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# Site-Selective $\gamma$ -Trihalomethylation and $\gamma$ -Dihalomethylidenation of Silyl Dienol Ethers under Organophotoredox Catalysis

Camille Banoun,<sup>[a]</sup> Flavien Bourdreux,<sup>[a]</sup> Emmanuel Magnier,<sup>[a]</sup> and Guillaume Dagousset\*<sup>[a]</sup>

We report a general remote tribromo- and trichloromethylation process using  $\text{CBr}_4$  and  $\text{CCl}_3\text{Br}$  as readily available sources of trihalomethyl radicals. This method operates under mild and metal-free photocatalyzed conditions and enables the access to  $\gamma$ -trihalomethylated enals with complete regioselectivity in up

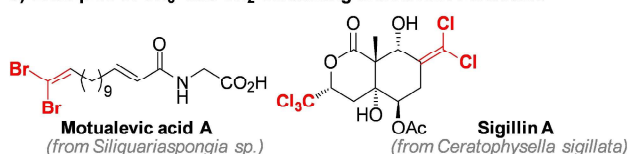
to 71% isolated yield. Importantly, this protocol is easily adapted to the selective one-pot synthesis of the corresponding  $\gamma$ -dihalomethylidenated enals in up to 49% overall yield. Mechanistic studies are in favor of a radical chain propagation initiated by an oxidative quenching of the photocatalyst.

## Introduction

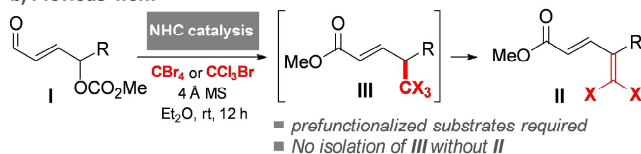
Trihalomethyl and dihalomethylidene moieties ( $-\text{CX}_3$  and  $=\text{CX}_2$ , X=Cl, Br) play a central role in chemistry. On the one hand, they are key intermediates in organic synthesis. For instance, the Ramirez olefination of carbonyl compounds gives access to the corresponding *gem*-dibromoalkene, which can lead to the corresponding alkyne in the well-known Corey-Fuchs reaction.<sup>[1]</sup> On the other hand, they are found in a large number of natural products and bioactive compounds,<sup>[2,3]</sup> which is linked to the fact that the incorporation of halogen atoms into drug candidates generally improves their lipophilicity, metabolic stability, and drug target affinity.<sup>[4]</sup> For instance, Motualevic acid A is a  $\text{CBr}_2$ -containing natural compound extracted from marine sponge *Siliquariaspongia sp.* which exhibits antibacterial activity (Scheme 1a).<sup>[3a]</sup> Sigillin A, isolated from the snow flea *Ceratophysella sigillata*, has a structure containing both trichloromethyl and dichloromethylidene groups.<sup>[3b]</sup> As a consequence, the development of new methodologies to directly introduce these moieties into organic substrates has been the subject of intense research over the last decade.<sup>[5]</sup>

Remote C–H functionalization is a powerful concept which involves the selective transformation of one C–H bond located at a distal position of a reactive center.<sup>[6]</sup> However, despite the recent achievements in the trihalomethyl/dihalomethylidene chemistry,<sup>[5]</sup> the insertion of these functional groups at a remote position of a substrate remains a significant synthetic challenge.<sup>[7]</sup> To the best of our knowledge, the only general

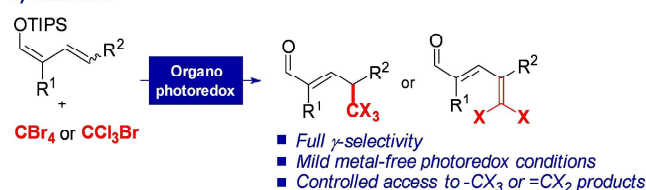
### a) Examples of $\text{CX}_3$ - and $\text{CX}_2$ -containing bioactive molecules



### b) Previous work



### c) This work



**Scheme 1.** Selected examples of  $\text{CX}_3$ - and  $\text{CX}_2$ -containing molecules of interest, and remote trihalomethylation and dihalomethylidenation methodologies. X=Br, Cl.

