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Visible Light-Driven, Persulfate-Mediated Hydrocarboxylation of Vinylsulfones

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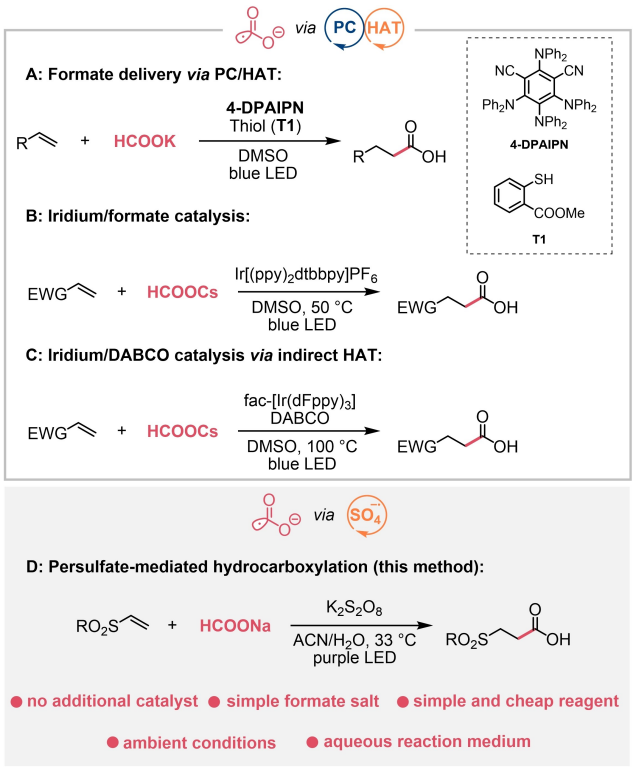
Abstract: We report a visible light-mediated approach for the radical hydrocarboxylation of vinylsulfone derivatives. Using cheap and easily accessible sodium formate as C1-source and $K_2S_2O_8$ as reagent, a set of vinylsulfone substrates could be efficiently hydrocarboxylated in aqueous medium without any additional catalyst or reagent; and the concept could be also applied for direct hydroacylations, hydroalkylations and hydrophosphorylations. The control experiments clearly indicated that the reaction proceeds *via* radical mechanism without the generation of electron donor-acceptor (EDA) complexes; supporting the working model of $K_2S_2O_8$-initiated *in situ* formation of CO_2 radical anion.

Keywords: Hydrocarboxylation; CO_2 radical anion; Potassium persulfate; Visible light; Hydrogen atom transfer

The hydrocarboxylation of alkenes is a fundamental strategy for the synthesis of carboxylic acids. Such reactions are mostly carried out with gaseous CO by means of classical transition metal catalysis and therefore hampered by harsh reaction conditions and by using toxic reagents.[1–3] Formic acid and its salts provide non-toxic and easy-to-handle alternative C1-sources, and was found as an attractive tool for transition metal-catalyzed hydrocarboxylations. While these reactions could indeed circumvent the use of CO, they still required elevated temperature.[4–6]

In the last decade, the field of photochemistry went through tremendous developments, and it became a crucial tool to access novel reaction methodologies.[7] Apart from energy transfer (EnT) or single-electron transfer (SET) processes, the field of hydrogen atom transfer (HAT)[8] has emerged as an intensively investigated area within photochemistry. As such, this methodology enables the use of simple, non-functionalized reagents regardless to its redox potential; and it was successfully applied for various hydrofunctionalization processes by means of C–H activation.[9] As for (hydro)carboxylation purposes; various methods *via* reductive activation of gaseous CO_2 by SET have been recently exploited.[10–15] Furthermore, a few strategies for the activation of formate salts *via* HAT have been also reported. As such, the C–H bond of a formate (BDE = 86 kcal/mol)[16] is activated by means of photoinduced HAT, affording carbon dioxide radical anion ($CO_2^{\bullet-}$). This species is a potent reductant ($E_{1/2}$ = −2.2 V vs. SCE),[17] which makes it among others suitable for radical arylations[18] and defluoroalkylations.[19] Furthermore, $CO_2^{\bullet-}$ can also undergo Giese-type addition to unsaturated bonds, affording hydrocarboxylation products. As such, Wickens and co-workers developed a photocatalytic, thiol-mediated formate delivery (Scheme 1, A);[20] which could be later also applied for unactivated alkene substrates.[21] Meanwhile, Huang *et al.* (Scheme 1, B),[22] as well as Mita and co-workers (Scheme 1, C)[23] developed photocatalytic hydrocarboxylation processes *via* direct or indirect HAT, respectively.



