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Visible-Light-Mediated Iodoperfluoroalkylation of Alkenes in Flow and Its Application to the Synthesis of a Key Fulvestrant Intermediate

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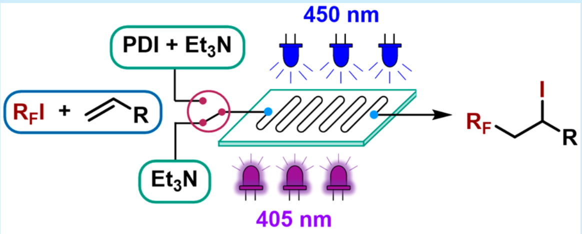
Supporting Information

ABSTRACT: Two efficient continuous flow iodoperfluoroalkylation methods are described: using 0.05 mol % perylene diimide (PDI) photocatalyst under 450 nm irradiation or substoichiometric triethylamine under 405 nm irradiation. These methods enable dramatically elevated productivity versus batch processes. The triethylamine-mediated method is explored mechanistically and in substrate scope. The gram-scale synthesis of an active pharmaceutical ingredient side chain is also reported in flow, via a photochemical iodoperfluoroalkylation followed by hydrogenolysis.



✓ Choice of methods at different wavelengths
✓ Productivity up to 7.6 g h^{-1}
✓ Gram-scale application to drug side chain

Fluorination reactions have received significant interest in recent years as a means to prepare high-value organic compounds.[1] As a consequence of modified physicochemical features, fluorinated molecules are broadly employed in medicinal chemistry, agrochemistry, and materials science.[2] Iodoperfluoroalkylation of olefins is a classical strategy for accessing this class of compounds.[3] Since the first examples in the 1950s,[4] atom-transfer radical addition (ATRA) methodologies have been studied using both thermal and photochemical activation. In general, thermal activation requires harsh reaction conditions[5] and/or potentially explosive radical initiators.[6]

With the recent resurgence of synthetic organic photochemistry, a multitude of mild iodoperfluoroalkylation protocols have been developed.[3] In most cases these have employed the following: expensive Ru/Ir/Cu metal complexes;[7] organic dyes, often in relatively high loading;[8] a significant excess of the perfluoroalkyl iodide reagent; or several additives, under UV or visible light irradiation.[9] A further advance within this field involves metal-free photocatalytic systems capable of working under visible light irradiation in low loadings. Recently, we reported an efficient method for the iodoperfluoroalkylation of alkenes, driven by the photochemical activity of a simple perylene diimide sensitizer (**PDI**, Scheme 1), in extremely low loading (0.05 mol % = 500 ppm), under blue light irradiation.[10]

In order to transform the resulting perfluorinated compounds **3** into suitable derivatives for the aforementioned applications, a preparative scale process is necessary. Photochemical transformations often have limited scale-up potential, because they can be hampered by significant light attenuation, as the size of a reaction vessel increases (as described by the Beer−Lambert law).[11] Continuous flow photochemistry can alleviate this limitation by using a short irradiated path length, which, when combined with the correct light source, can improve photochemical efficiency, leading to shorter reaction times and higher productivity.[12] Many examples of other photochemical fluorination processes have been demonstrated in flow,[13] offering efficient and selective reactivity, when compared to their batch equivalents.

Despite the industrial importance of the corresponding products, a limited number of alkene perfluoroalkylations have been performed in flow,[14] and to the best of our knowledge, none of these methods make use of UV or visible light irradiation. Herein we report and exemplify two complemen-

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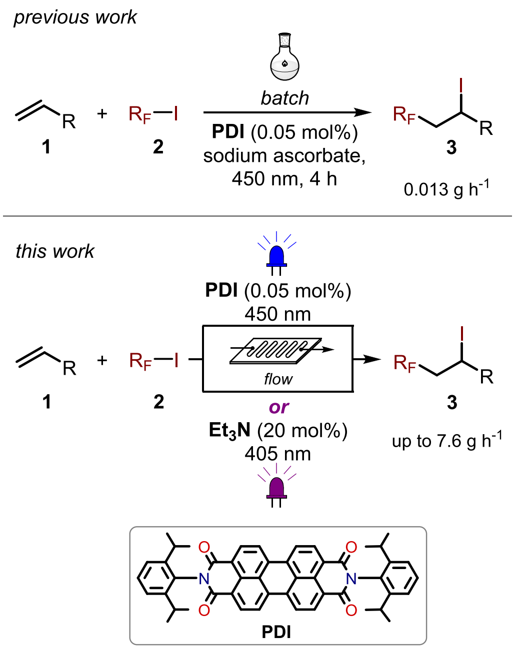
Scheme 1. Iodoperfluoroalkylation of Alkenes in Batch and Flow



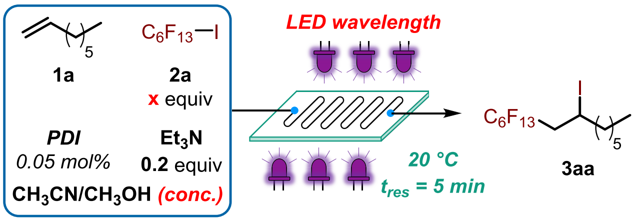
tary continuous flow iodoperfluoroalkylation protocols: using **PDI** as a photocatalyst under blue light irradiation (450 nm) or through the use of inexpensive triethylamine additive under shorter wavelength blue light irradiation (405 nm, Scheme 1).