example was reported by Sun *et al.* in 2016.<sup>[7a]</sup> In this work, they described the NHC-catalyzed synthesis of  $\gamma$ -dihalomethylidenated  $\alpha,\beta$ -unsaturated esters II (Scheme 1b). Although efficient, the requirement for prefunctionalized substrates I bearing a carbonate group in  $\gamma$  position hampers the application scope of this methodology, and makes it unsuitable for late-stage dihalomethylidenation of more complex compounds. In addition, although the formation of the corresponding  $\gamma$ -trihalomethylated intermediate III was demonstrated, no suitable reaction conditions were found to isolate this intermediate without any dehydrohalogenation into the  $\gamma$ -dihalomethylidenated adduct II. Based on the capacity of silyl dienol ethers to selectively trap electrophilic radicals in their remote  $\gamma$  position,<sup>[8]</sup> and considering the high compatibility and mildness of the reaction conditions generally associated to photoredox catalysis,<sup>[9]</sup> we reasoned that the development of a photocatalyzed process

[a] Dr. C. Banoun, F. Bourdreux, Dr. E. Magnier, Dr. G. Dagousset  
Université Paris-Saclay, UVSQ, CNRS, UMR 8180, Institut Lavoisier de  
Versailles, 45 avenue des Etats-Unis, 78000 Versailles, France  
E-mail: guillaume.dagousset@uvsq.fr

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would help fill this gap in synthetic methodology. Herein, we disclose a general and selective metal-free photocatalyzed method which allows the controlled synthesis of either  $\gamma$ -trihalomethylated enals or their  $\gamma$ -dihalomethylidenated analogues (Scheme 1c).

## Results and Discussion

Our investigation began with silyl dienol ether **1a** derived from (*E*)-2-dodecenal as the model substrate, which was reacted in the presence of a photocatalyst, CBr<sub>4</sub> **2a** (a well-known precursor of electrophilic CBr<sub>3</sub> radical under photoredox catalysis),<sup>[10]</sup> and a base in order to avoid hydrolysis of **1a** (Table 1). Several organic photocatalysts were first evaluated (entries 1–4). Pleasingly, under 18 W blue LED irradiation, the  $\gamma$ -tribromomethylated enal **3a** was obtained in all cases, Rhodamine B being the most efficient photocatalyst (80% NMR yield, entry 4). Variations of light source (green LEDs, entry 5), and

solvents (entries 6–7) did not lead to any yield improvement. It is worth noting that corresponding  $\gamma$ -dibromomethylidenated compound **5a**, which would result from HBr elimination, was not detected despite the presence of K<sub>2</sub>CO<sub>3</sub> as base. Finally, changing the stoichiometry (entries 8–9) led to a slight increase in yield, the combination of 2 equiv. of CBr<sub>4</sub> and 1.5 equiv. of K<sub>2</sub>CO<sub>3</sub> being the optimal reaction conditions (88% NMR yield, entry 9). Delightfully, even in the presence of the unsubstituted nucleophilic  $\alpha$ -carbon of substrate **1a**, enal **3a** was always obtained with perfect  $\gamma$ -regioselectivity, and no trace of the corresponding  $\alpha$ -CBr<sub>3</sub> enal could be detected after analysis of the crude NMR spectra. Control experiments were performed without Rhodamine B and in the dark, and confirmed that both the photocatalyst and the light were necessary for the reaction to take place (entries 10–11). Interestingly, the corresponding  $\gamma$ -dibromomethylidenated adduct **5a** resulting from HBr elimination was observed as the major product when the reaction was performed in the presence of Et<sub>3</sub>N as the base (entries 12–13). However, the overall efficiency of the process was lower than with K<sub>2</sub>CO<sub>3</sub>, presumably due to the reductive quenching of Rhodamine B by Et<sub>3</sub>N which may hamper the formation of the desired product.<sup>[11]</sup> In order to both avoid this issue and selectively obtain the  $\gamma$ -CBr<sub>2</sub> product **5a**, we thought of developing a one-pot two-step protocol, without isolating adduct **3a**. Hence, after 1 h irradiation of silyl dienol ether **1a** and CBr<sub>4</sub> **2a** under the previously optimized conditions of entry 9, Et<sub>3</sub>N (5 equiv.) was directly added in the crude reaction mixture. After stirring overnight without irradiation, we were pleased to see complete disappearance of **3a** in favor of the  $\gamma$ -CBr<sub>2</sub> product **5a**, which could be isolated in 45% yield over two steps (entry 14).

