theoretical investigations were also performed to obtain a better understanding of this novel reaction. Initially, in order to explore the spectral characteristics and energy data of the catalyst from a theoretical perspective, TD-DFT calculations were used to calculate the excited state of **3f**. Based on the calculation results and following a natural transition orbital analysis (NTO), we have drawn a graph of the energy that yields the excited sulfonamides; see Scheme 6 for details. The thiourea needs 4.04 eV to transition from the ground state,  $S_0$  to  $S_1$  (see ESI for details). This  $\pi$  to  $\pi^*$  transition has a 58% chance of the electron moving from the highest occupied natural transition orbitals (HONTOs) to the lowest unoccupied natural transition orbital (LUNTO). The energy corresponding to the  $T_1$  state of **3f** is 3.45 eV and the corresponding one for **4a** is 3.32 eV

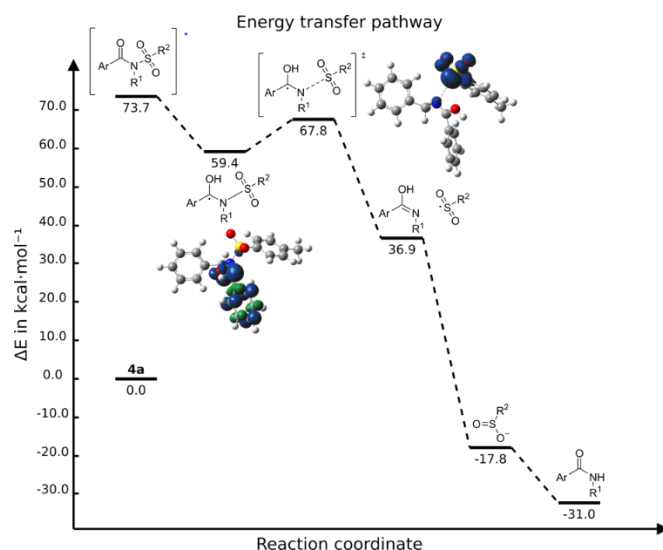
( $\Delta E = 9.61$  kcal/mol). More detailed calculation data are listed in the ESI (Table S1).

**Scheme 6. Diagram of 3f orbital transitions.**



Next, to gain information about the energy transfer mechanism as well as the nature of the N–S bond cleavage, DFT and TD-DFT calculations using CAM-B3LYP/6-31++G(d,p) were conducted on the ground and triplet excited states of the substrates. The results are summarized in Scheme 7. Following a hydrogen atom transfer, the cleavage proceeds via a TS with an elongated N–S bond (+0.2 Å, see ESI for details) and an activation barrier  $\Delta G^\ddagger = 8.4$  kcal/mol. The small energy barrier for the N–S cleavage suggests that rapid dissociation to form two fragments takes place prior to the conformational change observed for the amide. The calculated spin density shows a shift from the benzylic carbon to the sulfur atom prior to dissociation (see Scheme 6 and Figure S6). All these theoretical evidences are in agreement with the proposed mechanism.

**Scheme 7. Computationally established mechanism of the reaction and its corresponding free energy profile**



## CONCLUSIONS

We have developed a mild photodesulfonylation of sulfonamides. This light-driven reductive cleavage of N–S bonds is promoted by readily available thiourea organophotosensitizers. The reaction tolerates different substituents on the starting materials, and various sulfonyl groups can be easily cleaved under the optimized reaction conditions. Experimental mechanistical investigations and theoretical calculations suggest that this reaction occurs through energy transfer from the excited thiourea catalyst to the reaction substrates.

## EXPERIMENTAL SECTION

**General Remarks.** All reactions were carried out under inert atmosphere (in oven-dried glassware, using dry solvents), unless otherwise specified. All commercially available compounds, including anilines **1a–f** and isothiocyanates **2a–c**, were purchased from Merck, Fisher Scientific or TCI chemicals and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck 60F254) visualized with a UV lamp (254 nm). Flash chromatography was performed on silica gel (60–230 mesh) unless otherwise specified. Organic extracts were dried over anhydrous  $\text{MgSO}_4$ . NMR spectra ( $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$ ) were recorded on Bruker Avancell 500 spectrometer, at 500 MHz (H value) in  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$ . Spectra were referenced to residual chloroform (7.26 ppm,  $^1\text{H}$ ; 77.0 ppm,  $^{13}\text{C}\{^1\text{H}\}$ ) or dimethyl sulfoxide (2.50 ppm,  $^1\text{H}$ ; 39.52 ppm,  $^{13}\text{C}\{^1\text{H}\}$ ). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet or overlap of nonequivalent resonances), dd (doublet of doublet), td (triplet of doublet), and br (broad signal). Coupling constants,  $J$ , are reported in hertz (Hz). All NMR spectra were obtained at 300K unless otherwise specified. IR spectra were obtained using a spectrum one FT-IR spectrometer (Perkin Elmer). High Resolution mass spectra were recorded on a ThermoFischer Exactive Orbitrap spectrometer. HPLC analyses were performed on a Shimadzu chromatograph equipped with a diode array UV/VIS detector. Optical rotations ( $[\alpha]_D$ ) at 20 °C. All photochemical transformations have been performed in a Rayonet RPR-200 photochemical reactor (Manufacturer: The Southern New England Ultraviolet Co) equipped with eight 350 nm lamps (12" in length, 14 w. Manufacturer: The Southern New England Ultraviolet Co Reference: RPR-3500A). Borosilicate glass vials (sealed tubes) placed in the middle of the reactor chamber were employed to run the reactions (distance from the light source to the irradiation vessel ~ 12 cm). For more information about the photochemical apparatus see the supporting information.

### Representative Procedure for the synthesis of the photocatalysts: Synthesis of Compound 3a.

A microwave vial was charged with *o*-anisidine (**1a**, 1 eq., 0.09 mL, 0.81 mmol) under an argon atmosphere. Dry THF (5 mL) was then added, and the resulting mixture was stirred at RT for 5 min. 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.210 mL, 1.14 mmol) was finally

added. The tube was sealed, then evacuated and refilled with argon three times. The reaction was heated at 60 °C in an oil bath and stirred for 16 h. The mixture was then cooled back to RT and evaporated under reduced pressure. The crude product was purified by trituration using cyclohexane as the solvent, yielding the pure thiourea **3a** as an off-white solid (311 mg, 0.79 mmol, 97 %). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.98 (s, 1H), 7.96 (s, 2H), 7.87 (s, 1H), 7.69 (s, 1H), 7.59 (d, *J* = 6.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.04 (dd, *J* = 12.9, 8.0 Hz, 2H), 3.89 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 179.4, 152.4, 139.5, 132.2 (q, *J* = 33.8 Hz), 128.5, 125.1, 124.8, 124.2 (br d, *J* = 3.2 Hz), 122.9 (q, *J* = 273.0 Hz), 121.3, 119.3 (dt, *J* = 7.3, 3.6 Hz), 112.0, 55.8 ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.6 (6F) ppm. IR (neat): ν 3629, 3012, 1737, 1530, 1510, 1375, 1284, 1180, 1128, 1118, 1022, 949, 892, 758 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>16</sub>H<sub>13</sub>F<sub>6</sub>N<sub>2</sub>OS: 395.0647; found: 395.0638.

**Compound 3b.** According to the representative procedure, starting from *p*-anisidine (**1b**, 1 eq., 0.094 mL, 0.81 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.208 mL, 1.14 mmol); trituration gave compound **3b** (304 mg, 0.77 mmol, 95 %) as a purple solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.14 (s, 1H), 10.03 (s, 1H), 8.25 (s, 2H), 7.78 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 179.9, 157.1, 142.0, 131.2, 129.9 (q, *J* = 32.8 Hz), 126.3, 123.5, 123.2 (q, *J* = 272.7 Hz), 116.6, 114.0, 55.3 ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.6 (6F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>31</sup>

**Compound 3c.** According to the representative procedure, starting from 4-aminobenzonitrile (**1c**, 1 eq., 100 mg, 0.85 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.208 mL, 1.14 mmol); trituration gave compound **3c** (326 mg, 0.84 mmol, 99 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.62 (s, 1H), 10.52 (s, 1H), 8.24 (s, 2H), 7.89 – 7.76 (m, 3H), 7.73 (d, *J* = 8.8 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 179.9, 143.3, 141.4, 132.9, 130.2 (q, *J* = 32.9 Hz), 123.7, 123.2 (q, *J* = 272.7 Hz), 123.0, 119.0, 117.4, 106.2 ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.5 (6F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>32</sup>

**Compound 3d.** According to the representative procedure, starting from *p*-fluoroaniline (**1d**, 1 eq., 0.086 mL, 0.9 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.23 mL, 1.26 mmol); trituration gave compound **3d** (341 mg, 0.89 mmol, 99 %) as a purple solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.23 (s, 1H), 10.17 (s, 1H), 8.25 (s, 2H), 7.79 (s, 1H), 7.52 – 7.41 (m, 2H), 7.28 – 7.15 (m, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 180.2, 159.6 (d, *J* = 242.4 Hz), 141.8, 134.9, 130.0 (q, *J* = 32.9 Hz), 126.6 (d, *J* = 8.4 Hz), 123.6 (d, *J* = 3.0 Hz), 123.2 (q, *J* = 272.8 Hz), 116.9 (dd, *J* = 11.0, 3.6 Hz), 115.4 (d, *J* = 22.6 Hz) ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.6 (6F), -117.0 (F) ppm. IR (neat): ν 3629, 3035, 1548, 1508, 1384, 1278, 1232, 1167, 1139, 981, 887, 840 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>15</sub>H<sub>8</sub>F<sub>7</sub>N<sub>2</sub>S: 381.0302; found: 381.0300.