Initial studies focused on the translation of our previously reported process[10] from batch to flow, using a commercially available plate-based photoreactor (Corning Advanced-Flow Lab Photo Reactor, 2.8 mL volume).[15] The previous system, which used sodium ascorbate as a substoichiometric electron donor, was unsuitable for flow processing, due to its heterogeneity. Accordingly, it was decided to employ triethylamine (Et_3N) as an alternative organic-soluble reductant. Preliminary optimization (Table 1) was performed on the iodoperfluoroalkylation of 1-octene (**1a**) by perfluorohexyl iodide (**2a**, 2 equiv) in the presence of **PDI** (0.05 mol %) as the photocatalyst and Et_3N (0.2 equiv).[16]

Under blue light irradiation (450 nm) the ATRA product **3aa** was observed in 95% yield, in a residence time of only 5 min (entry 1). A series of control experiments confirmed that no reaction occurs in the absence of **PDI** (entry 2) nor when using 610 nm (red) light (entry 3). However, green light (540 nm) was found to be marginally less effective in promoting the reaction, resulting in an 88% yield of **3aa** (entry 4). Reducing the loading of perfluorohexyl iodide (**2a**, 1.2 equiv) lowered the yield of **3aa** to 83% (entry 5), but this was restored to its original level (entry 6) by increasing the concentration to 0.2 M. Under these conditions, a 90% yield of the ATRA product **3aa** was isolated, translating to a high throughput of 6.1 g h^{-1}.

Upon undertaking a more detailed screen of irradiation wavelengths, reactivity was observed even in the absence of **PDI**, when using irradiation wavelengths of 422 nm or shorter.[16] This result can be attributed to the photoactivation of perfluoroalkyl iodide **2a** by Et_3N, through the formation of a halogen-bonded electron donor−acceptor (EDA) complex.[9a,c,17] Such complexes absorb most strongly in the deep UV region, but can often be exploited at UVA or even some visible wavelengths.

Table 1. Flow Photochemical ATRA Optimization Studies[a]



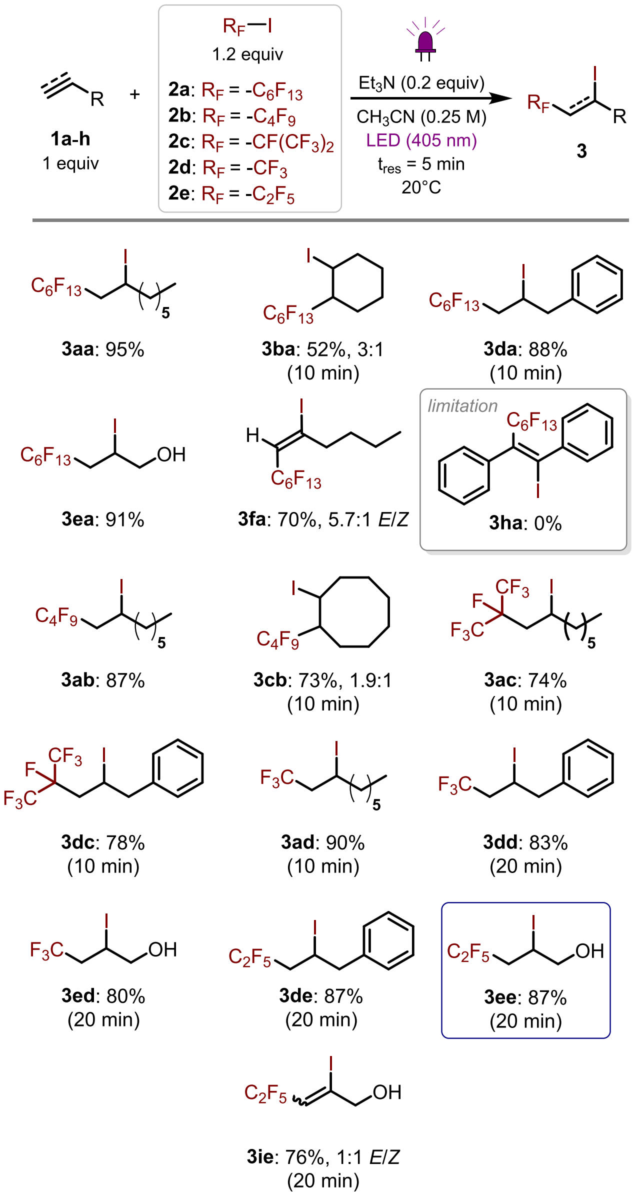
entry	PDI	wavelength (nm)	concn (M)	**2a** (equiv)	yield (%)[b]
1	Y	450	0.1	2	95
2	N	450	0.1	2	0
3	Y	610	0.1	2	0
4	Y	540	0.1	2	88
5	Y	450	0.1	1.2	83
6	**Y**	**450**	**0.2**	**1.2**	**95 (90)**
7	N	422	0.1	2	34
8	N	405	0.1	2	94
9[c]	N	405	0.1	2	0
10	N	405	0.1	1.2	82
11[d]	N	405	0.1	1.2	92
12[d]	**N**	**405**	**0.25**	**1.2**	**98 (95)**

