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Visible-Light Photocatalytic Tri- and Difluoroalkylation Cyclizations: Access to a Series of Indole[2,1-*a*]isoquinoline Derivatives in Continuous Flow

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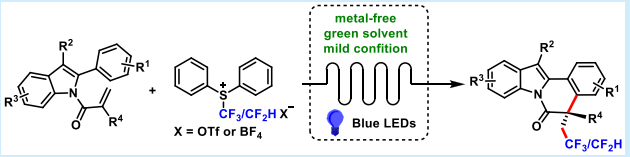
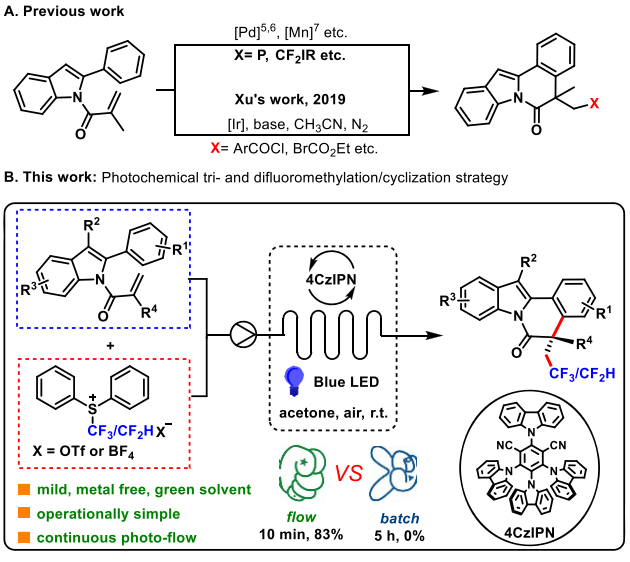
ABSTRACT: A process for achieving photocatalyzed tri- and difluoromethylation/cyclizations for constructing a series of tri- or difluoromethylated indole[2,1-*a*]isoquinoline derivatives is described. This protocol utilized an inexpensive organic photoredox catalyst and provided good yields. Moreover, the combination of continuous flow and photochemistry, designed to provide researchers with a unique green process, was also shown to be key to allowing the reaction to proceed (product yield of 83% in flow vs 0% in batch).



Due to their synthetic utility and various biological activities, nitrogen-containing heterocycles, particularly fused indole derivatives, are of great importance in organic synthesis and pharmaceuticals.[1−3] The compounds have attracted considerable attention from both synthetic and medicinal chemists.[4] In the past few years, much effort has been devoted to constructing the indole[2,1-*a*]isoquinoline core structure, and this effort has predominantly relied on a cyclization strategy chiefly employing transition metal complexes (e.g., Pd,[5,6] Mn[7]) as catalysts (Scheme 1A). However, the utility of these protocols for large-scale synthesis is still rather limited due to relatively high toxicity levels and costs of the transition metal complexes. Thus, it is highly desirable to design green and sustainable synthetic routes to construct indole[2,1-*a*]isoquinoline derivatives. The resurgence of visible-light-mediated photoredox catalysis and electrocatalysis have resulted in an operationally simple strategy for the construction of these compounds.[8−10] Notably, Xu's group have developed a powerful transformation for the synthesis of the indole[2,1-*a*]isoquinoline skeleton via an iridium (Ir)-based catalyzed radical cascade cyclization reaction.[11] Due to the high costs of the common metal catalysts used, i.e., of the Ru and Ir complexes, the relatively inexpensive organic donor−acceptor fluorophore photocatalysts, which also display broad redox capabilities, offer an intriguing alternative.[12−14]

The methods for the incorporation of fluorine atoms into organic molecules have attracted considerable attention because the fluorine-containing compounds widely exist in pharmaceuticals and agrochemicals and materials.[15−18] However, almost all of the classical protocols suffer from harsh conditions and require expensive metal catalysts or toxic solvents.[19] On the other hand, visible-light photoredox catalysis also offers a novel and efficient method to access the construction of fluoro-

Scheme 1. Overview of the Fluoroalkylation/Cyclization/Indole Strategy Employed in This Study



containing heterocycles.[20,21] Recently, practical fluoralkylation has been realized by the action of visible-light catalysis on a variety of fluorinating sources such as Togni, Umemoto, and

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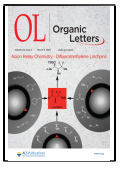