**Compound 3e.** According to the representative procedure, starting from 2-fluoroaniline (**1e**, 1 eq., 0.087 mL, 0.9

mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.23 mL, 1.26 mmol); trituration gave compound **3e** (341 mg, 0.89 mmol, 99 %) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.37 (s, 1H), 9.99 (s, 1H), 8.29 (s, 2H), 7.82 (s, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.26 – 7.17 (m, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 181.0, 156.6 (d, *J* = 246.9 Hz), 141.7, 130.1 (q, *J* = 32.9 Hz), 128.8, 128.1 (d, *J* = 7.7 Hz), 126.3 (d, *J* = 12.0 Hz), 124.4 (d, *J* = 3.2 Hz), 123.3 (d, *J* = 2.3 Hz), 123.2 (q, *J* = 272.7 Hz), 117.0 (br), 116.0 (d, *J* = 19.9 Hz) ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.5 (6F), -121.4 (F) ppm. IR (neat): ν 3629, 3015, 1738, 1549, 1383, 1279, 1168, 1131, 981, 890, 746 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>15</sub>H<sub>8</sub>F<sub>7</sub>N<sub>2</sub>S: 381.0302; found: 381.0300.

**Compound 3f.** According to the representative procedure, starting from aniline (**1f**, 1 eq., 0.098 mL, 1.074 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2a**, 1.4 eq., 0.27 mL, 1.503 mmol); trituration gave compound **3f** (387 mg, 1.063 mmol, 99 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.29 (s, 1H), 10.21 (s, 1H), 8.27 (s, 2H), 7.79 (s, 1H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 179.8, 141.9, 138.6, 130.0 (q, *J* = 32.9 Hz), 128.7, 125.2, 124.0, 123.4 (br), 123.2 (q, *J* = 272.7 Hz), 116.8 (br) ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -61.6 (6F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>33</sup>

**Compound 3g.** According to the representative procedure, starting from aniline (**1f**, 1 eq., 0.098 mL, 1.074 mmol) and phenyl isothiocyanate (**2b**, 1.4 eq., 0.18 mL, 1.503 mmol); trituration gave compound **3g** (233 mg, 1.02 mmol, 95 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 14.52 (s, 2H), 12.21 (d, *J* = 7.5 Hz, 4H), 12.11 – 12.06 (m, 4H), 11.88 (t, *J* = 7.4 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 179.9, 139.6, 128.7, 124.8, 124.1 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>34</sup>

**Compound 3h.** According to the representative procedure, starting from aniline (**1f**, 1 eq., 0.098 mL, 1.074 mmol) and 1-isocyanato-3,5-bis(trifluoromethyl)benzene (**2c**, 1.4 eq., 0.26 mL, 1.503 mmol); trituration gave compound **3h** (367 mg, 1.052 mmol, 98 %) as a white solid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.37 (s, 1H), 8.96 (s, 1H), 8.13 (s, 2H), 7.63 (s, 1H), 7.51 – 7.44 (m, 2H), 7.34 – 7.26 (m, 2H), 7.05 – 6.98 (m, 1H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 152.4, 141.9, 139.0, 130.7 (q, *J* = 32.6 Hz), 128.8, 123.3 (q, *J* = 272.8 Hz), 122.5, 118.9, 118.0 (br), 114.3 (br) ppm. <sup>19</sup>F NMR (471 MHz, DMSO-*d*<sub>6</sub>): δ -63.1 (6F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>33</sup>

#### Representative Procedure for the tosylation reactions: Synthesis of Compound 4r

A flame-dried vial was charged with benzylamine (1 eq., 0.408 mL, 3.73 mmol), triethylamine (1.5 eq., 0.78 mL, 5.6 mmol) and DCM (30 mL) under an argon atmosphere. Tosyl chloride (1.1 eq., 783 mg, 4.106 mmol) was then added, and the resulting mixture was stirred at RT overnight. Water was then added, the immiscible phases were separated, and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered,

and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using EtOAc/Cy (1:9) as the eluent to afford compound **4r** (966 mg, 3.7 mmol, 99 %) as a pinkish solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.26 (m, 5H), 7.19 (d, *J* = 7.4 Hz, 2H), 4.59 (br s, 1H), 4.13 (d, *J* = 6.2 Hz, 2H), 2.44 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 143.6, 136.9, 136.3, 129.8, 128.7, 128.0, 127.9, 127.2, 47.3, 21.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>35</sup>

**Compound S1.** According to the representative procedure, starting from benzylamine (1 eq., 400 mg, 0.408 mL, 3.73 mmol) and benzenesulfonyl chloride (1.1 eq., 725 mg, 0.52 mL, 4.106 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **S1** (914 mg, 3.7 mmol, 99 %) as an amorphous white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 7.51 (m, 2H), 7.34 – 7.25 (m, 3H), 7.18 (d, *J* = 6.9 Hz, 2H), 4.86 – 4.58 (m, 1H), 4.14 (d, *J* = 6.0 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 140.0, 136.2, 132.9, 129.3, 128.9, 128.1, 128.0, 127.2, 47.4 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>36</sup>

**Compound S2.** According to the representative procedure, starting from benzylamine (1 eq., 300 mg, 0.306 mL, 2.8 mmol) and 2-mesitylenesulfonyl chloride (1.1 eq., 674 mg, 3.08 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **S2** (717 mg, 2.48 mmol, 89 %) as an amorphous white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.29 – 7.22 (m, 3H), 7.20 – 7.14 (m, 2H), 6.96 (s, 2H), 4.72 (t, *J* = 5.9 Hz, 1H), 4.07 (d, *J* = 6.2 Hz, 2H), 2.64 (s, 6H), 2.31 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 141.8, 138.6, 135.8, 132.9, 131.5, 128.1, 127.4, 46.3, 22.4, 20.4 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>37</sup>

**Compound S3.** According to the representative procedure, starting from benzylamine (1 eq., 0.26 mL, 2.3 mmol) and mesyl chloride (1.1 eq., 0.20 mL, 2.6 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **S3** (300 mg, 1.62 mmol, 69 %) as a colourless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37 – 7.23 (m, 5H), 4.57 (s, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 2.81 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 136.6, 129.0, 128.2, 127.9, 47.3, 41.2 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>38</sup>

**Compound (±)-S4.** According to the representative procedure, starting from DL-α-methylbenzylamine (1 eq., 0.213 mL, 1.65 mmol) and tosyl chloride (1 eq., 314 mg, 1.65 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound (±)-**S4** (448 mg, 1.63 mmol, 99 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.19 (m, 5H), 7.12 – 7.07 (m, 2H), 5.06 – 4.76 (br m, 1H), 4.46 (p, *J* = 6.9 Hz, 1H), 2.38 (s, 3H), 1.42 (d, *J* = 6.9 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 143.3, 142.1, 137.7, 129.6, 128.7, 127.6 (br), 127.2, 126.2, 53.7, 23.7, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>39</sup>

**Compound (S)-S4.** According to the representative procedure, starting from (L)-(-)-1-phenylethylamine (1 eq., 0.158 mL, 1.24 mmol) and tosyl chloride (1 eq., 236 mg, 1.24 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9

to 2:8) gave compound (S)-**S4** (327 mg, 1.19 mmol, 96 %) as a white solid. Spectroscopic data were identical to those of compound (±)-**S4**. [α]<sub>D</sub><sup>20</sup> –8.0 (c 0.3, CHCl<sub>3</sub>).

**Compound S5.** According to the representative procedure, starting from 4-fluorobenzylamine (1 eq., 0.18 mL, 1.6 mmol) and tosyl chloride (1.1 eq., 335 mg, 1.76 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **S5** (442 mg, 1.58 mmol, 99 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.16 (dd, *J* = 8.3, 5.5 Hz, 2H), 6.95 (t, *J* = 8.5 Hz, 2H), 4.86 (s, *J* = 40.1 Hz, 1H), 4.08 (d, *J* = 6.2 Hz, 2H), 2.43 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 162.5 (d, *J* = 246.6 Hz), 143.8, 136.9, 132.2 (d, *J* = 2.9 Hz), 129.9, 129.7 (d, *J* = 8.3 Hz), 127.3, 115.7 (d, *J* = 21.5 Hz), 46.7, 21.7 ppm. <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ –114.3 (F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>40</sup>

**Compound S6.** According to the representative procedure, starting from 4-methoxybenzylamine (1 eq., 0.19 mL, 1.46 mmol) and tosyl chloride (1.1 eq., 306 mg, 1.604 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **S6** (421 mg, 1.44 mmol, 99 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.82 – 6.78 (m, 2H), 4.54 (t, *J* = 5.8 Hz, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 159.3, 143.5, 136.8, 129.7, 129.3, 128.2, 127.2, 114.1, 55.3, 46.8, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>36</sup>

