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# Forging C–S Bonds on the Azetidine Ring by Continuous Flow Photochemical Addition of Thiols and Disulfides to Azetines

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A strategy for *anti*-Markovnikov hydroalkyl/aryl thiolation and disulfidation of 2-azetines under continuous flow conditions has been developed. Thiyl radicals are generated from thiols or disulfides and subsequently propagate into the azetine unsaturation to forge the C–S bond and shape a secondary radical intermediate. This carbon-centered radical chain transfers to

another thiol via hydrogen atom transfer (HAT) or another disulfide to regenerate the key thiyl radical intermediates. The use of flow technology ensures efficient irradiation of the reaction mixture leading to extremely fast, robust, and scalable protocols. Furthermore, ethyl acetate was adopted as an environmentally responsible solvent.

## Introduction

The success of drug discovery campaigns is inextricably linked to its available chemical space.<sup>[1]</sup> Hence, innovative synthetic strategies that expand the medicinal chemist toolbox are essential to developing new therapeutics. In the area of saturated nitrogen heterocycles, the shortage of robust and versatile strategies to access the strained azetidine ring has historically limited its installation in the structure of drug candidates, when compared to larger ring counterparts, namely pyrrolidine and piperidine. However, due to the recent development of robust and versatile strategies for its preparation, the popularity of the four-membered nitrogen nucleus is dramatically increasing.<sup>[2]</sup> Indeed, azetidine-containing compounds with anticancer, antibacterial, antimicrobial, antischizophrenic, anti-malarial, antiobesity, anti-inflammatory, antidiabetic, and anti-

viral activity have been disclosed.<sup>[3]</sup> Improved pharmacokinetic properties, such as solubility, lipophilicity, and metabolic stability have been attributed to the azetidine introduction into drug candidates. As a consequence of this growing interest, azetidine-containing derivatives are often included in substrate scope when a new synthetic methodology is presented. Photo-induced cyclization,<sup>[4]</sup> halogen-Atom Transfer (XAT) reactions,<sup>[5]</sup> visible-light promoted decarboxylation protocols,<sup>[6]</sup> strain-release reactions of ABBs (1-azabicyclo[1.1.0]butanes),<sup>[7]</sup> metalation-electrophilic trapping sequences<sup>[8]</sup> are the most advanced methods to access functionalized azetidines. Among these strategies, the manipulation of 2-azetidines is emerging as a powerful tool to decorate the azetidine ring. Indeed, 2-azetidines have been recently adopted as versatile synthetic platforms to access functionalized azetidines through cycloadditions,<sup>[9]</sup> batch and flow metal catalyzed hydrogenations,<sup>[10,11]</sup> acid<sup>[10b]</sup> and base-promoted<sup>[12]</sup> additions, and metal-catalyzed transformations.<sup>[13,14]</sup>

However, the use of 2-azetidines *en route* to azetidines through the addition of radicals has been little explored. Zard and coworkers reported the radical addition to *N*-protected 2-azetidines using xanthates as radical precursors.<sup>[15]</sup> In 2020, Zhang succeeded in the arylidifluoroalkylation of Boc-protected 2-azetidines promoted by a difluoroacetyl radical.<sup>[16]</sup> In both cases, the addition of radicals across the olefinic  $\pi$ -bond of 2-azetidines occurs regioselectively at the C3, generating the C2-centered azetidiny radical to produce *trans* 2,3-disubstituted azetidines (Scheme 1). As proposed by Zard,<sup>[15c]</sup> the observed C3-regioselectivity for the radical addition was explained by both steric and electronic effects. Indeed, the Boc group could hinder the attack at C2 while the  $\alpha$ -nitrogen could stabilize the azetidiny radical at C2. In this context, the addition of sulfur atom to unsaturated bonds (i.e. thiol-ene reaction) represents a useful click-type tool in organic synthesis, bioconjugation, or material science.<sup>[17]</sup> In addition, the merging of advanced light-emitting diode (LED) irradiation technology and the narrow channel of a typical flow microreactor tremendously stimulated the field of