Scheme 1. Different concepts for hydrocarboxylations with formates.

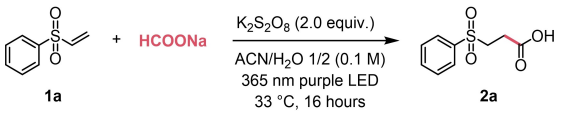
Inexpensive and readily accessible persulfate salts emerged as attractive reagents for a broad range of oxidative transformations.[24] The thermal, photochemical or electrochemical activation of the persulfate provides sulfate radical anions ($SO_4^{\bullet-}$) *in situ*, which can then activate C–H bonds *via* hydrogen atom transfer. Apart from metal-catalyzed and metal-free thermal activation, persulfates were also found to be suitable for various visible light-promoted transformations, providing an efficient alternative for C–H functionalizations under mild reaction conditions.[25] Among others, persulfate salts were successfully applied in visible light-driven Minisci-type alkylations,[26] difluoroarylmethylation,[27] or amidoalkylations.[28]

Encouraged by these, we envisioned to use a persulfate-based strategy for the visible light-driven hydrocarboxylation of vinylsulfones with sodium formate (Scheme 1, D). We hypothesized that either single electron oxidation (E_{ox} (CHO_2^-) = +1.25 V vs. SCE) or hydrogen atom abstraction (BDE = 86 kcal/mol) from a formate by $SO_4^{\bullet-}$ would provide $CO_2^{\bullet-}$ as key intermediate for the hydrocarboxylation. To the best of our knowledge, this is the first procedure which requires neither a (photo)catalyst, nor expensive reagents or harsh reaction conditions for the efficient formate delivery.

Initially, we aimed for the catalyst-free hydrocarboxylation of the (vinylsulfonyl)benzene **1a**. After a short optimization, the vinyl sulfone **1a** could be very efficiently hydrocarboxylated, providing full conversion and 81% isolated yield within 16 hours by means of photochemical activation (Table 1, entry 1). Importantly, both the control experiment in dark and with additional TEMPO resulted only in traces of product formation, indicating the radical nature of the reaction (Table 1, entries 1 vs. 2–3); meanwhile – unsurprisingly – no conversion was observed without potassium persulfate (table 1, entry 4). While some other reactive oxygen species (ROSs) like *t*BuOOH and H_2O_2 also enabled the reaction, the use of potassium persulfate was clearly beneficial (Table 1, entries 1 vs 5–6). The hydrocarboxylation of **1a** could be also successfully promoted by sunlight irradiation, which gave 52% conversion (Table 1, entry 7). When decreasing the $K_2S_2O_8$-loading to 0.2 equivalent, only a moderate conversion of 25% was observed; proving the necessity of an over-stoichiometric reagent loading (Table 1, entry 8). An excess of sodium formate of 5.0 equivalent was beneficial in order to sufficiently suppress polymerization of the vinylsulfone substrate **1a**.

With these encouraging results in hand, we aimed for exploring the scope and limitation of our concept (Scheme 2). The functionalization of the arene moiety was well tolerated, as the hydrocarboxylation of aromatic vinylsulfones with different steric and electronic properties afforded the corresponding products (**2a–j**) in good to excellent yields. Difunctionalized

Table 1. Parameter optimization for the hydrocarboxylation of **1a**.