**Compound S7.** According to the representative procedure, starting from tryptamine (1 eq., 250 mg, 1.56 mmol) and tosyl chloride (1.1 eq., 327 mg, 1.72 mmol); flash chromatography on silica gel (EtOAc/Cy, 3:7) gave compound **S7** (380 mg, 1.209 mmol, 77 %) as a pinkish solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.06 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.09 – 7.03 (m, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 4.42 (t, *J* = 6.0 Hz, 1H), 3.27 (q, *J* = 6.5 Hz, 2H), 2.93 (t, *J* = 6.6 Hz, 2H), 2.40 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 143.3, 136.7, 136.4, 129.6, 127.0, 126.8, 122.6, 122.3, 119.5, 118.5, 111.6, 111.3, 43.0, 25.5, 21.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>41</sup>

**Compound S8.** According to the representative procedure, starting from methylamine (33 wt. % in absolute ethanol, 1 eq., 300 mg, 3.19 mmol) and tosyl chloride (1.1 eq., 668 mg, 3.51 mmol); compound **S8** (300 mg, 1.62 mmol, 51 %) was isolated as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.82 – 7.70 (m, 2H), 7.36 – 7.26 (m, 2H), 4.51 (s, 1H), 2.64 (s, 3H), 2.43 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 143.6, 135.8, 129.8, 127.3, 29.4, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>42</sup>

**Compound S9.** According to the representative procedure, starting from N-methylethylenediamine (1 eq., 0.12 mL, 1.35 mmol) and tosyl chloride (2 eq., 728 mg, 2.70 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:1) gave compound **S9** (226 mg, 0.59 mmol, 44 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.77 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 8.3 Hz, 4H), 4.94 (dd, *J* = 14.3, 5.8 Hz, 1H), 3.13 (q, *J* = 5.8 Hz, 2H), 3.03 (t, *J* = 5.8 Hz, 2H), 2.65



(s, 3H), 2.44 (s, 3H), 2.42 (s, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.9, 143.6, 136.6, 133.7, 129.9, 129.8, 127.4, 127.2, 49.8, 41.4, 36.1, 21.57, 27.56 ppm. IR (neat) :  $\nu$  3308, 2882, 2254, 1598, 1453, 1333, 1159, 1090, 1048, 906, 730  $\text{cm}^{-1}$ . HRMS (ESI-Orbitrap) :  $m/z$  [ $\text{M}-\text{H}^+$ ] calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2$  : 381.0948; found : 381.0954.

**Compound S10.** According to the representative procedure, starting from butylamine (1 eq., 200 mg, 0.27 mL, 2.73 mmol) and tosyl chloride (1 eq., 521 mg, 2.73 mmol); solvent evaporation gave compound **S10** (615 mg, 2.71 mmol, 99 %) as a clear oil. **S10** was used in the next synthetic step without further purification.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.68 (d,  $J$  = 8.3 Hz, 2H), 7.24 (d,  $J$  = 8.4 Hz, 2H), 4.39 (t,  $J$  = 5.6 Hz, 1H), 2.86 (dd,  $J$  = 13.6, 6.8 Hz, 2H), 2.36 (s, 3H), 1.42 – 1.32 (m, 2H), 1.22 (dq,  $J$  = 14.5, 7.3 Hz, 2H), 0.78 (t,  $J$  = 7.3 Hz, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.3, 137.1, 129.7, 127.1, 42.9, 31.6, 21.5, 19.7, 13.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>43</sup>

**Compound S11.** According to the representative procedure, starting from hexylamine (1 eq., 250 mg, 0.33 mL, 2.47 mmol) and tosyl chloride (1 eq., 471 mg, 2.47 mmol); flash chromatography on silica gel (EtOAc/Pentane, 2:8) gave compound **S11** (530 mg, 2.08 mmol, 84 %) as a clear oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 (d,  $J$  = 8.2 Hz, 2H), 7.31 (d,  $J$  = 8.3 Hz, 2H), 4.86 (s, 1H), 2.93 (dd,  $J$  = 12.3, 6.7 Hz, 2H), 2.44 (s, 3H), 1.50 – 1.41 (m, 2H), 1.28 – 1.17 (m, 6H), 0.85 (t,  $J$  = 7.0 Hz, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.3, 137.1, 129.7, 127.1, 43.2, 31.2, 29.5, 26.2, 22.4, 21.5, 13.9 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>43</sup>

**Compound S12.** According to the representative procedure, starting from allylamine (1 eq., 500 mg, 0.66 mL, 8.76 mmol) and tosyl chloride (1 eq., 1.67 g, 8.76 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9 then 2:8) gave compound **S12** (1.54 g, 7.28 mmol, 83 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.76 (d,  $J$  = 8.3 Hz, 2H), 7.31 (d,  $J$  = 8.4 Hz, 2H), 5.72 (ddt,  $J$  = 16.2, 10.3, 5.8 Hz, 1H), 5.17 (dd,  $J$  = 17.1, 1.5 Hz, 1H), 5.09 (dd,  $J$  = 10.2, 1.1 Hz, 1H), 4.61 (s, 1H), 3.58 (t,  $J$  = 6.0 Hz, 2H), 2.43 (s, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.5, 137.0, 133.0, 129.7, 127.2, 117.7, 45.8, 21.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>44</sup>

#### Representative Procedure for the acylation reactions: Synthesis of Compound 4a.

A round-bottomed flask containing *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 1.05 g, 4.02 mmol), DMAP (0.1 eq., 49 mg, 0.402 mmol) and triethylamine (1.5 eq., 0.84 mL, 6.03 mmol) dissolved in DCM (30 mL), was cooled to 0 °C. Benzoyl chloride (1.5 eq., 0.7 mL, 6.03 mmol) was then added dropwise. The reaction was warmed up to RT and stirred overnight. Water was then added, the immiscible phases were separated, and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using EtOAc/Cy (1:9) as the eluent to afford compound **4a** (1.14 g, 3.13 mmol, 78 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58 (d,  $J$

= 8.3 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.33 (t,  $J$  = 7.7 Hz, 2H), 7.26 – 7.18 (m, 7H), 4.98 (s, 2H), 2.41 (s, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.6, 144.7, 136.3, 136.0, 135.0, 131.7, 129.4, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 51.2, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>19</sup>

**Compound 4b.** According to the representative procedure, starting from *N*-benzylbenzenesulfonamide (**S1**, 1 eq., 980 mg, 3.96 mmol) and benzoyl chloride (1.5 eq., 0.69 mL, 5.94 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4b** (1.3 g, 3.69 mmol, 93 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.76 – 7.70 (m, 2H), 7.59 (t,  $J$  = 7.5 Hz, 1H), 7.51 – 7.41 (m, 5H), 7.37 – 7.34 (m, 2H), 7.29 – 7.24 (m, 3H), 7.23 – 7.19 (m, 2H), 5.03 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.5, 138.8, 136.0, 134.7, 133.6, 131.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8, 51.3 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>45</sup>

**Compound 4c.** According to the representative procedure, starting from *N*-benzyl-2,4,6-trimethylbenzene-1-sulfonamide (**S2**, 1 eq., 150 mg, 0.52 mmol) and benzoyl chloride (1.5 eq., 0.09 mL, 0.78 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4c** (122 mg, 0.31 mmol, 60 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 – 7.36 (m, 1H), 7.35 – 7.21 (m, 9H), 6.93 (s, 2H), 5.02 (s, 2H), 2.62 (s, 6H), 2.29 (s, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.3, 143.7, 140.4, 136.5, 135.2, 133.0, 132.1, 131.1, 128.6, 128.1, 127.8, 127.7, 127.4, 50.2, 22.4, 21.0 ppm. IR (neat):  $\nu$  2977, 2255, 1681, 1603, 1344, 1278, 1165, 1056, 911, 733  $\text{cm}^{-1}$ . HRMS (ESI-Orbitrap):  $m/z$  [ $\text{M}+\text{H}^+$ ] calcd for  $\text{C}_{23}\text{H}_{24}\text{NO}_3\text{S}$ : 394.1471; found: 394.1467.

**Compound 4d.** According to the representative procedure, starting from *N*-benzylmethanesulfonamide (**S3**, 1 eq., 150 mg, 0.81 mmol) and benzoyl chloride (1.5 eq., 0.14 mL, 1.22 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9 to 2:8) gave compound **4d** (222 mg, 0.77 mmol, 95 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70 – 7.60 (m, 2H), 7.56 (t,  $J$  = 7.5 Hz, 1H), 7.47 (t,  $J$  = 7.6 Hz, 2H), 7.38 – 7.27 (m, 3H), 7.21 – 7.11 (m, 2H), 4.99 (s, 2H), 3.04 (s, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.6, 135.6, 133.8, 132.3, 129.0, 128.9, 128.4, 128.1, 52.2, 42.9 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>14</sup>

**Compound ( $\pm$ )-4e.** According to the representative procedure, starting from 4-methyl-*N*-(1-phenylethyl)benzene-1-sulfonamide ( $(\pm)$ -**S4**, 1 eq., 448 mg, 1.63 mmol) and benzoyl chloride (1.5 eq., 0.28 mL, 2.44 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound  $(\pm)$ -**4e** (600 mg, 1.58 mmol, 97 %) as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51 (d,  $J$  = 8.3 Hz, 2H), 7.41 (t,  $J$  = 7.3 Hz, 1H), 7.34 – 7.24 (m, 9H), 7.19 (d,  $J$  = 8.1 Hz, 2H), 5.48 (q,  $J$  = 7.0 Hz, 1H), 2.41 (s, 3H), 1.91 (d,  $J$  = 7.1 Hz, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.3, 144.6, 139.3, 136.6, 136.3, 131.4, 129.4, 128.9, 128.4, 128.2, 127.9, 127.82, 127.77, 58.7, 21.8, 18.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>16</sup>

**Compound (S)-4e.** According to the representative procedure, starting from 4-methyl-*N*-(1-phenylethyl)benzene-1-sulfonamide (*S*-**S4**, 1 eq., 100 mg, 0.36 mmol) and benzoyl

chloride (1.5 eq., 0.06 mL, 0.54 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound (S)-**4e** (74 mg, 0.20 mmol, 54 %) as a white solid. Spectroscopic data were identical to those of compound ( $\pm$ )-**4e**. [ $\alpha$ ]<sub>D</sub><sup>20</sup> -64 (c 0.25, CHCl<sub>3</sub>).