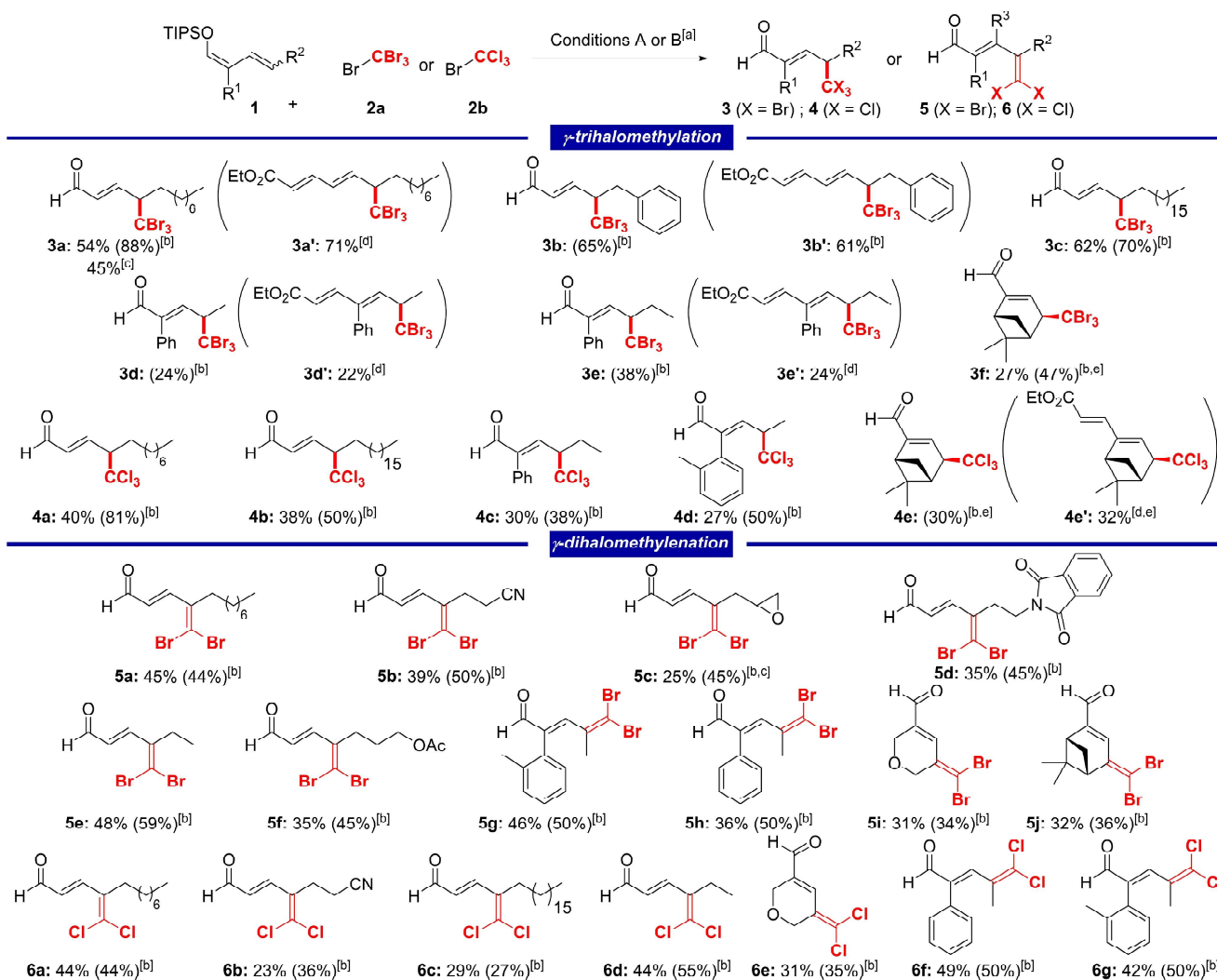
Having determined both optimal reaction conditions towards the controlled synthesis of either  $\gamma$ -CBr<sub>3</sub> or  $\gamma$ -CBr<sub>2</sub> adducts, we then turned our attention to the application scope of this metal-free methodology (Scheme 2). First, to show its synthetic utility, a 1 mmol scale experiment was performed with substrate **1a**. Under the same conditions,  $\gamma$ -CBr<sub>3</sub> product **3a** was produced with almost the same efficiency, pointing out the simplicity to scale up the process. It is worth noting that it was difficult to separate the desired product from triisopropylsilylanol TIPSOH, formed as a side-product of the reaction. To avoid this issue, enal **3a** was in situ engaged in a Wittig reaction with ethyl (triphenylphosphoranylidene)acetate, thus providing the corresponding  $\alpha,\beta,\gamma,\delta$ -unsaturated ester **3a'** in better yield (71% over two steps), closer to the NMR yield of the corresponding enal (88%). Then, other  $\alpha$ -unbranched  $\gamma$ -tribromomethylated enals **3b–3c** could be prepared in good yields. The process was also compatible with the synthesis of  $\alpha$ -arylated  $\gamma$ -CBr<sub>3</sub> enals **3d–3e**, albeit with a lower efficiency. Remarkably, this tribromomethylation protocol was successfully applied to the synthesis of more complex molecules, such as  $\gamma$ -CBr<sub>3</sub> enal **3f** derived from the natural bicyclic monoterpene (–)-Myrtenal.<sup>[12]</sup>