[a] Reaction conditions: 1-octene (**1a**), perfluorohexyl iodide (**2a**, 1.2 or 2 equiv), Et_3N (0.2 equiv) and PDI (0.05 mol %) in CH_3CN/CH_3OH (4:3). Reactions were performed using a 5 mL sample loop and a 5 min residence time (0.56 mL/min). [b] Yield was determined by GC-FID vs *n*-dodecane as internal standard. Isolated yield is shown in parentheses. [c] Reaction was performed in the absence of Et_3N. [d] Reaction was performed using only CH_3CN as solvent.

Encouraged by this scenario, a second iodoperfluoroalkylation protocol was optimized under blue/purple light irradiation, in the absence of any photocatalyst. Primary investigations examined the wavelength-dependence, highlighting a complete lack of reactivity at 450 nm (entry 2), moderate response at 422 nm (34% yield, entry 7), and finally a 94% yield of **3aa** at 405 nm (entry 8). A control experiment ascertained the need for the amine additive, since no ATRA product **3aa** was detected in the absence of Et_3N (entry 9). Reducing the loading of perfluorohexyl iodide **2a** (1.2 equiv) decreased the yield of **3aa** to 82% (entry 10), but was partially restored by changing the solvent to only CH_3CN (92%, entry 11). Finally, almost quantitative GC yield of **3aa** was observed by increasing the reaction concentration to 0.25 M, resulting in a 95% isolated yield (entry 12). Thanks to the increased reaction concentration allowed by this protocol, a further increase in productivity was accessed, versus the PDI-catalyzed method (7.6 g h^{-1} vs 6.1 g h^{-1}). For this reason, and the simplified reaction composition, we opted to further explore this method under visible light (405 nm) irradiation. However, in cases with light-sensitive substrates, the PDI-catalyzed method may prove advantageous, since it allows reaction at less energetic wavelengths, even down to green light (540 nm).

The synthetic potential of the catalyst-free flow procedure was then examined (Scheme 2), demonstrating its generality with respect to both the olefin (**1**) and perfluoroalkyl iodide components (**2**). A standard residence time of 5 min was found to be suitable for most alkene substrates when paired with the highly reactive perfluoroalkyl iodide **2a**. Less reactive alkenes **1b** and **1d** required elongated residence times to reach full conversion, whereby **3ba** was isolated in a moderate 52% yield as a 3:1 mixture of diastereomers. Diphenylacetylene

Scheme 2. Flow Photochemical ATRA Reaction Scope[a]



[a] Reaction conditions: alkene or alkyne (**1**, 1 equiv), perfluoroalkyl iodide (**2a**−**c**: 1.2 equiv, or **2d**−**e**: 4 equiv), and Et$_3$N (0.2 equiv) in CH$_3$CN (0.25 M). Reactions were performed on 1.25 mmol (5 mL) scale in 5 min residence time, unless otherwise specified. *E*/*Z* ratio and *d.r.* determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

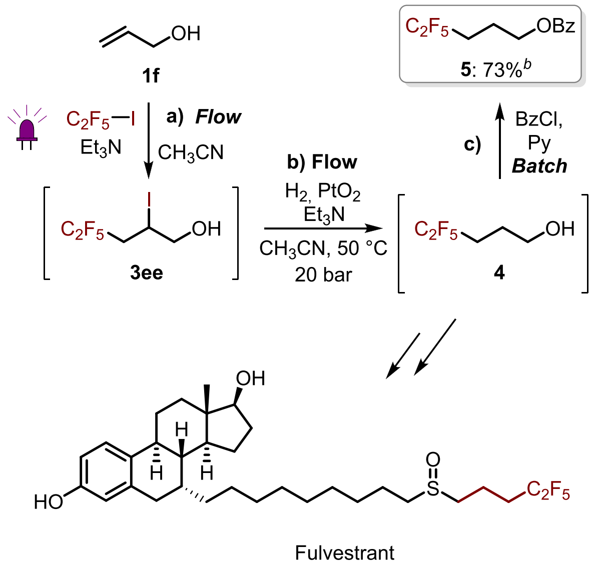
derivative **1h** proved to be completely unreactive, as has been observed previously for styrene-type substrates in ATRA reactions.[7a]