**Compound 4f.** According to the representative procedure, starting from *N*-[(4-fluorophenyl)methyl]-4-methylbenzene-1-sulfonamide (**S5**, 1 eq., 200 mg, 0.72 mmol) and benzoyl chloride (1.5 eq., 0.12 mL, 1.074 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4f** (273 mg, 0.71 mmol, 99 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.57 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.44 - 7.41 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.25 - 7.19 (m, 4H), 6.95 (t, *J* = 8.7 Hz, 2H), 4.94 (s, 2H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.5, 162.4 (d, *J* = 246.7 Hz), 144.8, 135.9, 135.0, 132.0 (d, *J* = 3.1 Hz), 131.8, 130.0 (d, *J* = 8.2 Hz), 129.5, 128.4, 128.3, 128.2, 115.5 (d, *J* = 21.6 Hz, 2CH), 50.3, 21.6 ppm. <sup>19</sup>F NMR (471 MHz, DMSO):  $\delta$  -114.24 (F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>16</sup>

**Compound 4g.** According to the representative procedure, starting from *N*-[(4-methoxyphenyl)methyl]-4-methylbenzene-1-sulfonamide (**S6**, 1 eq., 200 mg, 0.67 mmol) and benzoyl chloride (1.5 eq., 0.17 mL, 1.43 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4g** (255.17 mg, 0.65 mmol, 94 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.58 (d, *J* = 8.3 Hz, 2H), 7.49 - 7.41 (m, 3H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.92 (s, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.6, 159.2, 144.6, 136.0, 135.0, 131.7, 129.5, 129.4, 128.4, 128.31, 128.25, 128.19, 113.9, 55.3, 50.7, 21.6 ppm. IR (neat):  $\nu$  2981, 1686, 1613, 1598, 1514, 1447, 1357, 1249, 1167, 1087, 1033, 955, 814, 731 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>22</sub>H<sub>22</sub>NO<sub>4</sub>S: 396.1264; found: 396.1257.

**Compound 4h.** According to the representative procedure, starting from *N*-[2-(1*H*-indol-3-yl)ethyl]-4-methylbenzene-1-sulfonamide (**S7**, 1 eq., 200 mg, 0.64 mmol) and benzoyl chloride (1.5 eq., 0.11 mL, 0.95 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4h** (158 mg, 0.302 mmol, 48 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.37 (d, *J* = 8.3 Hz, 1H), 7.75 - 7.67 (m, 4H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.40 (qd, *J* = 5.6, 2.7 Hz, 1H), 7.37 - 7.32 (m, 1H), 7.25 - 7.17 (m, 8H), 7.04 (s, 1H), 4.17 - 4.04 (m, 2H), 3.14 - 2.99 (m, 2H), 2.39 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.4, 168.4, 144.9, 136.3, 136.0, 134.8, 134.5, 131.9, 131.4, 130.4, 129.5, 129.2, 128.7, 128.4, 128.1, 127.7, 125.8, 125.2, 123.9, 118.6, 117.5, 116.6, 47.6, 25.6, 21.6 ppm. IR (neat):  $\nu$  2924, 2255, 1683, 1600, 1453, 1376, 1356, 1167, 910, 732 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>31</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>S: 523.1686; found: 523.1678.

**Compound 4i.** According to the representative procedure, starting from *N*-methyl-*p*-toluenesulfonamide (**S8**, 1 eq., 150 mg, 0.81 mmol) and benzoyl chloride (1.5 eq., 0.14 mL, 1.22 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4i** (242 mg, 0.81 mmol, quantitative) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.84 (d, *J* = 8.3 Hz, 2H), 7.68 - 7.48 (m, 3H), 7.41 (dd, *J* = 10.8, 4.5 Hz, 2H),

7.33 (d, *J* = 8.3 Hz, 2H), 3.28 (s, 3H), 2.44 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.5, 144.9, 135.1, 134.4, 132.0, 129.6, 128.50, 128.47, 128.44, 128.3, 35.6, 21.7 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>46</sup>

**Compound 4j.** According to the representative procedure, starting from *N*-butyl-4-methylbenzene-1-sulfonamide (**S10**, 1 eq., 250 mg, 1.1 mmol) and benzoyl chloride (1.5 eq., 0.19 mL, 1.65 mmol); flash chromatography on silica gel (EtOAc/Pentane, 2:8) gave compound **4j** (262 mg, 0.079 mmol, 72 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.78 (d, *J* = 8.4 Hz, 2H), 7.53 - 7.48 (m, 3H), 7.44 - 7.37 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.84 - 3.75 (m, 2H), 2.45 (s, 3H), 1.67 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.27 (dt, *J* = 14.8, 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.6, 144.6, 136.2, 135.4, 131.6, 129.5, 128.4, 128.2, 128.1, 47.9, 31.7, 21.6, 19.8, 13.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>18</sup>

**Compound 4k.** According to the representative procedure, starting from *N*-hexyl-4-methylbenzene-1-sulfonamide (**S11**, 1 eq., 550 mg, 2.15 mmol) and benzoyl chloride (1.5 eq., 0.38 mL, 3.23 mmol); flash chromatography on silica gel (EtOAc/Cy, 5:95) gave compound **4k** (100 mg, 0.278 mmol, 13 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.76 (d, *J* = 8.3 Hz, 2H), 7.51 - 7.46 (m, 3H), 7.42 - 7.35 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.81 - 3.69 (m, 2H), 2.43 (s, 3H), 1.64 (dd, *J* = 14.5, 7.1 Hz, 2H), 1.27 - 1.06 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.6, 144.6, 136.2, 135.4, 131.5, 129.5, 128.4, 128.2, 128.1, 48.1, 31.1, 29.6, 26.2, 22.4, 21.6, 13.9 ppm. IR (neat):  $\nu$  2958, 2932, 2862, 2258, 1792, 1686, 1359, 1169, 910, 734 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>26</sub>H<sub>26</sub>NO<sub>3</sub>S: 360.1628; found: 360.1630.

**Compound 4l.** According to the representative procedure, starting from 4-methyl-*N*-(prop-2-en-1-yl)benzene-1-sulfonamide (**S12**, 1 eq., 300 mg, 1.42 mmol) and benzoyl chloride (1.5 eq., 0.25 mL, 2.13 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4l** (421 mg, 1.33 mmol, 94 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.74 (d, *J* = 8.4 Hz, 2H), 7.43 - 7.37 (m, 3H), 7.32 - 7.26 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.76 (ddt, *J* = 17.0, 10.4, 5.7 Hz, 1H), 5.10 (ddd, *J* = 18.2, 13.8, 1.1 Hz, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 2.37 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  171.4, 144.8, 136.1, 134.9, 132.8, 131.6, 129.5, 128.7, 128.2, 128.0, 118.8, 50.3, 21.7 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>19</sup>

**Compound 4m.** According to the representative procedure, starting from *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 150 mg, 0.57 mmol) and 4-fluorobenzoyl chloride (1.5 eq., 0.10 mL, 0.86 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4m** (226 mg, 0.57 mmol, quantitative) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.58 (d, *J* = 8.4 Hz, 2H), 7.56 - 7.45 (m, 2H), 7.35 - 7.16 (m, 7H), 7.09 - 6.94 (m, 2H), 4.92 (s, 2H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  170.6, 164.8 (d, *J* = 253.5 Hz), 144.8, 136.0, 135.6, 131.2 (d, *J* = 3.4 Hz), 131.1 (d, *J* = 9.1 Hz), 129.5, 128.6, 128.3, 128.0, 127.8, 115.3 (d, *J* = 22.1 Hz), 51.1, 21.6 ppm. <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  -106.3 (F) ppm.