With these first successful results in hand, we then decided to extend the scope of this process to the synthesis of  $\gamma$ -trichloromethylated analogues. Indeed, CBrCl<sub>3</sub> **2b** has a redox potential slightly higher than the one of CBr<sub>4</sub> ( $E_{1/2}$ (**2b**) = –0.18 V

**Table 1.** Optimization studies for the  $\gamma$ -tribromomethylation and  $\gamma$ -dibromomethylidenation of silyl dienol ether **1a**.

Entry	PC	Solvent	Additive	Yield (%) of <b>3a</b> <sup>[a,b]</sup>	Yield (%) of <b>5a</b> <sup>[a,b]</sup>
1	EY	MeCN	K <sub>2</sub> CO <sub>3</sub>	63	–
2	RB	MeCN	K <sub>2</sub> CO <sub>3</sub>	59	–
3	Rh 6G	MeCN	K <sub>2</sub> CO <sub>3</sub>	54	–
4	Rh B	MeCN	K <sub>2</sub> CO <sub>3</sub>	80	–
5 <sup>[c]</sup>	Rh B	MeCN	K <sub>2</sub> CO <sub>3</sub>	70	–
6	Rh B	THF	K <sub>2</sub> CO <sub>3</sub>	30	–
7	Rh B	CH <sub>2</sub> Cl <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	32	–
8 <sup>[d]</sup>	Rh B	MeCN	K <sub>2</sub> CO <sub>3</sub>	82	–
9 <sup>[d,e]</sup>	<b>Rh B</b>	<b>MeCN</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>88 (54)<sup>[f]</sup></b>	–
10 <sup>[d,e]</sup>	None	MeCN	K <sub>2</sub> CO <sub>3</sub>	Trace	–
11 <sup>[d,e,g]</sup>	Rh B	MeCN	K <sub>2</sub> CO <sub>3</sub>	–	–
12 <sup>[d]</sup>	Rh B	MeCN	Et <sub>3</sub> N	10	18
13 <sup>[h]</sup>	Rh B	MeCN	Et <sub>3</sub> N	6	24
14 <sup>[e,h,i]</sup>	<b>Rh B</b>	<b>MeCN</b>	<b>Et<sub>3</sub>N</b>	–	<b>44 (45)<sup>[f]</sup></b>

[a] General conditions: **1a** (0.15 mmol), CBr<sub>4</sub> **2a** (0.225 mmol, 1.5 equiv.), PC (0.003 mmol, 2 mol%), additive (0.15 mmol, 1 equiv.) in 1.5 mL of solvent irradiated with 18 W blue LEDs at RT for 1 h. [b] Yields determined by <sup>1</sup>H NMR spectroscopy using 1,3-dinitrobenzene as an internal standard. [c] With 18 W green LEDs. [d] With 1.5 equiv. (0.225 mmol) of additive. [e] With 2 equiv. of CBr<sub>4</sub>. [f] Yield into brackets refers to chromatographically pure product. [g] Without blue LEDs. [h] With 5 equiv. of additive. [i] Reaction performed following a two-step one-pot procedure. See ESI for more details. EY = Eosin Y. RB = Rose Bengal. Rh = Rhodamine. PC = photocatalyst.