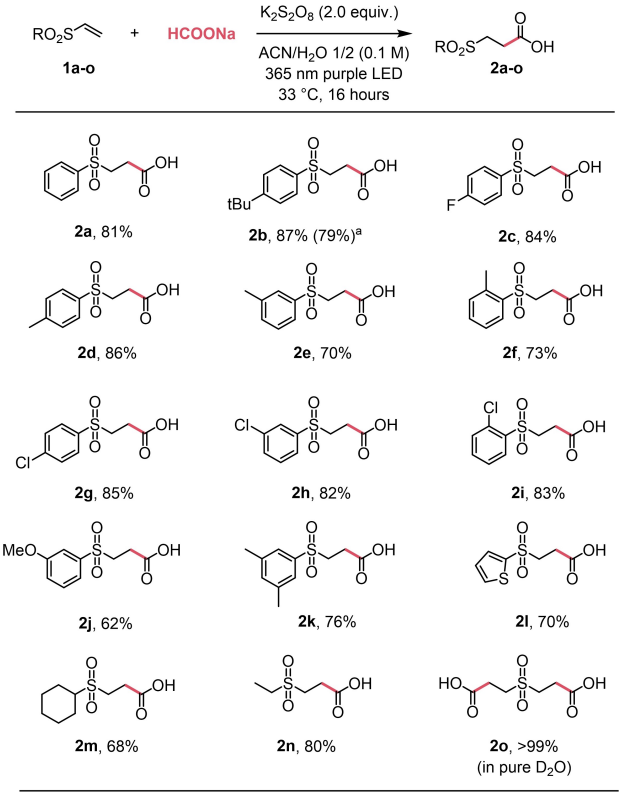


1a 2a

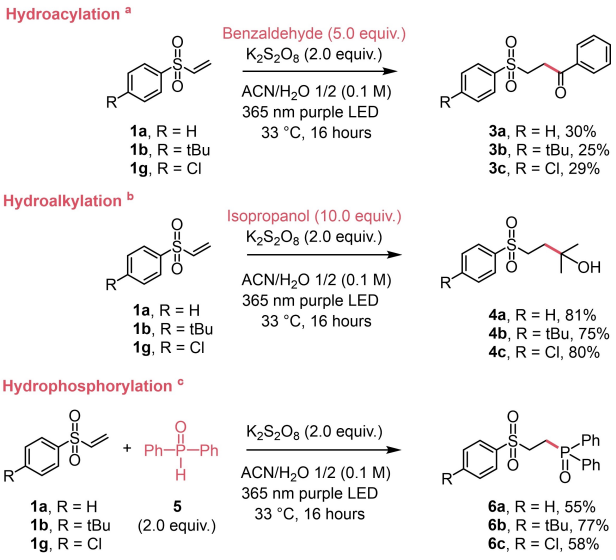
Entry	Variation form standard condition	Conversion[b]
1[a]	**None**	**>99 (81)**
2	In dark at 33 °C	5
3	5.0 equiv. TEMPO as additive	9
4	Without $K_2S_2O_8$	n.r.
5	*t*BuOOH instead of $K_2S_2O_8$	55
6	H_2O_2 instead of $K_2S_2O_8$	21
7	Sunlight irradiation	52
8	With 0.2 equiv. $K_2S_2O_8$	25

[a] Performed with 0.20 mmol (vinylsulfone)benzene (**1a**), 1.0 mmol (5.0 equiv.) $NaHCO_2$ and 0.4 mmol (2.0 equiv.) $K_2S_2O_8$ in 2.0 mL acetonitrile/water mixture (V/V 1/2, 2.0 mL, 0.1 M) under purple light irradiation (λ_{max} = 365 nm) at 33 °C for 16 hours.

[b] Determined by crude NMR analysis after extractive work-up. Isolated yield in parenthesis.



Scheme 2. Hydrocarboxylation of vinylsulfone derivatives. Reactions were performed on a 0.20 mmol scale using **1a–o** (0.2 mmol, 1.0 equiv.), $NaHCO_2$ (68.0 mg, 1.0 mmol, 5.0 equiv.) and $K_2S_2O_8$ (108 mg, 0.4 mmol, 2.0 equiv.) in 2.0 mL acetonitrile/water mixture (V/V 1/2, 2.0 mL, 0.1 M) under purple light irradiation (λ_{max} = 365 nm) at 33 °C for 16 hours. Yields refer to pure products after extractive work-up and (when applicable), further purifications by crystallization. [a] Reaction was performed on a 2.0 mmol scale.

