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Visible light-mediated difluoromethylation/cyclization in batch and flow: scalable synthesis of CHF₂-containing benzimidazo- and indolo[2,1-*a*]isoquinolin-6(5*H*)-ones†

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We report here a practical and cost-effective method for the synthesis of CHF₂-containing benzimidazo- and indolo[2,1-*a*]isoquinolin-6(5*H*)-ones through a visible light-mediated difluoromethylation/cyclization cascade. The method, which affords functionalized multifused N-heterocyclic scaffolds in moderate to high yields under mild reaction conditions, is also easily scalable using low-cost 3D printed photoflow reactors.

In recent years, visible light-induced synthetic transformations have played a pivotal role in the synthesis and functionalization of a variety of fused polycyclic biologically relevant nitrogen-containing heterocycles.^{1,2} Benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones represent one such privileged structure featured in an array of biologically active molecules, pharmaceuticals and functional materials.³ As a result, several photoinduced approaches have been developed to access these types of compounds in a straightforward and efficient way.⁴ Furthermore, it is also well established that the introduction of fluorine-containing groups on a bioactive molecule can alter its properties by potentially modulating its lipophilicity and/or its pharmacokinetics.⁵ Accordingly, the incorporation of fluorinated functional groups on the benzimidazoiso-quinolin-6(5*H*)-one scaffold has gained momentum in the last few years. Lv, Yu and co-workers, for example, adopted a visible light-mediated electron-donor-acceptor (EDA) complex-driven radical cascade approach for the synthesis of perfluoroalkyl-substituted benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones (Fig. 1A).⁶ He, Guan and co-workers, on the other hand, developed an iridium-catalyzed radical cascade enabling

the synthesis of CF₂CO₂Et- and CF₃-containing benzo[4,5]imidazo[2,1-*a*]isoquinolinones in good to excellent yields under mild reaction conditions (Fig. 1B).⁷ More recently, Pan and co-workers reported an iridium-catalyzed trifluoromethylation/cyclization sequence using trifluoroacetic anhydride as the trifluoromethyl radical precursor, albeit the method was only applied to one substrate (Fig. 1C).⁸ Surprisingly, despite significant strides in fluorination⁹ and trifluoromethylation chemistry,¹⁰ the incorporation of a CHF₂ group has only recently started to see an increase in activity.¹¹ This is particularly unexpected given that the CHF₂ group can act as a lipophilic substitute for hydroxyl, thiol, amine, and hydroxamic acid functional groups due to its capacity to act as a weak hydrogen bond donor. Nonetheless, there is, to the best of our knowledge, no report of a radical cascade annulation combining a *N*-acryloyl-2-arylbzimidazole derivative with a CHF₂ radical precursor leading

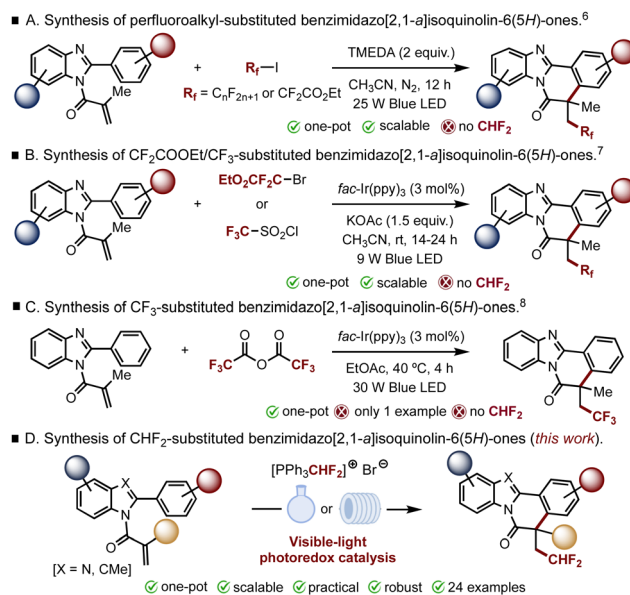


Fig. 1 Representative syntheses of fluoroalkylated benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives.

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to the formation of CHF₂-containing benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones. Considering the significant bioactivity of these compounds and our experience in the fields of visible light mediated radical cascades¹² and difluoromethylation chemistry,¹³ we became interested in exploring this idea (Fig. 1D). Indeed, our proposed domino strategy would not only offer an attractive option for a sustainable synthesis of this new family of CHF₂-containing heterocyclic scaffolds, it would also offer the opportunity to delve into unexplored chemical space. We report here the results of our endeavor.