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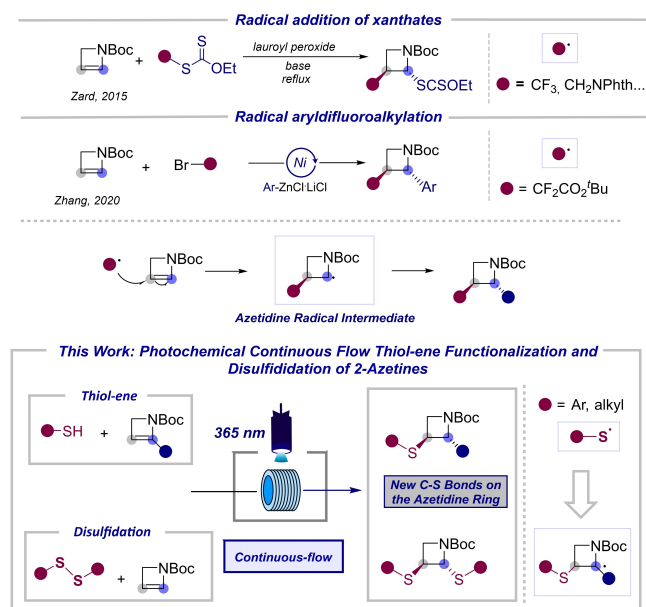
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Scheme 1. Radical additions to 2-azetines.

continuous flow photochemical transformations. Due to the importance of thiol-ene reactions, several groups recently developed light-mediated thiol-ene transformations under continuous flow conditions.<sup>[18]</sup> These reactions usually require a photocatalyst to promote the process, albeit catalyst-free thiol-ene reactions have also been developed.<sup>[19]</sup> In these latter cases, as reported by Bowman,<sup>[20]</sup> a direct photolysis of the S–H bond could be achieved by using a high-energy light source (centered around 254 nm). However, the key thiyl radical could also be generated using a lower energy light (> 300 nm) following a still unclarified mechanism. To the best of our knowledge, 2-azetines has never been adopted as unsaturated acceptor in thiol-ene transformations. To fill this gap, we report herein a strategy for anti-Markovnikov hydroalkyl/aryl thiolation and disulfenylation of 2-azetines under continuous flow photochemical conditions. With the exception of aliphatic thiols, which requires the use of a photocatalyst when reacted to unsubstituted 2-azetines, the generation of the key thiyl radical proceeds in the absence of the initiator under UV-A irradiation (365 nm). We believe that this approach represents a straightforward strategy to forge C–S bonds on the azetidine nucleus, accessing to unexplored chemical entities.

## Results and Discussion

At the outset of our investigations, we selected 2-substituted 2-azetidine **1a** and thiophenol **2a** as model substrates for the optimization study under batch conditions. To our delight, by irradiating the reaction mixture with a UV-A LED source ( $\lambda = 365$  nm, 128 W) in dichloromethane using a 2:1 molar ratio between **1a**:**2a**, the desired azetidine **3aa** was obtained in 80% yield with a noteworthy trans-stereoselectivity ( $dr = 85:15$ ). The

use of higher wavelengths (i.e. 395 nm, and 457 nm) reduced the yields sensibly. Furthermore, by following the reaction evolution over time, we realized that the transformation needed 2 hours to completion. Control experiments also confirmed the radical pathway. Indeed, in the absence of the light source or in the presence of TEMPO as a radical scavenger the reaction does not take place. Leveraging on our experience in the field of flow technology<sup>[21]</sup> and encouraged by these preliminary results under batch conditions, we evaluated the opportunity to develop a greener, faster, and easy-to-scale process under continuous flow conditions.

For our purpose, we adopted the PhotoCube™ photo-flow reactor equipped with a PTFE coil reactor (volume = 8 mL), and with a long-wave (UV-A) ultraviolet lamp ( $\lambda = 365$  nm). Compounds **1a**, **2a** were selected as standard substrates, and DCM as reaction solvent for the initial optimization studies. Preliminary experiments suggested that the reaction could be carried out under flow conditions observing, after only 5 minutes, **3aa** in 80% yield comparable to what observed under batch conditions (Table 1, entry 1). The use of higher residence time was detrimental for the yield (Table 1, entries 2, 3). Next, with the aim to develop a greener protocol, we screened other solvents. An unsatisfactory 30% yield was obtained using acetonitrile (Table 1, entry 4), while better results were obtained using 2-MeTHF (Table 1, entry 5, 60% yield) and ethyl acetate (Table 1, entry 7, 70% yield) adopting 5 minutes as the residence time. The higher sustainability profile of ethyl acetate prompted us to further optimize the thiol-ene addition using this solvent. We found that the reaction performed better increasing the residence time (Table 1, entry 10). Furthermore,

Table 1. Optimization studies for the reaction of 2-azetidine **1a** with thiophenol **2a**.