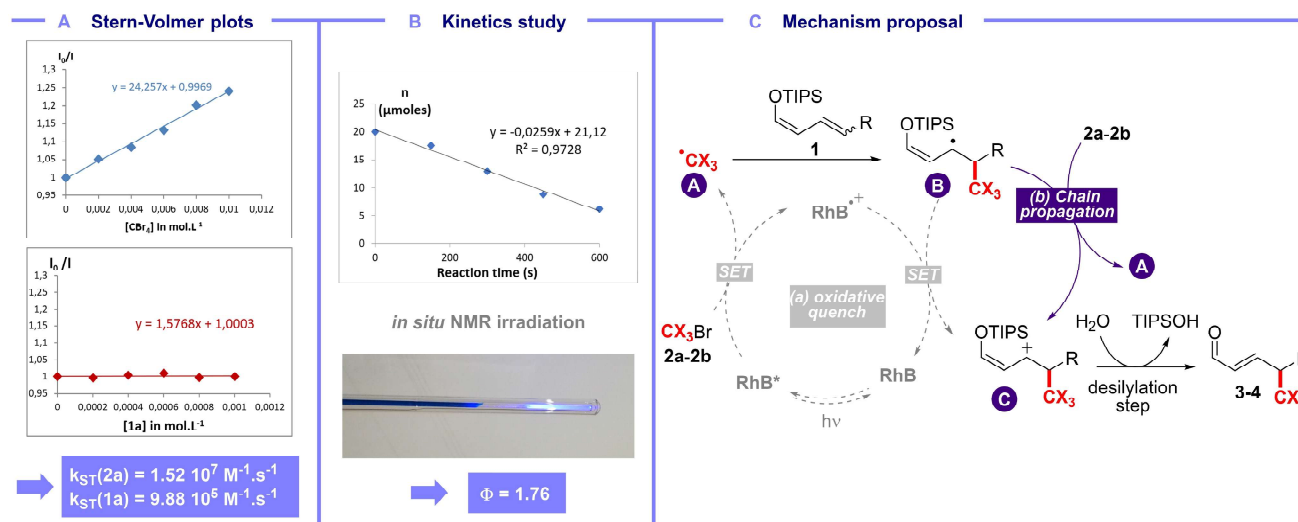


**Scheme 2.** Scope of the  $\gamma$ -trihalomethylation and  $\gamma$ -dihalomethylidation reaction. [a] Conditions A for  $\gamma$ -CX<sub>3</sub> products: **1** (0.15 mmol), **2a** (0.30 mmol) or **2b** (0.30 mmol), Rh B (0.003 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.225 mmol) in 1.5 mL of MeCN irradiated with 18 W blue LEDs at RT for 1 h. Conditions B for  $\gamma$ -CX<sub>2</sub> products: **1** (0.15 mmol), **2a** (0.30 mmol) or **2b** (0.30 mmol), Rh B (0.003 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.225 mmol) in 1.5 mL of MeCN irradiated with 18 W blue LEDs at RT for 1 h, then Et<sub>3</sub>N (5 equiv., 0.75 mmol) was added and the reaction was stirred at RT for 18 h in the dark. Unless otherwise noted, given yields refer to chromatography pure products. [b] Yield in brackets corresponds to <sup>1</sup>H NMR yield using nitrobenzene as internal standard. [c] Performed on a 1 mmol scale of **1a**. [d] Overall isolated yield of the corresponding  $\alpha,\beta,\gamma,\delta$ -unsaturated ester **3'** after Wittig reaction with ethyl (triphenylphosphoranylidene)acetate. See ESI for more details. [e] dr > 95:5. dr = diastereomeric ratio.