Spectroscopic data were consistent with the literature data for this compound.<sup>16</sup>

**Compound 4n.** According to the representative procedure, starting from *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 150 mg, 0.57 mmol) and 4-methoxybenzoyl chloride (1.5 eq., 0.12 mL, 0.86 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **4n** (182 mg, 0.46 mmol, 80 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.25 – 7.19 (m, 7H), 6.85 (d, *J* = 8.9 Hz, 2H), 4.89 (s, 2H), 3.83 (s, 3H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 171.3, 162.9, 144.5, 136.1, 135.8, 131.3, 129.5, 128.5, 128.4, 128.1, 127.7, 127.2, 113.5, 55.4, 51.4, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>47</sup>

**Synthesis of Compound 4o.** A round-bottomed flask containing *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 150 mg, 0.57 mmol), and DMAP (0.1 eq., 7 mg, 0.057 mmol), dissolved in THF (5 mL), was cooled to 0 °C. Boc<sub>2</sub>O (1.5 eq., 0.18 mL, 0.86 mmol) was then added. The reaction was warmed up to RT and stirred overnight. Water was then added, and the resulting aqueous mixture was extracted with DCM (3x). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluent: EtOAc/Cyclohexane 1:9) to afford compound **4o** (124 mg, 0.34 mmol, 60 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.59 – 7.53 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.27 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.04 (s, 2H), 2.41 (s, 3H), 1.31 (s, 9H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 151.1, 144.1, 137.4, 137.1, 129.1, 128.5, 128.2, 128.1, 127.7, 84.5, 49.7, 27.9, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>48</sup>

**Synthesis of Compound 4p.** A round-bottomed flask *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 100 mg, 0.38 mmol), K<sub>2</sub>CO<sub>3</sub> (6 eq., 317 mg, 2.3 mmol), and DMF (5 mL), was cooled to 0 °C. MeI (1.5 eq., 0.04 mL, 0.57 mmol) was then added. The reaction was warmed up to RT and stirred overnight. Water was then added, and the resulting aqueous mixture was extracted with DCM (3x). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluent: EtOAc/Cyclohexane 1:9) to afford compound **4p** (104 mg, 0.38 mmol, quantitative yield) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.36 (m, 3H), 7.35 – 7.28 (m, 4H), 4.12 (s, 2H), 2.58 (s, 3H), 2.46 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 143.5, 135.7, 134.2, 129.8, 128.6, 128.4, 127.9, 127.5, 54.1, 34.3, 21.6 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>21</sup>

**Compound 4q.** According to the representative procedure, starting from *N*-benzyl-4-methylbenzene-1-sulfonamide (**4r**, 1 eq., 150 mg, 0.57 mmol) and acetyl chloride (1.5 eq., 0.06 mL, 0.86 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **4q** (168 mg, 0.55 mmol, 96 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.35 – 7.23 (m, 5H), 5.08 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 170.4, 144.9, 136.7, 136.5, 129.8, 128.6, 128.0, 127.8, 49.5, 24.9, 21.6 ppm. Spectroscopic data

were consistent with the literature data for this compound.<sup>49</sup>

**Compound 4s.** According to the representative procedure, starting from *p*-toluenesulfonamide (1 eq., 500 mg, 2.92 mmol) and benzoyl chloride (1.1 eq., 0.37 mL, 3.21 mmol); flash chromatography on silica gel (EtOAc/Cy, 3:7) gave compound **4s** (1.3 g, 3.69 mmol, 93 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.33 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 2H), 2.44 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>) δ 164.7, 145.1, 135.7, 133.4, 131.5, 129.6, 128.8, 128.6, 127.9, 21.7. Spectroscopic data were consistent with the literature data for this compound.<sup>50</sup>

**Compound 4t.** According to the representative procedure, starting from *N*,4-dimethyl-*N*-(2-((4-methylphenyl)sulfonamido)ethyl)-benzenesulfonamide (**5g**, 1 eq., 150 mg, 0.26 mmol) and benzoyl chloride (1.5 eq., 0.05 mL, 0.39 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **4t** (126 mg, 0.26 mmol, quantitative yield) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.44 (m, 3H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 4H), 4.03 (t, *J* = 6.5 Hz, 2H), 3.25 (t, *J* = 6.5 Hz, 2H), 2.74 (s, 3H), 2.43 (s, 3H), 2.43 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 171.5, 145.1, 143.6, 135.6, 134.8, 134.1, 131.6, 129.8, 129.7, 128.5, 128.2, 127.4, 49.6, 45.3, 36.0, 21.7, 21.6 ppm. IR (neat) : ν 3068, 2980, 1688, 1598, 1345, 1163, 1089, 910, 731 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub>S: 487.1356; found : 487.1343.

**Representative Procedure for the photocleavage reactions: Synthesis of Compound 5a** (Table 3, entry 1).

A flame dried vial was charged with *N*-benzyl-*N*-(4-methylbenzenesulfonyl)benzamide (**4a**, 1 eq., 20 mg, 0.05 mmol), tetrabutylammonium borohydride (1.2 eq., 17 mg, 0.07 mmol) and photocatalyst **3a** (0.05 eq., 1 mg, 0.003 mmol) under an argon atmosphere. Dry DCM was then added, and the resulting mixture (0.05 M) was stirred at RT for 5 min. The tube was then sealed and evacuated and refilled with argon three times. The reaction was irradiated in a Rayonet chamber for 2 h (hν = 350 nm). H<sub>2</sub>O was then added, and the immiscible phases were separated. The aqueous layer was extracted with DCM (3x). The combined organic layers were dried over MgSO<sub>4</sub>, then concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using EtOAc/Cy as the eluent (2:8) to afford the compound **5a** (9 mg, 0.14 mmol, 76 %). As an off-white solid.

**Compound 5a (Scale-up).** According to the representative procedure, starting from *N*-(benzenesulfonyl)-*N*-benzylbenzamide (**4b**, 1 eq., 500 mg, 1.37 mmol) tetrabutylammonium borohydride (1.2 eq., 422 mg, 1.64 mmol) and photocatalyst **3a** (0.05 eq., 27 mg, 0.07 mmol) in dry DCM (20 mL) under an argon atmosphere and light irradiation for 4 h; flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5a** (220 mg, 1.04 mmol, 76 %) as an off-white solid.

**Compound 5a (Table 3, entry 2).** According to the representative procedure, starting from *N*-(benzenesulfonyl)-*N*-

benzylbenzamide (**4b**, 1 eq., 50 mg, 0.14 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5a** (22 mg, 0.10 mmol, 73 %) as an off-white solid.

**Compound 5a** (Table 3, entry 3). According to the representative procedure, starting from *N*-benzyl-*N*-(2,4,6-trimethylbenzenesulfonyl)benzamide (**4c**, 1 eq., 50 mg, 0.13 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5a** (21 mg, 0.10 mmol, 78 %) as an off-white solid.

**Compound 5a** (Table 3, entry 4). According to the representative procedure, starting from *N*-benzyl-*N*-(methylsulfonyl)benzamide (**4d**, 1 eq., 50 mg, 0.17 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5a** (28 mg, 0.13 mmol, 77 %) as an off-white solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.82 – 7.76 (m, 2H), 7.54 – 7.47 (m, 1H), 7.43 (m, 2H), 7.36 (d, *J* = 4.5 Hz, 4H), 7.30 (dq, *J* = 8.7, 4.2 Hz, 1H), 6.39 (br, s, 1H), 4.66 (d, *J* = 5.7 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.4, 138.1, 134.4, 131.6, 128.8, 128.6, 128.0, 127.7, 126.9, 44.2 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>51</sup>

**Compound (±)-5b** (Table 3, entry 5). According to the representative procedure, starting from *N*-(4-methylbenzenesulfonyl)-*N*-(1-phenylethyl)benzamide ((±)-**4e**, 1 eq., 50 mg, 0.13 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound (±)-**5b** (29 mg, 0.14 mmol, 71 %) as an off-white solid. Proton and carbon NMR data are identical to those of compound (*S*)-**5b** (vide infra).

**Compound (S)-5b**. According to the representative procedure, starting from *N*-(4-methylbenzenesulfonyl)-*N*-(1-phenylethyl)benzamide ((*S*)-**4e**, 1 eq., 50 mg, 0.13 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound (*S*)-**5b** (28 mg, 0.24 mmol, 70 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.76 (dd, *J* = 5.2, 3.4 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.32 (m, 5H), 7.31 – 7.24 (m, 2H), 6.33 (br s, 1H), 5.34 (p, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 166.6, 143.0, 134.5, 131.5, 128.7, 128.6, 127.5, 126.9, 126.2, 49.2, 21.7 ppm. Spectroscopic data were consistent with the literature data for these compounds.<sup>19</sup>

**Compound 5c** (Table 3, entry 6). According to the representative procedure, starting from *N*-[(4-fluorophenyl)methyl]-*N*-(4-methylbenzenesulfonyl)benzamide (**4f**, 1 eq., 50 mg, 0.13 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5c** (29 mg, 0.14 mmol, 74 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.82 – 7.76 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.37 – 7.31 (m, 2H), 7.07 – 7.01 (m, 2H), 6.40 (s, 1H), 4.63 (d, *J* = 5.7 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.3, 162.3 (d, *J* = 245.9 Hz), 134.2, 134.0 (d, *J* = 3.3 Hz), 131.7, 129.6 (d, *J* = 8.2 Hz), 128.7, 126.9, 115.6 (d, *J* = 21.4 Hz), 43.4 ppm. <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ - 114.8 (F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>52</sup>

**Compound 5d** (Table 3, entry 7). According to the representative procedure, starting from *N*-[(4-methoxyphenyl)methyl]-*N*-(4-methylbenzenesulfonyl)-benzamide (**4g**, 1 eq., 50 mg, 0.13 mmol) and photocatalyst **3a** (0.15 eq., 8 mg, 0.019 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5d** (25 mg, 0.104 mmol, 82

%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.81 – 7.76 (m, 2H), 7.53 – 7.48 (m, 1H), 7.46 – 7.40 (m, 2H), 7.32 – 7.27 (m, 2H), 6.92 – 6.86 (m, 2H), 6.31 (s, 1H), 4.59 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.2, 159.1, 134.4, 131.5, 130.2, 129.4, 128.6, 126.9, 114.2, 55.3, 43.7 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>52</sup>

**Compound 5e** (Table 3, entry 8). According to the representative procedure, starting from *N*-[2-(1-benzoyl-1H-indol-3-yl)ethyl]-*N*-(4-methylbenzenesulfonyl)benzamide (**4h**, 1 eq., 50 mg, 0.096 mmol) and photocatalyst **3a** (0.15 eq., 6 mg, 0.014 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5e** (25 mg, 0.067 mmol, 70 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.41 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 6.4 Hz, 4H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.54 – 7.37 (m, 6H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.15 (s, *J* = 8.8 Hz, 1H), 6.26 (s, 1H), 3.77 (q, *J* = 6.8 Hz, 2H), 3.03 (t, *J* = 6.8 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 168.3, 167.3, 136.3, 134.3, 134.2, 131.7, 131.4, 130.5, 128.8, 128.5, 128.44, 128.43, 126.6, 125.2, 124.8, 123.8, 118.9, 118.8, 116.5, 39.4, 25.0 ppm. IR (neat): ν 3346, 3066, 2930, 2489, 1679, 1644, 1537, 1453, 1378, 1357, 908, 712 cm<sup>-1</sup>. HRMS (ESI-Orbitrap): *m/z* [M+H<sup>+</sup>] calcd for C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>: 369.1598; found: 369.1594.