Entry	[1a]	[2a] (equiv.)	t <sup>R</sup> [min]	Solvent	3aa [%] <sup>[a]</sup>
1	0.05 M	2	5 <sup>[b]</sup>	DCM	80
2	0.05 M	2	8 <sup>[c]</sup>	DCM	65
3	0.05 M	2	30 <sup>[c]</sup>	DCM	60
4	0.05 M	2	5 <sup>[b]</sup>	MeCN	15
5	0.05 M	2	5 <sup>[b]</sup>	2-MeTHF	60
6	0.05 M	2	5 <sup>[b]</sup>	EtOAc	70
7	0.05 M	2	10 <sup>[d]</sup>	EtOAc	85
8	0.05 M	1	10 <sup>[d]</sup>	EtOAc	80
10	0.1 M	1	10 <sup>[d]</sup>	EtOAc	85

[a] NMR yields were calculated by using mesitylene as internal standard. The residence time was changed by adjusting the solution flow rates [b] Flow rate: 1.6 mL min<sup>-1</sup>, t<sup>R</sup>: 5 min. [c] Flow rate: 1.0 mL min<sup>-1</sup>, t<sup>R</sup>: 8 min. [c] Flow rate: 0.26 mL min<sup>-1</sup>, t<sup>R</sup>: 30 min. [d] Flow rate: 0.8 mL min<sup>-1</sup>, t<sup>R</sup>: 10 min.

an excess of **2a** was not pivotal for this transformation (Table 1, entry 8). Interestingly, doubling the concentration (0.1 M) resulted in 85% yield (Table 1, entry 9) allowing for better productivity of the flow process. Unfortunately, a further increase in reagent concentrations (0.2 M) resulted in solubility issues. As per the mechanism of the radical thiolation (Scheme 2b), it is likely that the process starts with the generation of the thiyl radical **A** promoted by light irradiation. Radical **A** reacts with 2-azetine **1** to provide an azetidiny radical **B** that undergoes thiol-mediated hydrogen radical transfer (HAT) to furnish the final product **3**. Remarkably, azetidiny radical **B** was trapped using TEMPO as radical scavenger leading to product **C** (see Supporting Information). With the optimal conditions in hand, the scope of the reaction was explored (Scheme 2c,d). First, varied 2-substituted 2-azetines (**1a–f**) were successfully coupled with several aromatic thiols (**2a–e**) (Scheme 2c). The transformation showed good functional group tolerance and furnished products **3** in good to excellent yields.

Switching to aliphatic thiols (**2f–h**), an increase of residence time, 15 minutes, was necessary to achieve complete conversion of the starting materials (Scheme 2c). The stereoselectivity of the reaction was affected by the steric requirement brought by the C2-substituent of the azetine, and the steric hindrance of the thiol. As observed for **3cd**, the steric requirement of the thiol seemed to be important for both stereoselectivity and reaction yield. Moreover, a complete cis-stereoselectivity was observed in **3ca** likely as the result of reduced steric requirement at C2 and at the thiol counterpart. Contrariwise, high level of trans stereoselectivity were observed when bulky substituents were installed at the C2. In striking contrast, reducing the steric requirement at C2 resulted in lower stereoselectivity (**3db** and **3df**). The radical protocol was found highly chemoselective as in the case of the reaction involving chiral azetine **2e** deriving from (–)-carvone. In fact, under radical conditions, only the azetine  $\pi$ -system was involved in the reaction, leaving untouched the remaining double bonds in **3ee**. Interestingly, using N-(tert-Butoxycarbonyl)-L-cysteine methyl ester as thiyl radical precursor, the thiol-ene reaction occurred smoothly furnishing the corresponding azetidines **3ah** in 90% yield (Scheme 2c). Notably, the use of azetine **2g**, derived from the biologically relevant estrone 3-methyl ether, produced the desired azetine **3hg** in good yield and excellent diastereoselectivity. Then, the thiol-ene addition of aromatic thiols (**2a–e** and **2i–m**) to unsubstituted 2-azetine (**1i**) was investigated (Scheme 2d). Pleasingly, the transformation furnished C3-functionalized azetidines in excellent yields using an extremely short residence time of 1 minute. The protocol could be applied to several substituted aromatics including the naphthyl substituent (**3ie**). The robustness of the protocol was demonstrated with the preparation of azetine **3ib** on 2 mmol scale with no loss of the process efficiency.