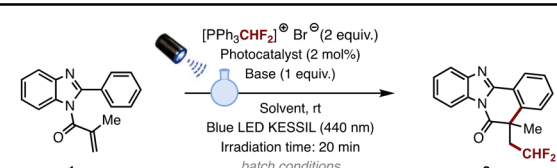
We initiated our study by conducting a first set of reactions in batch using **1a** as a model substrate and difluoromethyl triphenylphosphonium bromide as the CHF₂ radical precursor. The latter, first introduced by Burton,¹⁴ was found to be readily available and easy to handle compared to all the other difluoromethylation reagents. We evaluated four different photocatalysts as well as several reaction conditions as shown in Table 1. As a general trend, the best result was obtained when running the reaction in a 1:1 mixture of MeCN and DCM at rt under light irradiation (440 nm Kessil lamp) using 2 equiv. of PPh₃CHF₂Br, 1 equiv. of 2,6-lutidine and 2 mol% of *fac*-Ir(ppy)₃ (68%, Table 1, entry 4). In sharp contrast, the use of Ru(bpy)₃, 4CzIPN and Eosin Y under otherwise identical conditions did not provide the desired product (Table 1, entries 5–7). This disparity can be attributed to the large difference in the excited-state reduction potentials between [Ru(bpy)₃Cl₂] (−0.81 V vs. SCE), 4-CzIPN (−1.04 V vs. SCE), Eosin Y (−1.15 V vs. SCE) and *fac*[Ir(ppy)₃] (−1.73 V vs. SCE),¹⁵ the latter being the only one capable of generating the CHF₂ radical from PPh₃CHF₂Br (−1.2 V vs. SCE) *via* single-electron-transfer (SET). The use of other solvents, such as

MeCN, THF or DMSO (Table 1, entries 1–3), or other bases, such as DIPEA, NEt₃, K₂CO₃ or DABCO (Table 1, entries 8–11), led to the desired product, albeit in lower yields. Replacing PPh₃CHF₂Br by Akita's (difluoromethyl)bis(2,5-dimethylphenyl)sulfonium salt¹⁶ failed to provide the product (result not shown). Unsurprisingly, running the reaction in the absence of photocatalyst or light proved unproductive. Finally, as decreasing the amount of CHF₂ radical precursor from 2 equiv. to 1.2 equiv. did not drastically impact the yield (64%, Table 1, entry 4), we maintained this stoichiometry for the rest of the study. Also, while the use of the MeCN and DCM seems counterintuitive, it proved to work well when running our oxy-difluoromethylation reactions under continuous flow using 3D printed PhotoFlow reactors,^{13a} which we also wish to implement here.

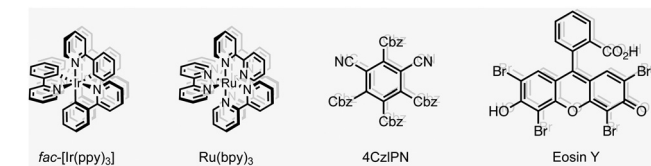
After identifying the best reaction conditions, we proceeded to examine the substrate scope by evaluating a broad range of *N*-substituted 2-aryl benzimidazoles (Fig. 2). As a general trend, the reaction appeared to be tolerant to substrates bearing both electron-withdrawing and electron-donating groups on the phenyl ring. Hence, the *para*-methyl (**1b**) and *para*-isopropyl (**1c**) derivatives were converted to the corresponding CHF₂-containing benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones **2b** and **2c** in 61% and 69% yield, respectively. Unsurprisingly, the *meta*-methoxy derivative **1d** provided two regioisomers (**2d** and **2d'**) in a 1:1 ratio and 44% combined yield. Likewise, the tri-methoxy derivative **1e** afforded the difluoromethylation/cyclization cascade product **2e** in 47% isolated yield. Interestingly, the 1-naphthyl and 2-naphthyl derivatives **1f** and **1g** were converted in 66% and 46% yield respectively. As mentioned previously, substrates bearing an electron-withdrawing group on the phenyl ring were also readily converted. Hence, the *para*-fluoro (**2h**, 49%), *para*-chloro (**2i**, 43%), *para*-bromo (**2j**, 53%), *para*-trifluoromethyl (**2k**, 41%), *ortho*-fluoro (**2l**, 43%), and *ortho*-bromo (**2m**, 23%) derivatives were all obtained, albeit in slightly lower yields. The method was also successfully applied to 2-phenyl benzimidazoles bearing various substituents on the benzimidazole ring. Again, both electron-donating and electron-withdrawing substituents were well tolerated as showcased by the moderate to good yields ranging from 36% to 72% obtained with all the substrates tested. Comparatively, substrates bearing an electron-donating group, such as the 4-methyl (**2n**, 61%) and the 5,6-dimethyl (**2o**, 72%) derivatives, were obtained in higher yields than the ones bearing an electron-withdrawing group such as the 5-bromo (**2p**, 37%), the 5,6-dichloro (**2q**, 38%) and the 5-phenylmethanone (**2r**, 36%) derivatives. We also explored the scope of the reaction with regards to the substituent on the *N*-acryloyl moiety. Interestingly, replacing the methyl group by a benzyl group did not hamper the reaction as the corresponding product **2s** was obtained in 52% yield.