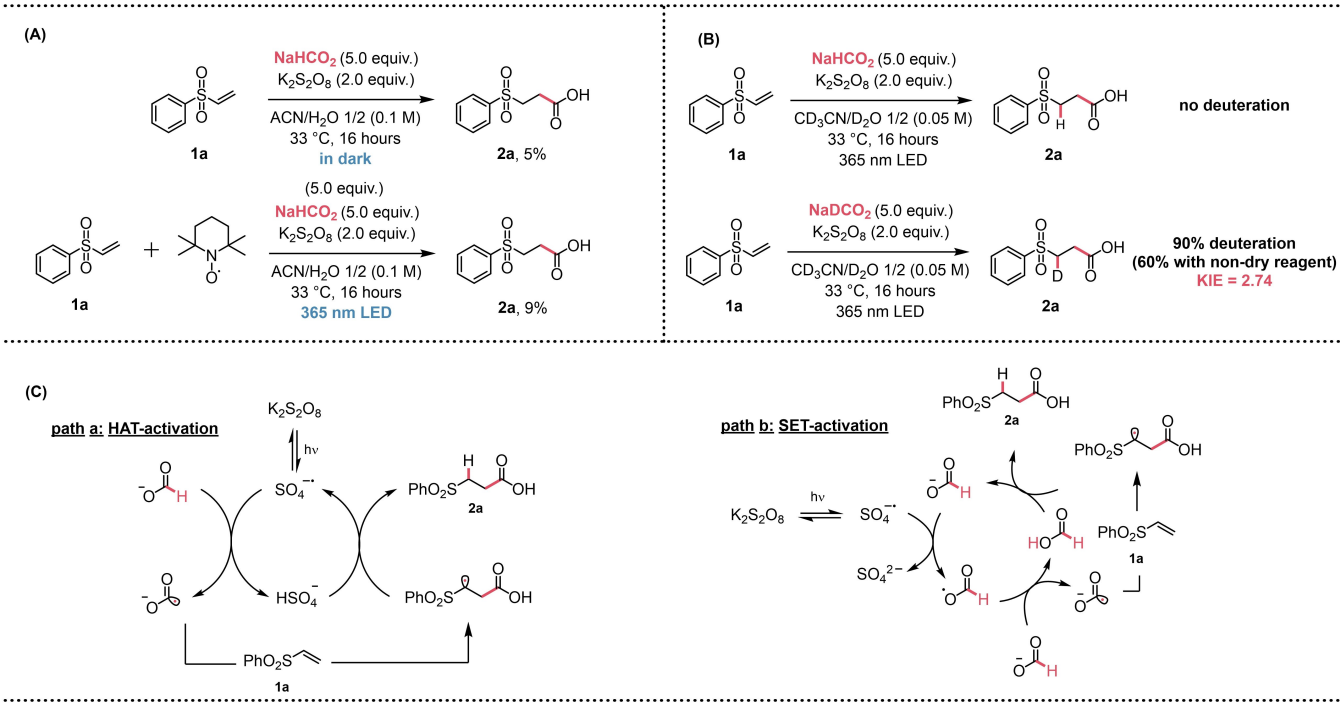


Scheme 3. Hydrofunctionalizations of vinylsulfone derivatives. Reactions were performed on a 0.20 mmol scale using **1a–b** or **1g** (0.2 mmol, 1.0 equiv.) with $K_2S_2O_8$ (108 mg, 0.4 mmol, 2.0 equiv.) in 2.0 mL acetonitrile/water mixture (V/V 1/2, 2.0 mL, 0.1 M) under purple light irradiation (λ_{max} = 365 nm) at 33 °C for 16 hours. Yields refer to pure products after extractive work-up and (when applicable), further purifications by column chromatography or preparative TLC. [a] Performed with 5.0 equiv. benzaldehyde [b] Performed with 10.0 equiv. isopropanol. [c] Performed with 2.0 equiv. diphenyl phosphine oxide (**5**).