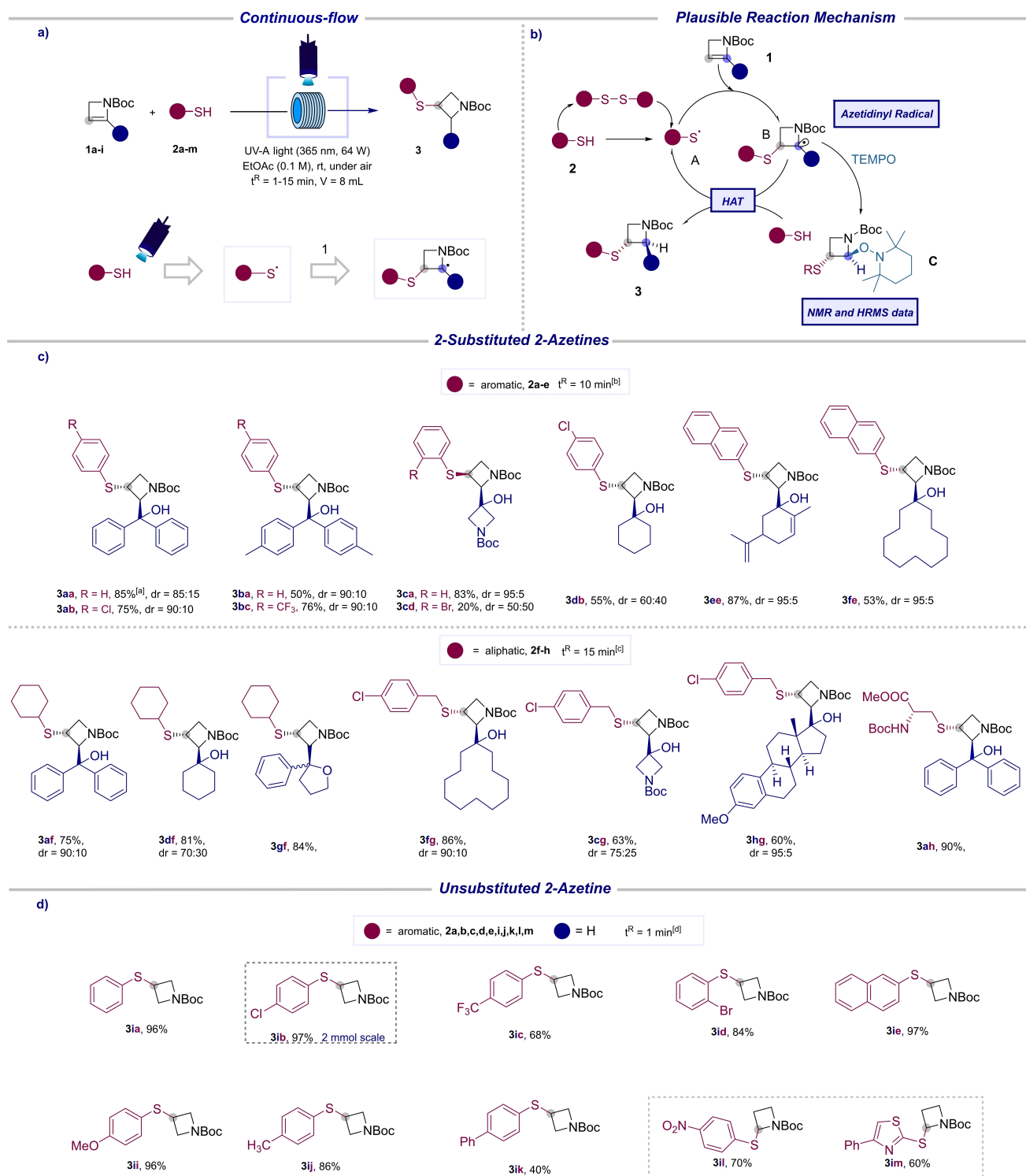
In striking contrast, the use of thiols **2l** and **2m** furnished, azetidines **3il** and **3im** (Scheme 2d) deriving from the functionalization at the C2 position of the azetine ring. We postulated that the use of more acidic thiols could promote an ionic addition to the 2-azetine via a C3 protonation followed by C2 thiolation. The radical addition of aliphatic thiols to 2-azetine **1i**

