

## Access to CHF<sub>2</sub>-Substituted Heterocycles via Flow Photochemistry using low-cost 3D Printed Reactors

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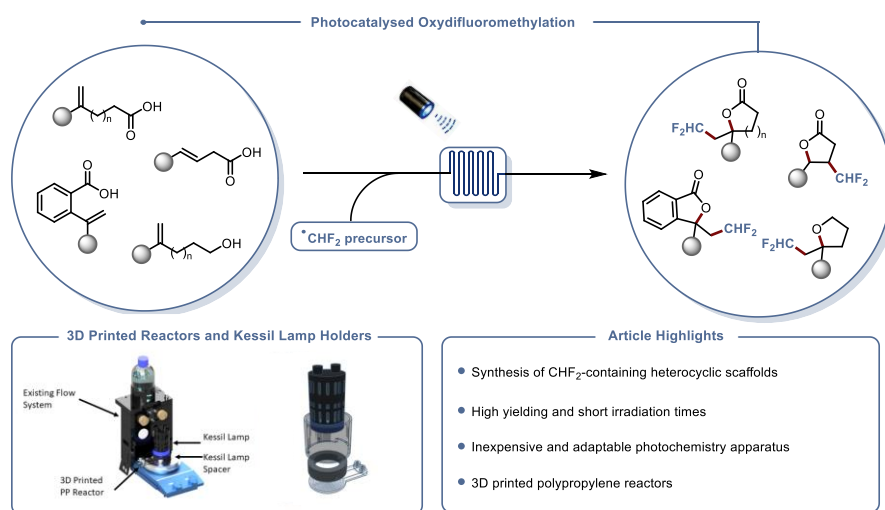
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The incorporation of fluorine atoms in active ingredients has been shown to often improve their metabolic stability, enhance their lipophilicity, and increase their membrane permeability and bioavailability.<sup>1</sup> This observation has thus triggered a broad body of work focused on the development of new synthetic methods allowing a straightforward access to fluorinated compounds, in particular difluoromethyl-containing compounds,<sup>2</sup> which are now prevalent in many pharmaceuticals and agrochemicals.<sup>3</sup>

Following the recent advances made in the field of visible light-mediated photoredox catalysis for the formation of CHF<sub>2</sub> radicals,<sup>4</sup> we decided to investigate further this area with the aim to provide a more sustainable alternative to the traditional radical-triggered reactions.



Despite all the progress made over the years, the development of flow photocatalytic processes to achieve CHF<sub>2</sub> incorporation in high yields and short reaction times remains limited.<sup>5</sup> In collaboration with the Hilton group at UCL, we've adapted a 3D printed standardized flow-photochemistry setup with pressure-driven flow, previously used for photoinduced bromination reactions,<sup>6</sup> to develop a selective oxydifluoromethylation reaction. The 3D printed polypropylene reactor combined with a Kessil LED lamp offers a practical, cost effective and rapid access to synthetically useful CHF<sub>2</sub>-containing heterocyclic scaffolds.

[1] Meanwell, N. A. *J. Med. Chem.* **2018**, 61, 5822. [2] Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. *J. Med. Chem.* **2017**, 60, 797. [3] Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881. [4] T. Koike, M. Akita, *Org. Biomol. Chem.*, **2019**, 17, 5413. [5] S. Barata-Vallejo, Al Postigo in *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications* (Eds. D. Cahard, J.-A. Ma) **2020** Wiley-VCH (Chapter 2). [6] M. Penny, S. Hilton, *ChemRxiv* **2020** (DOI: 10.33774/chemrxiv-2021-kmxgd).