**Compound 5f** (Table 3, entry 9). According to the representative procedure, starting from *N*-methyl-*N*-tosylbenzamide (**4i**, 1 eq., 50 mg, 0.17 mmol) and photocatalyst **3a** (0.15 eq., 10 mg, 0.026 mmol); flash chromatography on silica gel (EtOAc/Cy, 3:7) gave compound **5f** (16 mg, 0.12 mmol, 69 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.75 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.46 – 7.38 (m, 2H), 6.11 (s, 1H), 3.02 (d, *J* = 4.9 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 168.3, 134.7, 131.4, 128.6, 126.8, 26.9 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>53</sup>

**Compound 5g**. According to the representative procedure, starting from *N*-butyl-*N*-(4-methylbenzenesulfonyl)-benzamide (**4j**, 1 eq., 50 mg, 0.15 mmol) and photocatalyst **3a** (0.05 eq., 4.3 mg, 0.007 mmol); flash chromatography on silica gel (EtOAc/Pentane, 2:8) gave compound **5g** (17 mg, 0.096 mmol, 56 %) as a clear oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.79 – 7.72 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.40 (m, 2H), 6.13 (s, 1H), 3.46 (td, *J* = 7.2, 5.8 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.42 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.5, 134.9, 131.3, 128.6, 126.8, 39.8, 31.8, 20.2, 13.8 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>54</sup>

**Compound 5h**. According to the representative procedure, starting from *N*-hexyl-*N*-(4-methylbenzenesulfonyl)-benzamide (**4k**, 1 eq., 50 mg, 0.14 mmol) and photocatalyst **3a** (0.05 eq., 4.0 mg, 0.007 mmol); flash chromatography on silica gel (EtOAc/Pentane, 2:8) gave compound **5h** (39 mg, 0.19 mmol, 74 %) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 6.16 (s, 1H), 3.45 (dd, *J* = 13.2, 7.0 Hz, 2H), 1.61 (dt, *J* = 14.8, 7.3 Hz, 2H), 1.40 – 1.29 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.5, 134.9, 131.3, 128.5, 126.8, 40.1, 31.5, 29.7, 26.7, 22.6, 14.0

ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>55</sup>

**Compound 5i.** According to the representative procedure, starting from *N*-(4-methylbenzenesulfonyl)-*N*-(prop-2-en-1-yl)benzamide (**4l**, 1 eq., 50 mg, 0.16 mmol) and photocatalyst **3a** (0.05 eq., 4.6 mg, 0.007 mmol); flash chromatography on silica gel (EtOAc/Pentane, 3:7) gave compound **5i** (7 mg, 0.043 mmol, 27 %) as a clear oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.81 – 7.75 (m, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H), 6.19 (s, 1H), 5.95 (ddt, *J* = 17.0, 10.3, 5.7 Hz, 1H), 5.27 (ddd, *J* = 17.1, 3.0, 1.6 Hz, 1H), 5.19 (ddd, *J* = 10.2, 2.7, 1.3 Hz, 1H), 4.10 (tt, *J* = 5.7, 1.5 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 167.3, 134.5, 134.2, 131.5, 128.6, 126.9, 116.7, 42.4 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>56</sup>

**Compound 5j** (Table 3, entry 10). According to the representative procedure, starting from *N*-benzyl-4-fluoro-*N*-(4-methylbenzenesulfonyl)benzamide (**4m**, 1 eq., 50 mg, 0.13 mmol) and photocatalyst **3a** (0.15 eq., 8 mg, 0.02 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:9) gave compound **5j** (18 mg, 0.078 mmol, 60%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.84 – 7.77 (m, 2H), 7.39 – 7.33 (m, 4H), 7.34 – 7.29 (m, 1H), 7.14 – 7.08 (m, 2H), 6.36 (s, 1H), 4.64 (d, *J* = 5.6 Hz, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 163.7, 162.7 (d, *J* = 252.0 Hz), 135.9, 128.4 (d, *J* = 3.3 Hz), 127.2 (d, *J* = 8.9 Hz), 126.8, 125.9, 125.7, 113.6 (d, *J* = 21.9 Hz), 42.2 ppm. <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ –108.1 (F) ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>57</sup>

**Compound 5k** (Table 3, entry 11). According to the representative procedure, starting from *N*-benzyl-4-methoxy-*N*-(4-methylbenzenesulfonyl)benzamide (**4n**, 1 eq., 30 mg, 0.076 mmol) and photocatalyst **3a** (0.15 eq., 4 mg, 0.011 mmol); flash chromatography on silica gel (EtOAc/Cy, 2:8) gave compound **5k** (8 mg, 0.033 mmol, 44 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.76 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 4.3 Hz, 4H), 7.33 – 7.29 (m, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.31 (s, 1H), 4.65 (d, *J* = 5.6 Hz, 2H), 3.85 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 166.9, 162.2, 138.4, 128.8, 128.8, 128.0, 127.6, 126.6, 113.8, 55.4, 44.1 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>58</sup>

**Compound 5q.** According to the representative procedure, starting from *N*-(2-((*N*,4-dimethylphenyl)sulfonamido)ethyl)-*N*-tosylbenzamide (**4t**, 1 eq., 20 mg, 0.041 mmol); flash chromatography on silica gel (EtOAc/Cy, 3:7) gave compound **5q** (11 mg, 0.033 mmol, 81 %) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.87 – 7.82 (m, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 3.62 (dd, *J* = 11.0, 5.2 Hz, 2H), 3.26 – 3.20 (m, 2H), 2.84 (s, 3H), 2.43 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 166.7, 142.8, 133.2, 133.0, 130.5, 128.9, 127.6, 126.3, 126.0, 48.3, 36.9, 34.7, 20.5 ppm. IR (neat): ν 3383, 2885, 2253, 1649, 1537, 1336, 1160, 906, 730 cm<sup>-1</sup>. HRMS (ESI-Orbitrap) : *m/z* [M+H<sup>+</sup>] calcd for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>S: 333.1267; found : 333.1256.

Synthesis and photocleavage of a cyclic sulfonamide

**Synthesis of compound 5l3.** Phthalimide (1 eq., 1 g, 6.8 mmol) was suspended in THF (50 mL) under argon at

room temperature. Methylmagnesium bromide (2.5 eq., 3M, 16.99 mmol, 5.7 mL) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated NH<sub>4</sub>Cl, and the product was extracted with dichloromethane. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. After solvent evaporation, compound **5l3** (966 mg, 5.92 mmol, 87 %) was obtained as an off-white solid. **5l3** was used in the following synthetic step without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.55 – 7.43 (m, 3H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.86 (s, 1H), 3.56 (t, *J* = 12.0 Hz, 1H), 1.71 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 168.9, 149.3, 132.9, 130.0, 129.6, 123.5, 121.7, 86.0, 25.9 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>59</sup>

**Synthesis of compound 7a.** Under an argon atmosphere, 3-hydroxy-3-methyl-2,3-dihydro-1H-isoindol-1-one **5l3** (1 eq., 200 mg, 1.23 mmol) dissolved in MeOH (10 mL) was stirred at room temperature and then added portionwise to NaCNBH<sub>3</sub> (1.1 eq., 85 mg, 1.35 mmol) followed by concentrated HCl (a few drops). The reaction mixture was allowed to stir at room temperature for 2 h, and then concentrated *in vacuo*. The residue was taken up with ethyl acetate (5 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x10 mL). The organic layers were combined, washed with brine, dried with MgSO<sub>4</sub>, and then filtered. The filtration was concentrated *in vacuo*, and the resulting residue was purified with a silica gel chromatography column (EtOAc/Cy, 1:1) to afford compound **6a** (137 mg, 0.93 mmol, 76%) as an off-white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 6.55 (s, 1H), 4.70 (q, *J* = 6.7 Hz, 1H), 1.51 (d, *J* = 6.7 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.4, 148.8, 131.9, 131.4, 128.1, 123.8, 122.2, 52.4, 20.4 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>59</sup>

**Synthesis of compound 6a.** 3-Methyl-2,3-dihydro-1H-isoindol-1-one **6a** (1 eq., 137 mg, 0.93 mmol) was suspended in THF (10 mL) under argon in an ice bath. Sodium hydride (1.5 eq., 34 mg, 1.4 mmol) was added and the resulting mixture was stirred at 0 °C for 30 min. After that time, tosyl chloride (1.1 eq., 195 mg, 1.02 mmol) was added and the reaction was left to stir for 1 h at 0 °C. The reaction was quenched with water, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. After solvent evaporation, compound **7a** (240 mg, 0.797 mmol, 86 %) was obtained as an off-white solid without further purification. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.64 (td, *J* = 7.6, 0.7 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.30 (q, *J* = 6.5 Hz, 1H), 2.42 (s, 3H), 1.78 (d, *J* = 6.5 Hz, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>): δ 166.4, 147.4, 145.0, 136.3, 134.0, 129.6, 128.9, 128.8, 128.3, 125.0, 122.5, 58.7, 21.7, 21.5 ppm. Spectroscopic data were consistent with the literature data for this compound.<sup>60</sup>

**Photodesulfonylation of compound 6a.** According to the representative procedure, starting from 3-methyl-2-(4-

methylbenzenesulfonyl)-2,3-dihydro-1H-isindol-1-one (**6a**, 1 eq., 50 mg, 0.17 mmol) and photocatalyst **3a** (0.05 eq., 4.78 mg, 0.008 mmol); flash chromatography on silica gel (EtOAc/Cy, 1:1) gave compound **7a** (14 mg, 0.095 mmol, 57%) as an off-white solid.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

UV-vis absorption of compounds **3a-h**, **4a-t** and **7a**, cyclic voltammetry and NMR studies, details on the photochemical apparatus and triplet quenching experiments, theoretical data, copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra (PDF).