deserves a separate discussion. Indeed, our attempts to prepare azetidines **3**, adopting the reaction conditions described above, yielded the desired adducts only in traces. Considering the successful generation of aliphatic thiyl radical using 2-substituted 2-azetines as acceptor alkenes, we cannot conclusively rule out a possible supporting role of C-2 substituent on the generation of the aliphatic thiyl radical. Hence, to forge the targeted C–S bond we decided to add benzophenone as inexpensive photocatalyst for our transformation. Pleasingly, adopting this expedient, the C-3 functionalized azetidines were obtained in good to excellent yields (Scheme 3). As suggested by Kappe,<sup>[18c]</sup> an energy transfer catalysis is likely to explain the S–H photolysis mediated by a photosensitizer.

Spurred by these results, we next focused our attention on the formation of two different C–S bonds on the azetine core. Indeed, in principle, by using disulfides as reaction partners, a disulfidation reaction could take place. Hence, a series of aromatic disulfides were selected to react with azetine **11** (Scheme 4). With our delight, using a residence time of 1 minute, the desired 2,3-difunctionalized azetidines (**5ia–5ie**) were produced with good yield and high level of trans stereoselectivity, except for azetine **5id**. Unfortunately, when aliphatic disulfides were employed, disulfidation adducts were not observed, also using benzophenone or acetophenone as photosensitizers and performing reactions under an inert atmosphere. We postulated that the higher calculated bond dissociation energy of aliphatic disulfides (BDE = 65.2–69.0 kcal/mol) compared to multi-substituted diphenyldisulfides (46.5–58.2 kcal/mol) could explain this result.<sup>[22]</sup> Furthermore, and according to reported literature, the use of 2-substituted 2-azetine **1a** as acceptor alkenes in disulfide-ene reaction with diphenyl disulfide, yielded the hydrothiolation **3aa** adduct as the major product.<sup>[23]</sup>

To further explore the reactivity and usefulness of the C3 thiolate azetidines, we explored the preparation of the corresponding sulfoximines from azetidines **3ib**, **3id**, **3ie**, and **3ih** applying the hypervalent iodine-mediated strategy for the one-pot N- and O-transfer to the sulfur previously developed in our group.<sup>[24]</sup> The transformation occurred smoothly furnishing the desired sulfoximines **6** in high yield. Sulfoximine **7** (Scheme 5) was obtained by using a two-step sequence based on hypervalent iodine mediated N- and O-transfer on azetine **3ib**, followed by acidic removal of the Boc group.

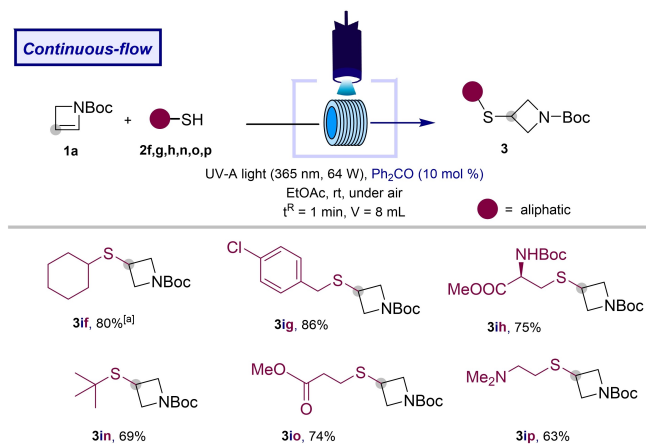
After assessing the feasibility of the continuous flow click thiolation of 2-azetines, we were keen to benchmark the greenness of the flow process compared to batch. Some key sustainability metrics were computed for two selected examples: the preparation of **3aa** and **3ib**. Along with the selection of EtOAc, which is included in the list of recommended reaction solvents,<sup>[25]</sup> atom efficiency (AE), stoichiometric factor (1/SF), space-time yield (STY), photochemical space-time yield (PSTY), the environmental factor (E-Factor), and the process mass intensity (PMI) were evaluated to assess the efficiency and greenness of the method (Table 2) As a result, improved STY (57.1 g/L\*h vs 4.48 g/L\*h) and PSTY (7.14 g/KW\*h vs 0.28 g/KW\*h) could be observed for the preparation of **3aa** switching from batch to flow (see Supporting Information), hence