vs. SCE in DMF,  $E_{1/2}(\mathbf{2a}) = -0.31$  V vs. SCE in DMF,<sup>[13]</sup> and it should therefore be more easily reduced into the corresponding  $\cdot\text{CCl}_3$  radical. Pleasingly, under the same metal-free conditions,  $\alpha$ -unbranched as well as  $\alpha$ -branched  $\gamma$ -CCl<sub>3</sub> enals **4a–4e** could be efficiently prepared. Once again, it is important to point out the high selectivity of the process, both with regard to  $\gamma$ -trichloromethylation and dehydrochlorination into the corresponding  $\gamma$ -dichloromethylidene product, which were not detected during the synthesis of **4a–4e**. Next, with the optimized one-pot procedure for  $\gamma$ -dibromomethylidation (Table 1, entry 14), the scope of this second reaction was evaluated. Pleasingly, a wide range of  $\gamma$ -dibromomethylidated enals **5a–5j** could be produced in up to 48% isolated yield over two steps, with full site selectivity regardless of the presence of a substituent in the  $\alpha$  position. Remarkably, many functionalities (cyano, epoxide, phthalimide, ester, ether) are

well-tolerated under these mild reaction conditions. In addition, the process could be successfully broadened to the synthesis of a variety of  $\gamma$ -dichloromethylidated enals **6a–6g** with the same level of efficiency and selectivity.

As both photocatalyst and light were required for the reaction to proceed (see Table 1, entries 10–11), a mechanism involving a radical pathway was considered. First, the redox potential of **1a** was measured by cyclic voltammetry. Its value ( $E_p(\mathbf{1a}) = +1.51$  V vs. SCE, see ESI for more details) shows that a reductive quenching cycle in which **1a** would be oxidized by the excited state of Rh B ( $E_{\text{RhB}^*/\text{RhB}} = +1.26$  V vs. SCE)<sup>[14]</sup> is unlikely, by contrast with a favored oxidative quenching cycle involving a single electron transfer (SET) reduction of CBr<sub>4</sub> by Rh B\* ( $E_{1/2}(\mathbf{2a}) = -0.31$  V vs. SCE,  $E_{\text{RhB}^*/\text{RhB}} = -1.31$  V vs. SCE, Scheme 4C, path a). To confirm this hypothesis, luminescence quenching experiments were carried out (Scheme 3A). Stern-Volmer plots

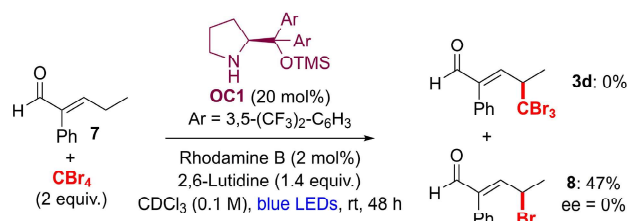


**Scheme 3.** Mechanistic studies. A) Stern-Volmer analysis with  $\text{CBr}_4$  and **1a** as quenchers. B) Kinetics of disappearance of **1a** recorded via *in situ* illuminated NMR spectroscopy. See ESI for more details. C) Proposed mechanism.

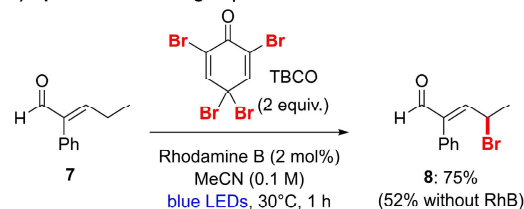
were drawn for both the substrate **1a** and reagent **2a**, and revealed that, indeed, only **2a** was able to efficiently quench the excited state of the photosensitizer  $\text{RhB}^*$  ( $k_{ST}(\mathbf{2a}) = 1.51 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  vs.  $k_{ST}(\mathbf{1a}) = 9.88 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ ). Hence, this first step would lead to  $\cdot\text{CBr}_3$  radical **A**, which would add onto silyl enol ether **1** in a  $\gamma$  regioselective manner, affording radical intermediate **B**. At this stage, **B** may evolve according to two different pathways. The first one involves a photocatalytic mechanism, in which radical **B** would be oxidized by  $\text{RhB}^+$  into the corresponding carbocation **C**, regenerating the ground state photocatalyst  $\text{RhB}$  (path a). The second pathway is based on a radical chain mechanism, during which carbocation **C** is formed via a SET between **B** and **2a-b** (Scheme 3C, path b). Another radical **A** is formed during this process, which ensures the chain propagation. A final desilylation step gives access to the expected products **3-4**.<sup>[15]</sup> In order to distinguish between these two mechanistic hypotheses, the quantum yield  $\phi$  of this photochemical reaction was determined thanks to the use of *in operando*  $^1\text{H}$  NMR spectroscopy, the reaction mixture being directly irradiated inside the NMR tube via an optical fiber (Scheme 3B, see ESI for more details).<sup>[16]</sup> The calculated value  $\phi = 1.76$  indicates that the radical chain mechanism would be more favored, and that a pure photocatalytic mechanism is unlikely.