Following these results, we decided to extend the method to another family of multifused *N*-heterocyclic scaffolds, namely the indolo[2,1-*a*]isoquinolin-6(5*H*)-ones, which are widely found in pharmaceuticals, natural products and functional materials.¹⁷ Pleasingly, the method could also be used to access these interesting compounds as showcased by the conversion of the 2-phenyl derivative **3a** to the corresponding CHF₂-containing indolo[2,1-*a*]isoquinolin-6(5*H*)-one **4a** in 78% yield. Once again, the method tolerated both electron-donating (**3b** and **3c**) and electron-withdrawing (**3d** and **3e**) substituents around the phenyl and the indole rings.

Table 1 Systematic study under batch conditions



Entry	Photocatalyst	Solvent	Base	Yield ^a (%)
1	<i>fac</i> -[Ir(ppy) ₃]	MeCN	2,6-Lutidine	54
2	<i>fac</i> -[Ir(ppy) ₃]	THF	2,6-Lutidine	34
3	<i>fac</i> -[Ir(ppy) ₃]	DMSO	2,6-Lutidine	63
4	<i>fac</i> -[Ir(ppy) ₃]	MeCN/DCM (1:1)	2,6-Lutidine	68 (64 ^b) (— ^c)
5	Ru(bpy) ₃	MeCN/DCM (1:1)	2,6-Lutidine	—
6	4CzIPN	MeCN/DCM (1:1)	2,6-Lutidine	—
7	Eosin Y	MeCN/DCM (1:1)	2,6-Lutidine	—
8	<i>fac</i> -[Ir(ppy) ₃]	MeCN/DCM (1:1)	DIPEA	35
9	<i>fac</i> -[Ir(ppy) ₃]	MeCN/DCM (1:1)	NEt ₃	39
10	<i>fac</i> -[Ir(ppy) ₃]	MeCN/DCM (1:1)	K ₂ CO ₃	51
11	<i>fac</i> -[Ir(ppy) ₃]	MeCN/DCM (1:1)	DABCO	67



^a Determined by ¹⁹F NMR using trifluorotoluene as an internal standard. ^b Reaction run with 1.2 equiv. of PPh₃CHF₂⁺Br[−]. ^c Reaction run either in the dark or without photocatalyst.