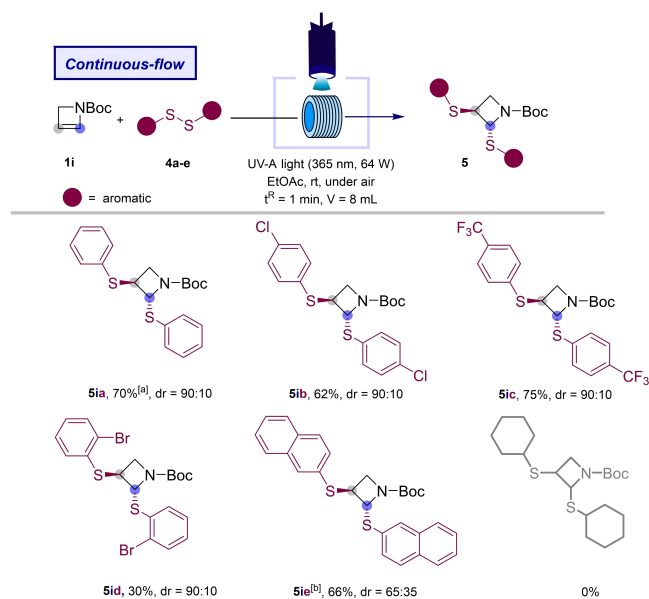
**Scheme 2.** a) Light-mediated hydrothiolation of 2-azetines under continuous flow conditions; b) proposed reaction mechanism; c) scope of the light-mediated hydrothiolation of 2-substituted 2-azetines using aliphatic and aromatic thiols; d) scope of the light-mediated hydrothiolation of unsubstituted 2-azetines using aromatic thiols. Reaction conditions: azetine (1 equiv), thiol (1 equiv), DCM (0.1 M), at room temperature using PhotoCube™ reactor ( $\lambda = 365$  nm, 64 W, reactor volume: 8 mL). [a] NMR yields were calculated by using mesitylene, 1,3,5-trimethoxybenzene, or CH<sub>2</sub>Br<sub>2</sub> as internal standard. [b] Flow rate: 0.8 mL min<sup>-1</sup>,  $t^R$ : 10 min. [c] Flow rate: 0.53 mL min<sup>-1</sup>,  $t^R$ : 15 min. [d] Flow rate: 8 mL min<sup>-1</sup>,  $t^R$ : 1 min.

suggesting the favorable scalability of the continuous flow protocol. Moreover, the flow route analysis reveals an impressive reduction of the E-factor by 55%, meaning that there is a

decreased amount of waste generated during the synthesis, and a process mass intensification reduction of 54%, suggesting that the route is becoming more efficient and streamlined,

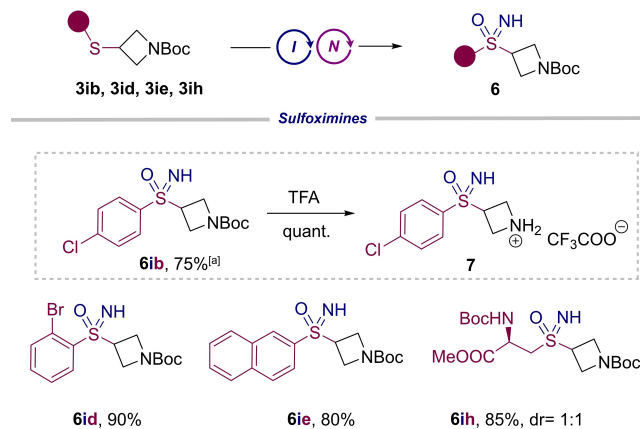


**Scheme 3.** Scope of thiol-ene reaction using aliphatic thiols. [a] The NMR yields were calculated by using CH<sub>2</sub>Br<sub>2</sub> as internal standard.



**Scheme 4.** Scope of disulfidation. [a] The NMR yields were calculated by using CH<sub>2</sub>Br<sub>2</sub> as internal standard. [b] Due to solubility issues, product **5e** was prepared using DCM as reaction solvent.

leading to reduced resource consumption and costs. These results are significant because they indicate a greener and more sustainable method of production. Other parameters such as the reaction yield (Rxn Yield=0.85) and the stoichiometric factor (1/SF=1) also took advantage from the use of the microfluidic technology, approaching the ideal standards. Similarly, the continuous flow preparation of **3ib** showed strongly improved metrics including STY (442.9 g/L\*h vs 169.3 g/L\*h), PSTY (52.9 g/KW\*h vs 10.6 g/KW\*h), and reduced waste generation (the E-factor and the PMI are both reduced by 2%). The computed metrics unequivocally point out the advantages related the use of microfluidic technology in accessing the functionalized azacycles reported herein.