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The manuscript was written through contributions of all authors.

## Notes

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## REFERENCES

- (1) P. G. M. Wuts, T. W. Greene *Greene's Protective Groups in Organic Synthesis*, Wiley: Hoboken (NJ), 2006, pp 895-1193.
- (2) Snyder, H. R.; Heckert, R. E. A Method for the Rapid Cleavage of Sulfonamides 1. *J. Am. Chem. Soc.* **1952**, *74*, 2006-2009.
- (3) Weisblat, D. I.; Magerlein, B. J.; Myers, D. R. The Cleavage of Sulfonamides. *J. Am. Chem. Soc.* **1953**, *75*, 3630-3632.
- (4) Wellner, E.; Sandin, H.; Pääkkönen, L. Synthesis of 6,6-Difluorohomopiperazines via Microwave-Assisted Detosylation. *Synthesis*, **2003**, *2*, 0223-0226.

- (5) Merrill, B. A.; LeGoff, E. A General Synthetic Route to 2,2':5',2''-terpyrrole, 2,5-di(2-Pyrryl)thiophene, and Alkyl-Substituted Analogs. *J. Org. Chem.* **1990**, *55*, 2904-2908.
- (6) Garg, N. K.; Sarpong, R.; Stoltz, B. M. The First Total Synthesis of Dragmacidin D. *J. Am. Chem. Soc.* **2002**, *124*, 13179-13184.
- (7) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A. J.; Bank, S.; Closson, W. D.; Wriede, P. A.; Cleavage of sulfonamides with sodium naphthalene. *J. Am. Chem. Soc.* **1967**, *89*, 20, 5311-5312.
- (8) Viaud, P.; Coeffard, V.; Thobie-Gautier, C.; Beaudet, I.; Galland, N.; Quintard, J.-P.; Le Grogne, E. Electrochemical Cleavage of Sulfonamides: An Efficient and Tunable Strategy to Prevent  $\beta$ -Fragmentation and Epimerization. *Org. Lett.* **2012**, *14*, 942-945.
- (9) Senboku, H.; Nakahara, K.; Fukuhara, T.; Hara, S. Hg Cathode-Free Electrochemical Detosylation of N,N-Di-substituted pToluenesulfonamides: Mild, Efficient, and Selective Removal of NTosyl Group. *Tetrahedron Lett.* **2010**, *51*, 435-438.
- (10) Coeffard, V.; Thobie-Gautier, C.; Beaudet, I.; Le Grogne, E.; Quintard, J.-P. Mild Electrochemical Deprotection of N-Phenylsulfonyl N-Substituted Amines Derived from (R)-Phenylglycinol. *Eur. J. Org. Chem.* **2008**, *2008*, 383-391.
- (11) Civitello, E. R.; Rapoport, H. The Regioselective Cleavage of Aryl Tosylates by Electrochemical Reduction. *J. Org. Chem.* **1992**, *57*, 834-840.
- (12) Ankner, T.; Hilmersson, G. Instantaneous Deprotection of Tosylamides and Esters with SmI<sub>2</sub>/Amine/Water. *Org. Lett.* **2009**, *11*, 503-506.
- (13) Vedejs, E.; Lin, S. Deprotection of Arenesulfonamides with Samarium Iodide. *J. Org. Chem.* **1994**, *59*, 1602-1603.
- (14) Knowles, H.; Parsons, A.; Pettifer, R. Desulfonylation of Amides Using Samarium Iodide. *Synlett* **1997**, *1997*, 271-272.
- (15) Jensen, K. L.; Franke, P. T.; Nielsen, L. T.; Daasbjerg, K.; Jørgensen, K. A. Anodic Oxidation and Organocatalysis: Direct Regio- and Stereoselective Access to Meta-Substituted Anilines by  $\alpha$ Arylation of Aldehydes. *Angew. Chem., Int. Ed.* **2010**, *49*, 129-133.
- (16) Blay, G.; Cardona, L.; Climent, E.; Pedro, J. R. Highly Enantioselective Zinc/binol-Catalyzed Alkynylation of N-Sulfonyl Aldimines. *Angew. Chem., Int. Ed.* **2008**, *47*, 5593-5596.
- (17) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. NBoc-L-Valine-Connected Amidomonophosphate Rhodium(I) Catalyst for Asymmetric Arylation of N-Tosylarylimines with Arylboroxines. *J. Am. Chem. Soc.* **2004**, *126*, 8128-8129.
- (18) Hasegawa, E.; Nagakura, Y.; Izumiya, N.; Matsumoto, K.; Tanaka, T.; Miura, T.; Ikoma, T.; Iwamoto, H.; Wakamatsu, K. Visible Light and Hydroxynaphthylbenzimidazole Promoted Transition-Metal-Catalyst-Free Desulfonylation of N-Sulfonylamides and N-Sulfonylamines. *J. Org. Chem.* **2018**, *83*, 18, 10813-10825.
- (19) Jun, X.; Bin-Jie, L.; Zhu-Jia, F.; Guo-Dong, S.; Huan-Huan, M.; Zhi-Wei, Y.; Jia-Rong, C.; Liang-Qiu, L.; Wen-Jing, X. Desulfonylation of tosyl amides through catalytic photoredox cleavage of N-S bond under visible-light irradiation. *Chem. Asian J.* **2013**, *8*, 1090-1094.
- (20) Hasegawa, E.; Tanaka, T.; Izumiya, N.; Kiuchi, T.; Ooe, Y.; Iwamoto, H.; Takizawa, S.; Murata, S. Protocol for Visible-Light-Promoted Desulfonylation Reactions Utilizing Catalytic Benzimidazolium Aryloxide Betaines and Stoichiometric Hydride Donor Reagents. *J. Org. Chem.* **2020**, *85*, 6, 4344-4353.