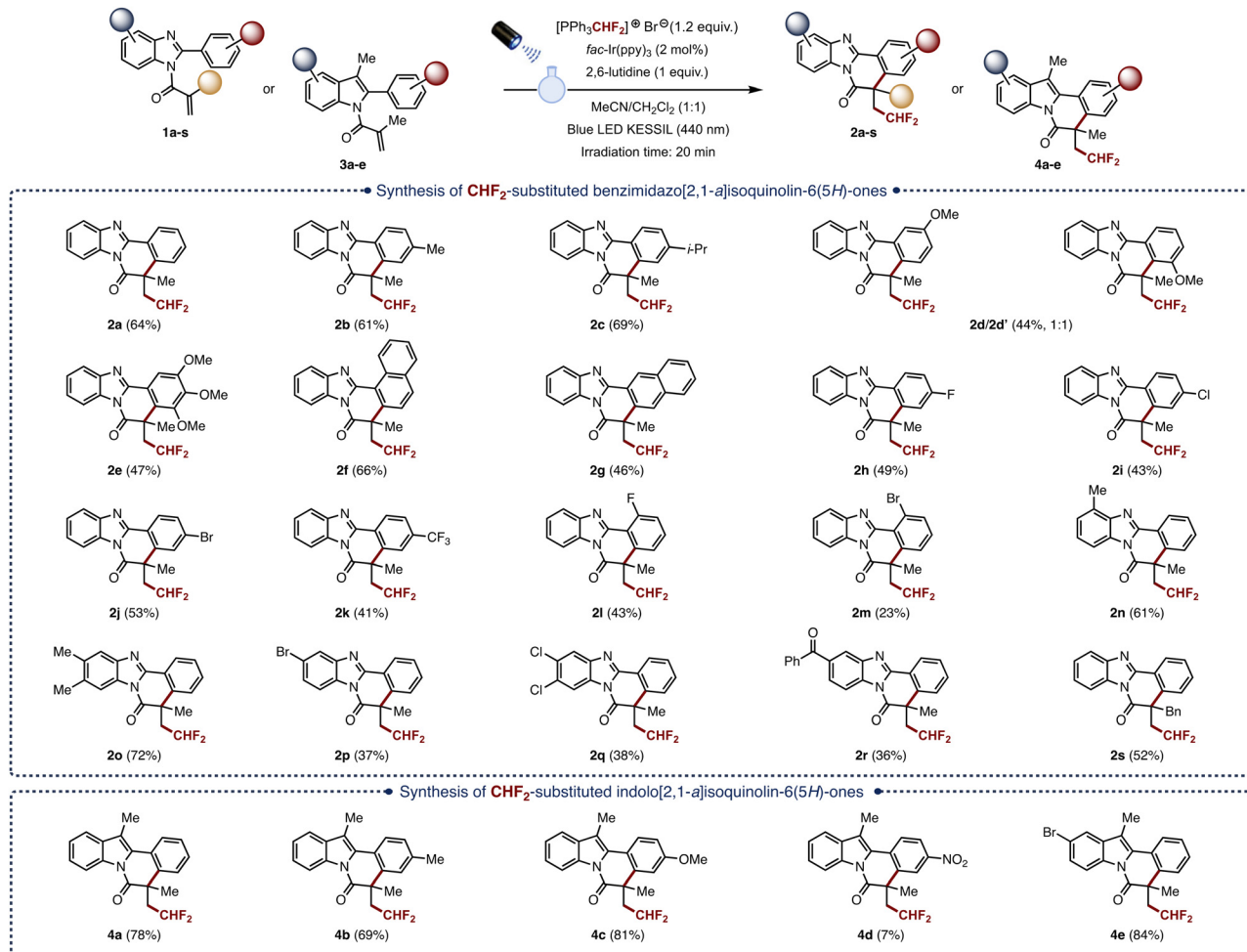


Fig. 2 Substrate scope. All reactions were run on a 0.2 mmol scale.

To confirm the mechanism, we conducted a fluorescence quenching and a radical trapping experiment using TEMPO (Fig. 3A). The latter resulted in the formation of 36% of the CHF₂-containing benzimidazo[2,1-a]isoquinolin-6(5H)-one **2a** along with 34% of the TEMPO-CHF₂ adduct, which strongly supports a one-electron reduction of PPh₃CHF₂Br and subsequent decomposition releasing the CHF₂ radical. The “ON-OFF” experiment (Fig. 3B) and quantum yield calculation ($\Phi = 0.615$) clearly show that the reaction doesn't proceed through a radical chain mechanism (see ESI† for more details). With these results in hand, we propose the following mechanism where the excited *Ir(ppy)₃ undergoes SET to the triphenyl phosphonium bromide, which leads to the release of a CHF₂ radical (Fig. 3C). This radical subsequently adds onto the acryloyl moiety to form a radical intermediate, which then undergoes intramolecular cyclization, oxidation and deprotonation to form the desired product and thus complete the photocatalytic cycle.

Finally, to demonstrate the scalability of the method, a 1 and a 5 mmol scale difluoromethylation/cyclization cascade were carried out on **1a** under continuous flow conditions using our

standardized 3D printed PhotoFlow reactors, which offer guarantees in terms of reproducibility (Fig. 3D).^{18,19} The reaction proved easy to set up and the product was isolated in 57% and 58% yield, respectively. Similarly, the scale-up of the indole derivative **3a** afforded the corresponding indolo[2,1-a]isoquinolin-6(5H)-one **4a** in 75% and 77% isolated yield.

In summary, we have developed a scalable, operationally trivial and highly straightforward access to CHF₂-containing benzimidazo[2,1-a]isoquinolin-6(5H)-ones through a visible light-mediated difluoromethylation/cyclization cascade. The method can also be used to synthesize CHF₂-containing indolo[2,1-a]isoquinolin-6(5H)-ones starting from the corresponding 2-aryl indole precursors. Interestingly, the use of standardized, low-cost, 3D printed PhotoFlow reactors facilitates reproducibility and scalability through a better control of the reaction parameters.