arenes (product **2k**) and heteroarenes (product **2l**) were also well tolerated. Nevertheless, the hydrocarboxylation of **1k** gave a minor side-product formation, most likely due to the generation of benzylic radicals by HAT, which resulted in benzylic carboxylation. Interestingly, such side-product formation was however, efficiently suppressed for the hydrocarboxylation of vinylsulfones **1d–f**. Apart from arene substitution, linear and bis(vinylsulfones) could be also applied, affording the carboxylic acids **2m–o** in high yields.

Eventually, the concept of persulfate-mediated direct HAT could be extended towards further catalyst-free functionalizations. For this purpose, benzaldehyde, isopropanol and diphenyl phosphine oxide (**5**) were chosen as representative reagents, together with three different vinylsulfone derivatives to investigate hydroacylation, hydroalkylation, and hydrophosphorylation reactions, respectively (Scheme 3). The hydroacylation products **3a–c** could be isolated in modest yields; meanwhile, moderate to good yields were obtained for the products **4a–c** and **6a–c**.

In order to get more mechanistic insight, control experiments and analytical studies were carried out for the hydrocarboxylation of **1a**. On performing the reaction in dark, only traces of product formation could be observed; meanwhile, the addition of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as radical scavenger also readily inhibited the reaction (Scheme 4, A). The light on-off experiment confirmed that a continuous light irradiation is necessary, as essentially no product formation was observed in the dark periods (see ESI page S20). Furthermore, a quantum yield of $\Phi = 0.26$ could be determined by ferrioxalate actinometry (see ESI page S24–S26). Nevertheless, this does not exclude a chain mechanism, as different non-productive processes like quenching with triplet oxygen, inefficient initiation or side reactions might negatively influence the quantum yield value.[29] UV-VIS measurements (see ESI, page S21) revealed no significant difference between the absorption spectra of **1a** and those of the reaction mixture, which indicates no EDA complex formation; thus, the direct photoexcitation of the persulfate salt remains as only viable activation mode. In order to obtain further mechanistic insight, deuterium labelling



Scheme 4. Mechanistic studies for the hydrocarboxylation of **1a**. (A) Control experiments in the dark and with TEMPO. (B): Deuterium labelling experiment. (C): The two plausible reaction mechanism by means of direct photoexcitation of the persulfate salt.

studies were also performed (Scheme 4, B). When performing the reaction in the mixture of CD_3CN/D_2O, no deuteration occurred, indicating that the solvents do not serve as hydrogen source. In contrast, 90% deuteration was observed when performing the same reaction in CD_3CN/D_2O with $NaDCO_2$ as reagent (Scheme 4, B), clearly suggesting that formate is the ultimate source of H-atom. Furthermore, a KIE of 2.74 was obtained; indicating, that the formation of $CO_2^{\bullet-}$ is the rate determining step.

Considering all experimental information, two plausible chain mechanisms have been proposed, depending on whether the formate is activated by means of a HAT or a SET process (Scheme 4, C). In both cases, the reaction is initiated by homolysis of the $K_2S_2O_8$ and sulfate radical anion is generated. In turn, this can undergo a HAT with the formate, therefore generating CO_2 anion radical with the concomitant formation of HSO_4^-. Subsequent Giese-type addition of $CO_2^{\bullet-}$ to **1a** and protonation could provide the product **2a** (Scheme 4, C, path a). Alternatively, the sulfate radical anion might oxidize the formate salt to $HCOO^{\bullet}$ radical. This could react with another molecule of formate, providing $CO_2^{\bullet-}$ and formic acid. Again, subsequent Giese-type addition of $CO_2^{\bullet-}$ to **1a** and protonation could provide the hydrocarboxylation product **2a** (Scheme 4, C, path b) For both pathways, the formate-related intermediates could eventually be further oxidized to carbon dioxide. This would explain, why over-stoichiometric amount of $NaHCO_2$ and $K_2S_2O_8$ were required; furthermore, it could indeed negatively impact the quantum yield value, resulting in a value well below 1.