- (21) MacKenzie, I. A.; Wang, L.; Onuska, N. P. R. Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. Discovery and characterization of an acridine radical photoreductant. *Nature* **2020**, *580*, 76-80.
- (22) Fang, X.; Wang, C.-J. Recent advances in asymmetric organocatalysis mediated by bifunctional amine-thioureas bearing multiple hydrogen-bonding donors. *Chem. Commun.*, **2015**, *51*, 1185.
- (23) Sun, Y.-L.; Wei, Y.; Shi, M. Applications of Chiral Thiourea-Amine/Phosphine Organocatalysts in Catalytic Asymmetric Reactions. *ChemCatChem* **2017**, *9*, 718-727.
- (24) Parvin, T.; Yadav, R.; Choudhury, L. H. Recent applications of thiourea-based organocatalysts in asymmetric multicomponent reactions *Org. Biomol. Chem.*, **2020**, *18*, 5513-5532.
- (25) Spiliopoulou, N.; Nikitas, N. F.; Kokotos, C. G. Photochemical synthesis of acetals utilizing Schreiner's thiourea as the catalyst. *Green Chem.* **2020**, *22*, 3539-3545.
- (26) Vallavoju, N.; Selvakumar, S.; Pemberton, B. C.; Jockusch, S.; Sibi, M. P.; Sivaguru, J. Insights into the Mechanistic Aspects of Thiourea-Mediated Intermolecular [2+2] Photocycloadditions. *Angew. Chem. Int. Ed.* **2016**, *55*, 5446 - 5451.
- (27) Art, J. F.; Kestemont, J. P.; Soumillion, J. P. Photodetosylation of sulfonamides initiated by electron transfer from an anionic sensitizer. *Tetrahedron Lett.* **1991**, *32*, 1425-1428.
- (28) Ullman, E. F.; Singh P. 3,3,4,4-Tetramethyl-1,2-diazetidine 1,2-Dioxide, a Useful Low-Energy Triplet Quencher. *J. Am. Chem. Soc.* **1972**, *74*, 5077-5078.
- (29) Lucarini, M.; Pedulli, G. F.; Alberti, A.; Paradisi, C.; Roffia S. Spontaneous and Photoinduced Formation of Radical Anions in the Reaction of Borohydrides with Unsaturated Compounds. *J. Chem. Soc. Perkin Trans. 2* **1993**, *1993*, 2083-2087.
- (30) Chatgililoglu, C.; Gilbert, B. C.; Norman, R. O. C. Investigations of Structure and Conformation. Part 12. The Structure of Aromatic Sulphonyl Radicals: An E.s.r. and INDO Molecular Orbital Study. *J. Chem. Soc. Perkin Trans. 2* **1979**, *1979*, 770-775.
- (31) Natarajan, A.; Guo, Y.; Arthanari, H.; Wagner, G.; Halperin, J.-A.; Chorev, M. Synthetic Studies toward Aryl-(4-aryl-4H-[1,2,4]triazole-3-yl)-amine from 1,3-Diarylthiourea as Urea Mimetics. *J. Org. Chem.* **2005**, *70*, 6362-6368.
- (32) Cheng, X. F.; Shi, E. B.; Hou, X.; Xia, S. G.; He, J. H.; Xu, Q. F.; Li, H.; Li, N. J.; Chen, D. Y.; Lu, J. M. Upgrading Electroresistive Memory from Binary to Ternary Through Single-Atom Substitution in the Molecular Design. *Chem. Asian J.*, **2017**, *12*, 45-51.
- (33) Martínez-Crespo, L.; Halgreen, L.; Soares, M.; Marques, I.; Félix, V.; Valkenier, H. Hydrazones in anion transporters: the detrimental effect of a second binding site. *Org. Biomol. Chem.* **2021**, *19*, 8324-8337.
- (34) Ramakrishna, K. K. G.; Gunjan, S.; Shukla, A. K.; Pasam, V. R.; Balamnavar, V. M.; Sharma, A.; Jaiswal, S.; Lal, J.; Tripathi, R.; Anubhooti, Ramachandran, R.; Tripathi, R. P. Identification of Novel Phenyl Butenonyl C-Glycosides with Ureidyl and Sulfonamidyl Moieties as Antimalarial Agents. *ACS Med. Chem. Lett.* **2014**, *5*, 8, 878-883.
- (35) Ninghui, Z.; Chunli, Z.; Xiaoping, H.; Xin, X.; Yuanhong, L. Nickel-Catalyzed C(sp<sup>3</sup>)-H Functionalization of Benzyl Nitriles: Direct Michael Addition to Terminal Vinyl Ketones. *Org. Lett.* **2021**, *23*, 15, 6004-6009.
- (36) Huiling, W.; Nianhua, L.; Qianheng, Z.; Renshi, L. Amide Iridium Complexes As Catalysts for Transfer Hydrogenation Reduction of N-sulfonylimine. *J. Org. Chem.* **2021**, *86*, 5, 3850-3859.
- (37) Reed-Berendt, B. G.; Morrill, L. C. Manganese-Catalyzed N-Alkylation of Sulfonamides Using Alcohols. *J. Org. Chem.* **2019**, *84*, 6, 3715-3724.
- (38) Ai, Y.; Liu, P.; Liang, R.; Liu, Y.; Li, F. The N-alkylation of sulfonamides with alcohols in water catalyzed by a water-soluble metal-ligand bifunctional iridium complex [Cp\*Ir (biimH<sub>2</sub>)(H<sub>2</sub>O)][OTf]<sub>2</sub>. *New J. Chem.*, **2019**, *43*, 10755-10762.
- (39) Murali, G. M.; Pradip, T. R.; Biplab, M. Boron-Catalyzed N-Alkylation of Arylamines and Arylamides with Benzylic Alcohols. *J. Org. Chem.* **2020**, *85*, 2, 806-819.
- (40) Aditya, B.; Pushendra, S.; Biswajit, M. Highly Selective and Catalytic C-N Bond Cleavage of Tertiary Sulfonamides: Scope and Mechanistic Insight. *ACS Omega* **2021**, *6*, 29, 18988-19005.
- (41) Priebsenow, D. L.; Henderson, L. C.; Pfeffer, F. M.; Stewart, S. G. Domino Heck-Aza-Michael Reactions: Efficient Access to 1-Substituted Tetrahydro-β-carbolines. *J. Org. Chem.* **2010**, *75*, 5, 1787-1790.
- (42) Wessig, P.; Krebs, S. N-Aroylsulfonamide-Photofragmentation (ASAP)-A Versatile Route to Biaryls. *Eur. J. Org. Chem.* **2021**, *2021*, 6367-6374.
- (43) Chow, S. Y.; Stevens, M. Y.; Odell, L. R. Sulfonyl Azides as Precursors in Ligand-Free Palladium-Catalyzed Synthesis of Sulfonyl Carbamates and Sulfonyl Ureas and Synthesis of Sulfonamides. *J. Org. Chem.* **2016**, *81*, 2681-2691.
- (44) Zhou, S.; Lv, K.; Fu, R.; Zhu, C.; Bao, X. Nickel/Photoredox Dual Catalytic Cross-Coupling of Alkyl and Amidyl Radicals to Construct C(sp<sup>3</sup>)-N Bonds. *ACS Catal.* **2021**, *11*, 5026-5034.
- (45) Knowles, H.-S.; Parsons, A.-F.; Pettifer, R.-M.; Rickling, S. Desulfonylation of Amides using Tributyltin Hydride, Samarium Diiodide or Zinc/Titanium Tetrachloride. A Comparison of Methods. *Tetrahedron*, **2000**, *56*, 979-988.
- (46) Xu, X.-H.; Zhen, J.-S.; Du, X.; Yuan, H.; Li, Y.-H.; Chu, M.-H.; Luo, Y. Visible-Light-Mediated Late-Stage Sulfonylation of Anilines with Sulfonamides. *Org. Lett.* **2022**, *24*, 853-858.
- (47) Ramkumar, R.; Chandrasekaran, S. Catalyst-Free, Metal-Free, and Chemoselective Transamidation of Activated Secondary Amides. *Synthesis*, **2019**, *51*, 4, 921-932.
- (48) Liu, Q.; Liu, Z.; Zhou, Y.-L.; Zhang, W.; Yang, L.; Liu, Z.-L.; Yu, W. Photochemical Desulfonylation of N-Tosyl Amides by 2-Phenyl-N,N'-Dimethylbenzimidazoline (PDMBI). *Synlett* **2005**, *16*, 2510-2512.
- (49) Stenfors, B. A.; Ngassa, F. N. The synthesis and crystallographic characterization of 4-methylbenzenesulfonamide derivatives. *Eur. J. Org. Chem.* **2021**, *12*, 109-116.
- (50) Yates, M. H.; Kallman, N. J.; Ley, C. P.; Wei, J. N. Development of an Acyl Sulfonamide Anti-Proliferative Agent, LY573636-Na. *Org. Process Res. Dev.* **2009**, *13*, 255-262.
- (51) Matsumoto, A.; Wang, Z.; Maruoka, K. Radical-Mediated Activation of Esters with a Copper/Selectfluor System: Synthesis of Bulky Amides and Peptides. *J. Org. Chem.* **2021**, *86*, 7, 5401-5411.
- (52) Pandey, V. K.; Tiwari, C. S.; Rit, A. Silver-Catalyzed Hydroboration of C-X (X= C, O, N) Multiple Bonds. *Org. Lett.* **2021**, *23*, 5, 1681-1686.
- (53) Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. The Ruthenium-Catalyzed Reduction and Reductive N-Alkylation of Secondary Amides with Hydrosilanes: Practical Synthesis of Secondary and Tertiary Amines by Judicious Choice of Hydrosilanes. *J. Org. Chem.* **2007**, *72*, 20, 7551-7559.
- (54) He, Y.; Zeng, L.; Li, M.; Gu, L.; Zhang, S.; Li, G. Electrochemical Oxidative C-C Bond Cleavage of Ketones for C-

- N Bond Formation: A Route to Amides. *J. Org. Chem.* **2022**, *87*, 12622-12631.
- (55) Ramachandran, P. V.; Hamann, H. J. Ammonia-borane as a Catalyst for the Direct Amidation of Carboxylic Acids. *Org. Lett.* **2021**, *23*, 2938-2942.
- (56) Forni, J. A.; Micic, N.; Connell, T. U.; Weragoda, G.; Polyzos, A. Tandem Photoredox Catalysis: Enabling Carbonylative Amidation of Aryl and Alkylhalides. *Angew. Chem. Int. Ed.* **2020**, *59*, 18646-18654.
- (57) Pei, Y.; Yuwei, W.; Zhigang, Z.; Yunfeng, C. Metal-Free C–N or C–C Bond Cleavages of  $\alpha$ -Azido Ketones: An Oxidative-Amidation Strategy for the Synthesis of  $\alpha$ -Ketothioamides and Amides. *J. Org. Chem.* **2019**, *84*, 14883-14891.
- (58) Bai, S.-T.; Bheeter, C. B.; Reek, J. N. H. Hydrogen Bond Directed ortho-Selective C–H Borylation of Secondary Aromatic Amides. *Angew. Chem. Int. Ed.* **2019**, *58*, 13039-13043.
- (59) Ruan, Y.-P.; Chen, M.-D.; He, M.-Z.; Zhou X.; Zhang, P.-Q. Synthesis of 3-Alkyl-2,3-dihydro-1H-isindolin-1-ones. *Synth. Commun.* **2004**, *34*, 853-861.
- (60) Ye Tao, Y.; Gilbertson, S. R. Diastereoselective synthesis of 1,3-disubstituted isoindolines and sultams via bronsted acid catalysis. *Chem. Commun.* **2018**, *54*, 11292-11295.
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