**Scheme 5.** Synthesis of sulfoximines using hypervalent iodine mediated NH transfer. Reactions were performed using sulfide (1 equiv), (Diacetoxyiodo)benzene (2.5 equiv), ammonium carbamate (2 equiv.), MeOH (0.5 M), 3 hours. Isolated yields are reported.

**Table 2.** Green metrics analysis.<sup>[a]</sup>

(a)

Parameter	Ideal	Batch	Flow	Gain
AE (%)	100	100	100	-
Yield (%)	100	40	85	112.5%
1/SF (%)	100	50	100	100%
STY (g L <sup>-1</sup> h <sup>-1</sup> )	-	2.24	28.6	1177%
PSTY (g KW <sup>-1</sup> h <sup>-1</sup> )	-	0.14	3.57	2450%
E-factor (-)	-	53	24	-55%
PMI (-)	-	54	25	-54%

(b)

Parameter	Ideal	Batch	Flow	Gain
AE (%)	100	100	100	-
Yield (%)	100	94	94	-
1/SF (%)	100	50	100	100%
STY (g L <sup>-1</sup> h <sup>-1</sup> )	-	84.6	211.5	150%
PSTY (g KW <sup>-1</sup> h <sup>-1</sup> )	-	5.29	26.4	399%
E-factor (-)	-	36	35	-2%
PMI (-)	-	37	36	-2%

[a] Comparison of green metrics for the batch protocol and continuous flow protocol for the preparation of **3aa** (panel a) and **3ib** (panel b). Batch reaction conditions for **3aa**: azetidine **1a** (0.067 g, 1 equiv), thiol **2a** (2 equiv), AcOEt (1.8 g, 0.1 M), at room temperature using PhotoCube™ reactor ( $\lambda = 365$  nm, 64 W, reactor volume: 4 mL, 2 hours). Flow reaction conditions for **3aa**: azetidine **1a** (0.067 g, 1 equiv), thiol **2a** (1 equiv), AcOEt (1.8 g, 0.1 M), at room temperature using PhotoCube™ reactor ( $\lambda = 365$  nm, 64 W, reactor volume: 8 mL,  $t^R$ : 10 min). Batch reaction conditions for **3ib**: azetidine **1i** (0.031 g, 1 equiv), thiol **2b** (2 equiv), AcOEt (1.8 g, 0.1 M), at room temperature using PhotoCube™ reactor ( $\lambda = 365$  nm, 64 W, reactor volume: 4 mL, 5 minutes). Flow reaction conditions for **3ib**: azetidine **1i** (0.031 g, 1 equiv), thiol **2b** (1 equiv), AcOEt (1.8 g, 0.1 M), at room temperature using PhotoCube™ reactor ( $\lambda = 365$  nm, 64 W, reactor volume: 8 mL,  $t^R$ : 1 min).

## Conclusions

In summary, we have detailed herein a continuous flow approach to forge C–S bonds on the azetidine ring. The method relies on the light-promoted radical addition of thiyl radicals to 2-azetines yielding the azetidiny radical. This carbon-centered radical chain transfers to another thiol via hydrogen atom transfer (HAT) or by another disulfide to regenerate the key thiyl radical. The generation of key thiyl radicals occurred without the use of photoinitiator molecules, except for the coupling between aliphatic thiols and unsubstituted *N*-Boc-2-azetidine. In the latter case, the use of benzophenone as a photosensitizer was mandatory to furnish the targeted thiyl radicals. The developed method allowed the preparation of a broad variety of functionalized azetidines accessing unexplored chemical space. The narrow channel of the microreactor provided the efficient irradiation of the reaction mixture with a substantial acceleration of the transformation switching from batch to flow conditions. STY and PSTY were computed to assess the higher scale-up potential of the flow method with respect to the batch processing. Furthermore, ethyl acetate was adopted as an environmentally responsible solvent. We envision that this approach represents a straightforward strategy to forge C–S bonds on the azetidine nucleus that will broaden the growing catalogue of azetidine decoration methods.