Given recent achievements to successfully trap electrophilic radicals in an enantioselective manner under dienamine/photoredox dual catalysis,<sup>[8d,17]</sup> we next sought of developing an enantioselective version of this new  $\gamma$ -trihalomethylation protocol. Surprisingly, when using 2-phenyl-2-pentenal **7** as substrate,  $\text{RhB}$  as photocatalyst and Hayashi-Jørgensen organocatalyst **OC1**,  $\gamma$ -bromo enal **8** was obtained as the major product without any trace of the expected  $\gamma$ - $\text{CBr}_3$  enal **3d** (Scheme 4a).<sup>[18]</sup> Further optimization and control experiments (see ESI for more details) revealed that no enantioinduction was observed, and chiral aminocatalyst **OC1** was not required for the reaction to proceed. This result can be rationalized by a

#### a) Attempt of enantioselective $\gamma$ -tribromomethylation



#### b) Optimized Wohl-Ziegler $\gamma$ -bromination



**Scheme 4.** a) Attempt of enantioselective  $\gamma$ -tribromomethylation of enal **7**; b) Wohl-Ziegler bromination of **7**.

Wohl-Ziegler bromination,<sup>[19]</sup> as  $\text{CBr}_4$  is known to generate  $\text{Br}_2$  under photochemical conditions.<sup>[20]</sup> Such allylic bromination is quite fast (complete conversion after 1 h), and most probably leaves insufficient time for the competitive formation of the dienamine. The bromine source could also be modified, TBCO (2,4,4,6-Tetrabromo-2,5-cyclohexadienone) being the optimal reagent (Scheme 4b, 75% yield).

## Conclusions

In conclusion, we have developed a new visible-light mediated remote trihalomethylation reaction. This efficient metal-free methodology allows the synthesis of  $\gamma$ -trihalomethylated enals with perfect  $\alpha$  vs.  $\gamma$  selectivity, regardless of their substitution pattern. Importantly, this mild protocol is compatible with a

wide range of functional groups, and has been successfully adapted to the one-pot synthesis of the corresponding  $\gamma$ -dihalomethylidenated enals. An unexpected photochemical  $\gamma$ -bromination of enal was also efficiently reported under similar metal-free conditions.

## Experimental Section

Details about the characterization methods can be found in the Supporting Information.

### Typical Procedure for the Synthesis of $\gamma$ -CX<sub>3</sub> Enals

A test-tube is charged with silyl dienol ether **1** (0.15 mmol, 1 equiv.), **2a** or **2b** (0.30 mmol, 2 equiv.), Rhodamine B (2 mol%) and K<sub>2</sub>CO<sub>3</sub> (0.225 mmol, 1.5 equiv.). MeCN (1.5 mL) is added and argon is bubbled into the solution during 5 min. The mixture is then irradiated with a blue LED lamp 450 nm, EvoluChem 450 PF, for 1 h. After completion of the reaction, the solvent is removed *in vacuo*, and the <sup>1</sup>H NMR yield is evaluated with 1,3-dinitrobenzene as internal standard. The crude product is purified by flash chromatography to afford the desired pure  $\gamma$ -trihalomethylated product **3–4**.

## Supporting Information Summary

The authors have cited additional reference within the Supporting Information (Ref. [21]).

## Acknowledgements

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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:** Trihalomethylation · Enals · Regioselective · Remote functionalization · Organophotoredox catalysis

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