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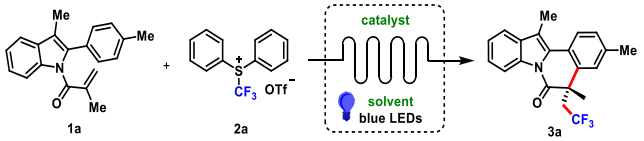
Langlois reagents.[22−26] Well-designed sources of CF_3/CF_2H are still not available, as recent studies have highlighted the problems with the currently available ones.[27,28] Moreover, we previously reported a useful method for carrying out trifluoromethylations/cyclizations of 1,7-enynes by using Ph_2SCF_3OTf as a CF_3 source in continuous flow.[29] In 2017, Akita and co-workers reported a shelf-stable easy-to-handle sulfonium salt, namely, $Ph_2SCF_2HBF_4$ (*S*-difluoromethyl-*S*-di(*p*-xylyl)sulfonium tetrafluoroborate).[30]

The use of light energy impairs the overall sustainability of the photocatalytic reactions as dictated by the Bouguer−Lambert−Beer law. Photochemical processes and continuous-flow chemistry have, when used in combination, led to the development of various reactions.[31−33] In continuous-flow chemistry, continuous reactions are carried out in tubes or a microreactor. The keys to the success of carrying out reactions using continuous flow have been shown to involve achieving an improved mixing ability and more efficient heat transfer as well as the ability to scale up such reactions.[34] Compared to the traditional batch reactions, continuous flow technology offers many advantages. This technology has been used in the screening and optimization of various reactions.[35,36] Jamison and Stephenson et al. have realized their unprecedent works in this area.[37] However, to the best of our knowledge, there has been no report on the construction of indole[2,1-*a*]isoquinoline derivatives in continuous flow under the condition of metal-free photocatalysts and green solvent without any other bases. Inspired by these achievements, we set out to and successfully developed photocatalyzed tri- and difluoromethylation/cyclization process for the construction of a series of tri- or difluoromethylated indole[2,1-*a*]isoquinoline derivatives in good yields under mild conditions via a noble metal-free protocol in continuous flow.

Initially, we commenced our study by employing (*S*)-3,5,12-trimethyl-5-(2,2,2-trifluoroethyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (**1a**) and diphenyl(trifluoromethyl)sulfonium trifluoromethane-sulfonate (**2a**) as the model set of substrates in CH_3CN to test the reaction conditions (Table S1, entry 8). Although the desired product **3a** was observed, the reaction generally proceeded slowly. Thus, we set up a continuous-flow photoreactor (Figure S2) made according to the needs of the reaction to speed up the efficiency of the transformation (Table S1, entry 7). Next, we investigated solvents of the reaction. To find lower toxicity and less costly green solvent, a series of other solvents including THF, DMSO, MeOH, 1,4-dioxane, and DMF were screened, but acetone was indicated from the results to be the best choice for this reaction (Table S1, entries 1−12). The use of EtOH reduced the onset potential of reaction due to its poor ability to dissolve both photocatalyst and reagents (Table 1, entry 3). To our delight, the desired indole[2,1-*a*]isoquinoline (**3a**) product was obtained in 10 min in 83% yield in acetone at room temperature when using the organic photocatalyst (4*s*,6*s*)-2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN)[13] as the photocatalyst, a PFA tube (ID = 600 μm, volume = 1.0 mL), a flow rate of 100 μL/min, and 50 W blue LED irradiation (Table 1, entry 1). In further optimization studies, *fac*-Ir(ppy)$_3$ displayed significantly lower catalytic efficacy (Table 1, entry 7). However, when Ph_2SCF_3OTf was replaced with CF_3SO_2Na as the source of CF_3, the yield of the product **3a** decreased to 28% while extra water was needed to achieve a clear reaction solution (Table 1, entry 4); the poorer yield was attributed to the presence of this extra water. The addition of bases resulted in less reactivity for this reaction (Table 1, entries 6 and 7). From

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	83
2	MeOH as the solvent	17
3	EtOH as the solvent	53
4[c]	CF_3SO_2Na as the CF_3 source	28
5	Et_3N as additive (2.0 equiv)	21
6	pyridine as additive (2.0 equiv)	40
7	*fac*-Ir(ppy)$_3$ as the catalyst	51
8[d]	in batch	0
9	without catalyst	2
10	two injection system	76
11	tube (ID = 800 μm)	75
12	200 μL/min	49

[a]Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), 4CzIPN (1.0 mol %) in 2.0 mL of acetone irradiated with light from 50 W blue LEDs (455 nm) at room temperature inside a 1.0 mL reactor of a flow system (PFA tube, ID = 600 μm, 100 μL/min). See the Supporting Information for more details. [b]The isolated yield of each recrystallized product was calculated based on **1a**. [c]CF_3SO_2Na as the CF_3 source; here another 0.5 mL of H_2O was needed for achieving a dissolution of the reaction mixture. [d]Air, 5 h.

control experiments, both light and the photocatalyst were concluded to be crucial to the success of the reaction (Table S4, entries 1−4). Using a batch condition, however, failed to deliver product **3a** by ^{19}F NMR, even when a longer reaction time was used (Table 1, entry 8). We speculate the continuous flow system was the most efficient as well as mixing ability compared to the batch. However, the mechanism of the phenomenon is not clear. The flow conditions were also examined, and use of a thicker pipe (ID = 800 μm) and faster rate (200 μL/min) provided lower yields (Table 1, entries 11 and 12).