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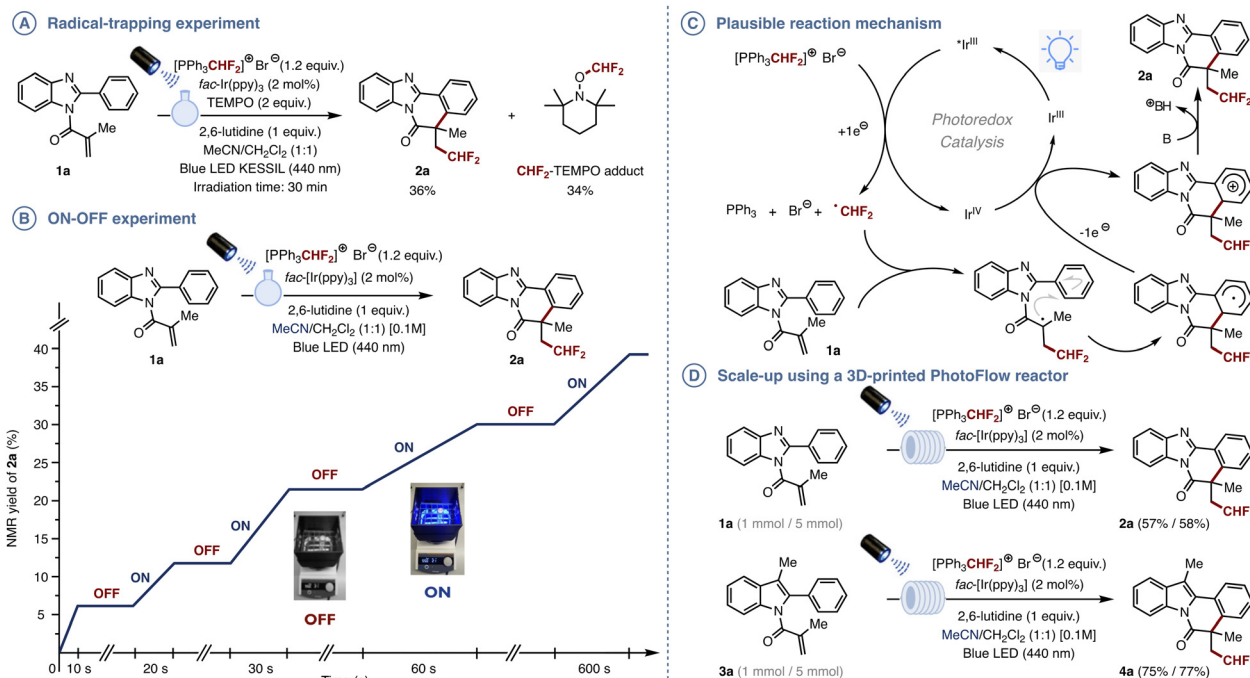


Fig. 3 (A) Radical-trapping experiment. (B) ON–OFF experiment. (C) Plausible reaction mechanism. (D) Scale-up using a 3D-printed PhotoFlow reactor.