A slightly shorter perfluorinated chain (iodide **2b**) provided products **3ab** and **3cb** in synthetically useful yields. However, the sterically hindered iodide **2c** required longer residence times to achieve good yields in both examined cases (**3ac** and **3dc**). Furthermore, as the perfluoroalkyl chain on iodide substrate **2** was shortened further, longer reaction times were required due to the less polarized (and therefore stronger) C−I bond. Gaseous iodide reagents **2d** and **2e** were used as solutions in CH$_3$CN and a small back pressure of 3 bar was applied to the reactor (using a Zaiput back pressure regulator) to prevent gassing out. These reagents warranted a larger excess (4 equiv), but also afforded their corresponding products with various alkenes (**3ad** to **3ie**) in good to excellent yields.

For further mechanistic insight, we sought to confirm the halogen-bonding activation of this ATRA reaction system. A series of ^{19}F NMR experiments were performed using different ratios of perfluorohexyl iodide (**2a**) and Et$_3$N in CD$_3$CN, whereby a Job plot analysis verified the formation of a 1:1 halogen-bonded complex.[9a,c,17] Previous reports have implied that involvement of solvent (THF) is required,[9a] which may also be the case in our system. In addition, an association constant of 1.57 M^{-1} was determined in CD$_3$CN.[16] This value is consistent with previously reported halogen bond complexes between perfluoroalkyl iodides and Et$_3$N in Lewis basic solvents.[18] Moreover, the kinetic profile of the model reaction revealed an induction period of at least 30 s, likely corresponding to the time taken to cleave enough C−I bonds for effective radical chain conjugation.[16]

Finally, we envisaged that this protocol could be used in the preparation of a perfluorinated side chain, for active pharmaceutical ingredient (API) preparation.[19] In particular, breast cancer drug Fulvestrant[20] contains a perfluorinated side chain, synthesized from intermediate alcohol **4** (Scheme 3), which, in turn, can be reached by hydrogenation/dehalogenation (hydrogenolysis) of product **3ee** or **3ie**. During commercial route development for Fulvestrant, the supply and cost of intermediate **4** were noted as a main concern,[19c] which highlights the need for a scalable synthesis, such as this flow methodology.

Scheme 3. Fulvestrant Side Chain Preparation[a]



[a] Reaction conditions: (a) as specified for **3ee** in Scheme 2; (b) crude mixture from previous transformation, sparged with argon, added Et$_3$N (2 equiv) and diluted to 0.1 M in CH$_3$CN, 50 °C, 20 bar pressure, 1 mL/min flow rate; (c) crude mixture from previous transformation, added benzoyl chloride (5 equiv) and pyridine (8 equiv), stirred at rt for 16 h. [b] Isolated yield (1.23 g) over three steps.

The required dehalogenation reaction was carried out in a continuous manner using an H-Cube Pro reactor equipped with a platinum oxide hydrogenation catalyst cartridge. For this manipulation, the crude mixture from the photochemical reactor was diluted to 0.1 M (to avoid precipitation), sparged with argon (to remove the excess of perfluoroalkyl iodide), and additional Et_3N (2 equiv) was added. Complete conversion of **3ee** into the deiodinated product **4** was observed in less than 1 min residence time (50 °C, 20 bar). The obtained pentafluoropentanol (**4**) is the desired side chain of Fulvestrant,[19c] but due to its volatility, it was decided to functionalize this intermediate further as its benzoyl ester **5** for isolation. To demonstrate the scalability of this protocol, a scale-out was successfully performed, allowing gram-scale isolation of **5** (1.23 g, 73% yield over three steps), with a single chromatographic purification step.

In summary, we report two complementary continuous flow methods for the photochemical iodoperfluoroalkylation of alkenes, with productivity up to 7.6 g h^{-1}. The ATRA reaction can be achieved under irradiation at 405 nm, using substoichiometric loading of an inexpensive amine base. Alternatively, reaction can also be achieved by irradiation at a longer wavelength (450 nm), in the presence of a low loading of PDI dye. In situations with light-sensitive substrates, this method could also prove to be of importance. Mechanistic insights were gained regarding the halogen-bond photoactivation of perfluoroalkyl iodides by Et_3N. Finally, a gram-scale preparation of a fluorinated API intermediate was demonstrated in two flow steps from inexpensive starting materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01992.

> Experimental procedures, and characterization of all products, including ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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