With optimized conditions in hand, we investigated the scopes of indole substrates and CF_3 sources for the photocatalytic di/trifluoromethylation/cyclization reaction. As shown in Scheme 2, a variety of functional groups were observed to be well tolerated, forming products bearing various substituted 2-arylindoles in the flow system. Notably, changing the electronic properties of the substituent (R^1) at the para position of the 2-phenyl moiety of the *N*-substituted 2-aryl indole was found to have little influence on its catalytic efficiency. Electron-neutral substituents (−Me), electron-withdrawing groups (−F, −Cl, −Br), and an electron-donating group (−OMe) were all compatible with this reaction, giving the corresponding products in 52−83% yields (**3a**−**3g**). Subsequently, the electronic nature of the substituent located on the C3 position of the indole ring was investigated; for two cases, products formed efficiently regardless of the electronic nature of the substituent (**3h** and **3i**). Various substituents at the C5 position of the indole ring were also readily tolerated in this system, delivering the corresponding products in good to moderate yields (**3j**−**3n**). Besides these examples, substrates containing different groups at the R^4 position also gave the corresponding products in moderate yields (**3o**−**3q**).

Due to their special chemical and biological properties, difluoromethyl compounds are significant and widely used in the

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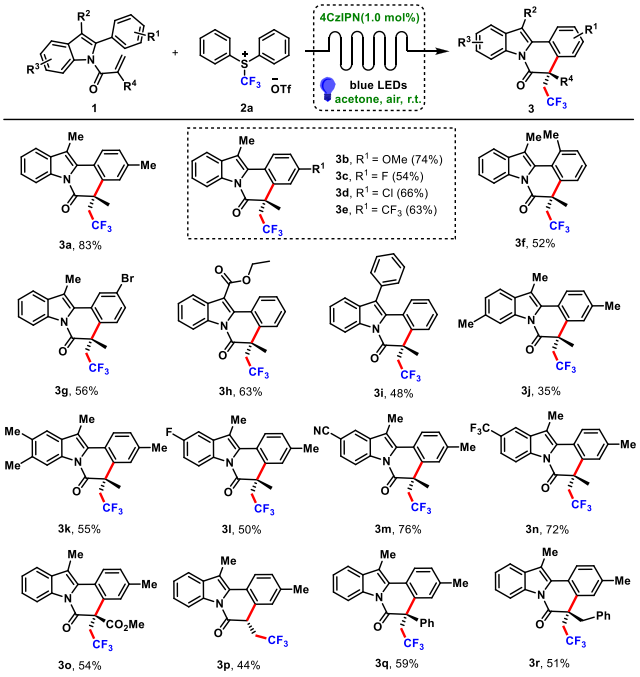
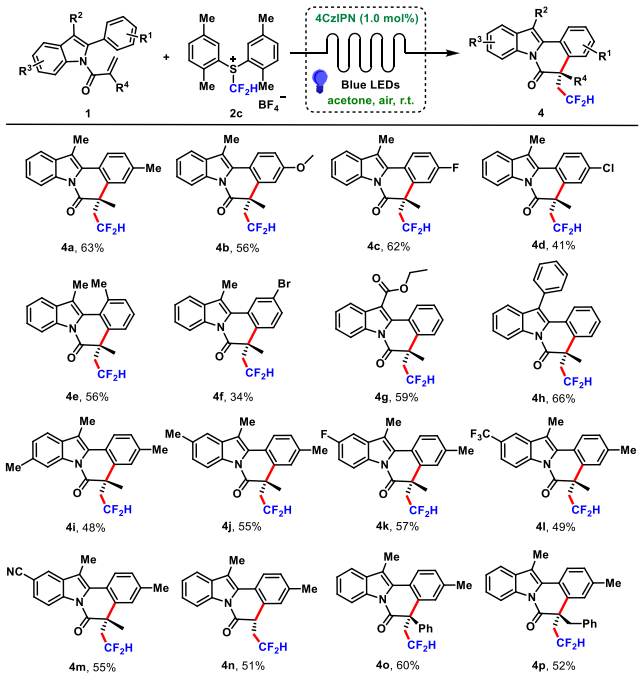
Scheme 2. Overview of the Trifluoromethylation/Cyclization Reaction[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), 4CzIPN (1.0 mol %), and acetone as the solvent (2.0 mL) in a PFA tube (ID = 600 μm, volume = 1.0 mL) at a flow rate of 100 μL/min under 50 W blue LED irradiation at room temperature after 10 min. [b]The isolated yield of each recrystallized product was calculated on the basis of **1**.