In summary, we have developed a protocol for the visible light-induced hydrocarboxylation of vinylsulfone derivatives with sodium formate. Using cheap and easily accessible potassium persulfate as reagent, a range of carboxylic acids could be synthesized in aqueous medium under mild reaction conditions, and the concept could be also extended toward other type of hydrofunctionalizations. The mechanistic investigations indicated that a radical mechanism is operative without the formation of EDA complexes, strongly suggesting that the reaction proceeds *via* direct photoexcitation of the potassium persulfate.

Experimental Section

Representative Procedure for the Synthesis of Vinylsulfones

Into a suspension of Cs_2CO_3 (11.7 g, 36.0 mmol, 3.0 equiv.) and 1,2-dibromoethane (3.12 mL, 36.0 mmol, 3.0 equiv.) in MeCN (0.33 M), the solution of the thiophenol derivative (12.0 mmol, 1.0 equiv.) in 10 mL MeCN was added dropwise at 0 °C. The resulting mixture was then allowed to warm up to room temperature and it was stirred for 16 hours. Then, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude intermediate was then dissolved in CH_2Cl_2 (0.33 M)

and mCPBA (8.26 g, 48.0 mmol, 4.0 equiv.) was added at 0 °C. The mixture was stirred at 0 °C for 30 minutes, after then it was allowed to warm up to room temperature and it was stirred for 16 hours. Then, the resulting suspension was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (2 × 30 mL) and with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. This was then dissolved in CH_2Cl_2 (0.33 M) and treated with Et_3N (5.0 mL, 36.0 mmol, 3.0 equiv.). After 30 minutes stirring at room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography (*silica gel, dry loading on silica gel, permanganate stain, eluents stated in the SI*), affording the desired products **1 b**–**m**.

General Procedure for the Hydrocarboxylation of Vinylsulfones

An 8 mL Schlenk tube or an 8 mL screw-cap vial (VWR) was charged with the substrate (*if solid*, 0.2 mmol, 1.0 equiv.), $NaHCO_2$ (68.0 mg, 1.0 mmol, 5.0 equiv.) and $K_2S_2O_8$ (108 mg, 0.4 mmol, 2.0 equiv.), followed by the addition of the pre-mixed acetonitrile/water (2.0 mL, 0.1 M, V/V 1/2) and the substrate (*if liquid*). The tube/vial was placed into a custom-made photoreactor (equipped with 365 nm purple LED strip) or in front of a 370 nm Kessil lamp (lowest light intensity, 25%) and it was irradiated at 33 °C for 16 hours. Subsequent extractive work-up (*conditions stated in the SI*) and – when applicable – further purification by crystallization afforded the corresponding products.

General Procedure for the Hydrofunctionalization of Vinylsulfones

An 8 mL Schlenk tube or an 8 mL screw-cap vial (VWR) was charged with the substrate **1 a**–**b** or **1 g** (0.2 mmol, 1.0 equiv.), reagent (0.40–2.0 mmol, 2.0–10.0 equiv., *if solid*, *conditions stated for the exact entries in the SI*) and $K_2S_2O_8$ (108 mg, 0.4 mmol, 2.0 equiv.). The tube was then evacuated and back-filled with argon three times, followed by the addition of the pre-mixed acetonitrile/water (2.0 mL, V/V 1/2, 0.1 M, purged with argon for 2 minutes prior use) and the reagent (*if liquid*). The tube/vial was placed into a custom-made photoreactor (equipped with 365 nm purple LED strip) or in front of 370 nm Kessil lamp (lowest light intensity, 25%) and it was irradiated at 33 °C for 16 hours. After the reaction, the mixture was diluted with water (2 mL) and brine (2 mL), and the aqueous phase was extracted with ethyl acetate (2 × 4 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Optionally, purification by column chromatography or by preparative TLC afforded the pure products.

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Conflict of Interest

The authors declare no conflicts of interest.

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