## Experimental Section

**General procedure for the light-mediated hydrothiolation of 2-substituted 2-azetines with aromatic thiols:** To a solution of 2-substituted azetidine **1** (0.2 mmol, 1 equiv) in ethyl acetate (2 mL), the desired aromatic thiol **2a–e** (0.2 mmol, 1 equiv) was added. Subsequently, the solution was loaded in a 2 mL PTFE loop connected with a PTFE coil reactor (8 mL) contained in a PhotoCube™ photo-flow reactor equipped with a UV-A lamp ( $\lambda = 365$  nm, 64 W). The solution was pumped (0.8 mL/min) through the coil employing a syringe pump equipped with a gastight syringe containing ethyl acetate (10 mL). The reaction mixture was collected after 10 minutes from the start for 150 seconds. The solvent was removed under reduced pressure. The desired product was obtained by washing the reaction crude with hexane/diethyl ether 9:1 (v/v) or after flash column chromatography.

**General procedure for the light-mediated hydrothiolation of 2-substituted 2-azetines with aliphatic thiols:** To a solution of 2-substituted azetidine **1** (0.2 mmol, 1 equiv) in ethyl acetate (2 mL), the desired aliphatic thiol **2f–h** (0.2 mmol, 1 equiv) was added. Subsequently, the solution was loaded in a 2 mL PTFE loop connected with a PTFE coil reactor (8 mL) contained in a PhotoCube™ photo-flow reactor equipped with a UV-A lamp ( $\lambda = 365$  nm, 64 W). The solution was pumped (0.53 mL/min) through the coil employing a syringe pump equipped with a gastight syringe containing ethyl acetate (10 mL). The reaction mixture was collected after 15 minutes from the start for 226 seconds. The solvent was removed under reduced pressure. The desired product was obtained by washing the reaction crude with hexane/diethyl ether 9:1 (v/v) or after flash column chromatography.

**General procedure for the light-mediated hydrothiolation of 2-azetidine **1i** with aromatic thiols:** To a solution of azetidine **1i** (0.2 mmol, 1 equiv) in ethyl acetate (2 mL), the desired aromatic thiol **2** (0.2 mmol, 1 equiv) was added. Subsequently, the solution

was loaded in a 2 mL PTFE loop connected with a PTFE coil reactor (8 mL) contained in a PhotoCube™ photo-flow reactor equipped with a UV-A lamp ( $\lambda = 365$  nm, 64 W). The solution was pumped (8 mL/min) through the coil employing a syringe pump equipped with a gastight syringe containing ethyl acetate (10 mL). The reaction mixture was collected after 1 minute from the start for 15 seconds. The solvent was removed under reduced pressure. The desired product was obtained after flash column chromatography.

**General procedure for the light-mediated hydrothiolation of 2-azetidine **1i** with aliphatic thiols:** To a solution of azetidine **1i** (0.2 mmol, 1 equiv) in ethyl acetate (2 mL), the desired aliphatic thiol **2** (0.2 mmol, 1 equiv), and benzophenone (0.02 mmol, 0.1 equiv) were added. Subsequently, the solution was loaded in a 2 mL PTFE loop connected with a PTFE coil reactor (8 mL) contained in a PhotoCube™ photo-flow reactor equipped with a UV-A lamp ( $\lambda = 365$  nm, 64 W). The solution was pumped (8 mL/min) through the coil employing a syringe pump equipped with a gastight syringe containing ethyl acetate (10 mL). The reaction mixture was collected after 1 minutes from the start for 15 seconds. The solvent was removed under reduced pressure. The desired product was obtained by washing the reaction crude with hexane or after flash column chromatography.

**General procedure for the light-mediated disulfidation of 2-azetidine **1i** with aromatic disulfides:** To a solution of azetidine **1i** (0.2 mmol, 1 equiv) in ethyl acetate (2 mL), the desired aromatic disulfide **4a–e** (0.2 mmol, 1 equiv) was added. Subsequently, the solution was loaded in a 2 mL PTFE loop connected with a PTFE coil reactor (8 mL) contained in a PhotoCube™ photo-flow reactor equipped with a UV-A lamp ( $\lambda = 365$  nm, 64 W). The solution was pumped (8 mL/min) through the coil employing a syringe pump equipped with a gastight syringe containing ethyl acetate (10 mL). The reaction mixture was collected after 1 minute from the start for 15 seconds. The solvent was removed under reduced pressure. The desired product was obtained after flash column chromatography.

## Supporting information

Additional references cited within the Supporting Information.<sup>[26–28]</sup>

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** azetidines · 2-azetidines · disulfide-ene · flow photochemistry · thiol-ene

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