Data availability

The data supporting this article have been included as part of the ESL†

Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

- (a) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (b) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113.
- (a) J. T. M. Correia, M. S. Santos, E. F. Pissinati, G. P. da Silva and M. W. Paixão, *Chem. Rec.*, 2021, **21**, 2666–2687; (b) S. Kumar Hota, D. Jinan, S. Prakash Panda, R. Pan, B. Sahoo and S. Murarka, *Asian J. Org. Chem.*, 2021, **10**, 1848–1860; (c) A. A. Festa, L. G. Voskressensky and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2019, **48**, 4401–4423; (d) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Acc. Chem. Res.*, 2016, **49**, 1911–1923; (e) L. Zhou, M. Lokman Hossain and T. Xiao, *Chem. Rec.*, 2016, **16**, 319–334; (f) B. Zhang and A. Studer, *Chem. Soc. Rev.*, 2015, **44**, 3505–3521.
- (a) M. J. Taublaender, F. Glöcklhofer, M. Marchetti-Deschmann and M. M. Unterlass, *Angew. Chem., Int. Ed.*, 2018, **57**, 12270–12274; (b) G. Yadav and S. Ganguly, *Eur. J. Med. Chem.*, 2015, **97**, 419–443.
- (a) F.-L. Zeng, K.-C. Xie, Y.-T. Liu, H. Wang, P.-C. Yin, L.-B. Qu, X.-L. Chen and B. Yu, *Green Chem.*, 2022, **24**, 1732–1737; (b) H.-L. Zhu, F.-L. Zeng, X.-L. Chen, K. Sun, H.-C. Li, X.-Y. Yuan, L.-B. Qu and B. Yu, *Org. Lett.*, 2021, **23**, 2976–2980.
- (a) S. Caron, *Org. Proc. Res. Dev.*, 2020, **24**, 470–480; (b) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880; (c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (d) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- F.-L. Zeng, K. Sun, X.-L. Chen, X.-Y. Yuan, S.-Q. He, Y. Liu, Y.-Y. Peng, L.-B. Qu, Q.-Y. Lv and B. Yu, *Adv. Synth. Catal.*, 2019, **361**, 5176–5181.
- L. Liu, D.-Y. Yang, Y.-H. He and Z. Guan, *J. Org. Chem.*, 2020, **85**, 11892–11901.
- Y. Song, B. Zheng, S. Yang, Y. Li, Q. Liu and L. Pan, *Org. Lett.*, 2023, **25**, 2372–2376.
- (a) P. A. Champagne, J. Desroches, J. D. Hamel, M. Vandamme and J. F. Paquin, *Chem. Rev.*, 2015, **115**, 9073–9174; (b) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264; (c) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477.
- (a) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682; (b) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598–6608.
- (a) J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. Am Ende, A. A. Trabanco and V. Gouverneur, *Chem. Soc. Rev.*, 2021, **50**, 8214–8247; (b) Y. Zafrani, S. Saphier and E. Gershonov, *Future Med. Chem.*, 2020, **12**, 361–365; (c) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797–804.
- (a) P. Meher, R. K. Samanta, S. Manna and S. Murarka, *Chem. Commun.*, 2023, **59**, 6092–6095; (b) S. K. Hota, S. P. Panda, S. Das, S. K. Mahapatra, L. Roy, S. De Sarkar and S. Murarka, *J. Org. Chem.*, 2023, **88**, 2543–2549; (c) S. Das, A. Azim, S. K. Hota, S. P. Panda, S. Murarka and S. De Sarkar, *Chem. Commun.*, 2021, **57**, 13130–13133; (d) S. Das, S. K. Parida, T. Mandal, S. K. Hota, L. Roy, S. De Sarkar and S. Murarka, *Org. Chem. Front.*, 2021, **8**, 2256–2262; (e) S. Das, S. K. Parida, T. Mandal, L. Sing, S. De Sarkar and S. Murarka, *Chem. – Asian J.*, 2020, **15**, 568–572.
- (a) J. Zhang, E. Selmi-Higashi, S. Zhang, A. Jean, S. T. Hilton, X. C. Cambeiro and S. Arseniyadis, *Org. Lett.*, 2024, **26**, 2877–2882; (b) E. Selmi-Higashi, J. Zhang, X. C. Cambeiro and S. Arseniyadis, *Org. Lett.*, 2021, **23**, 4239–4243; (c) N. Duchemin, R. Buccafusca, M. Daumas, V. Ferey and S. Arseniyadis, *Org. Lett.*, 2019, **21**, 8205–8210.
- D. J. Burton, *J. Fluorine Chem.*, 1983, **23**, 339–357.
- N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166.
- N. Noto, T. Koike and M. Akita, *Chem. Sci.*, 2017, **8**, 6375–6379.
- For selected papers, see: (a) J.-R. Zhang, H.-Y. Liu, T. Fan, Y.-Y. Chen and Y.-L. Xu, *Adv. Synth. Catal.*, 2021, **363**, 497–504; (b) K. Alam, S. W. Hong, K. H. Oh and J. K. Park, *Angew. Chem., Int. Ed.*, 2017, **56**, 13387–13391.
- (a) M. R. Penny and S. T. J. Hilton, *Flow. Chem.*, 2023, **13**, 435–442; (b) M. R. Penny, Z. X. Rao, B. F. Peniche and S. T. Hilton, *Eur. J. Org. Chem.*, 2019, 3783–3787.
- To obtain the 3D printed CAD designs along with the printing temperatures for polypropylene, see: (a) M. B. Montaner, M. R. Penny and S. T. Hilton, *Digital Discovery*, 2023, **2**, 1797–1805; (b) https://github.com/vernalis/3Dprint_files.