Scheme 3. Overview of the Difluoromethylation/Cyclization Reaction[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2c** (0.22 mmol, tests using $Ph_2SCF_2HBF_4$ as a CF_2H source), 4CzIPN (1.0 mol %), 2.0 mL of acetone as the solvent in a PFA tube (ID = 600 μm, volume = 1.0 mL) at a flow rate of 100 μL/min under 50 W blue LED irradiation at room temperature after 10 min. [b]The isolated yield of each recrystallized product was calculated on the basis of **1**.

pharmaceutical and agrochemical industries.[37] Therefore, we attempted to test the Ph_2SCF_2HOTf reagent (**2b**) as a CF_2H source but it decomposed about 2 h later when stored at room temperature or in solvents. We were able to test the *S*-(difluoromethyl)sulfonium reagent as the CF_2H source as it was easily synthesized and stable.[30] We tested the ability to use it to carry out the photocatalyzed difluoromethylation of **1** and give potentially useful CF_2H-substituted isoquinoline products (Scheme 3). The reaction of various forms of **1** bearing different functional groups such as Me, OMe, F, Cl, and Br among others afforded the corresponding CF_2H-substituted isoquinoline compounds (**4a**−**4p**) in 34−66% yields. Imidazole[2,1-*a*]-isoquinoline derivative products **6** are also suitable to this transformation from **5** (for details see the Supporting Information).

After finishing these, we next turned our attention to a mechanistic interrogation to determine the formation of C−C bond activation and CF_3/CF_2H radicals. A series of control reactions were carried out to determine and understand the reaction mechanism of the electrocatalytic fluoromethylation/cyclization reaction (Figure 1). First, the radical-trapping reagent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) serving as a radical scavenger was added to the reaction mixture under standard reaction conditions (Figure 1a). As expected, the reaction was completely quenched, and the corresponding **3a** failed to be detected, which indicated that a radical process occurred in this transformation. Second, Stern−Volmer studies were carried out to understand the process of the oxidative quenching mechanism. The results suggested that the excited-state PC* was quenched by **1a** more efficiently than by **2a**, which indicated a reductive quenching mechanism (Figure 1b−e).

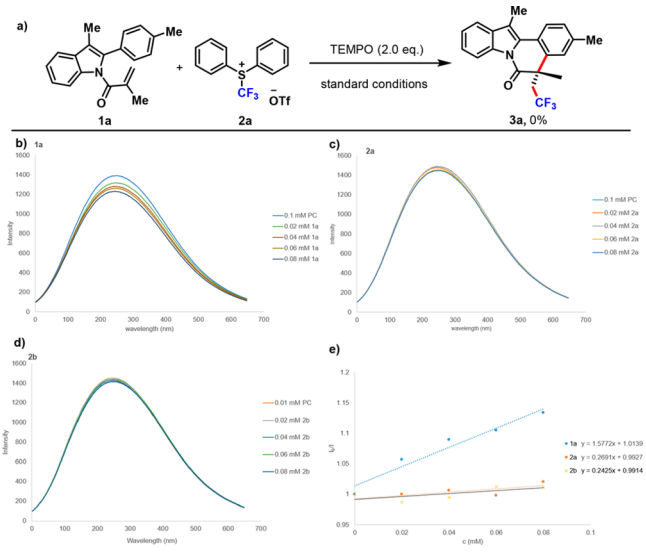


Figure 1. Mechanistic studies. (a) Radical trapping experiment. (b) Fluorescence quenching experiments with 4CzIPN and various concentrations of **1a**. (c) Fluorescence quenching experiments with 4CzIPN and various concentrations of **2a**. (d) Fluorescence quenching experiments with 4CzIPN and various concentrations of **2b**. (e) Stern−Volmer plots of 4CzIPN with different quenchers.

Furthermore, we conducted a scale-up (1.0 mmol) reaction based on **1a** under standard conditions (Scheme 4). To our delight, we could obtain the desired product **3a** with the yield of 80%. The satisfactory result indicated that the application of

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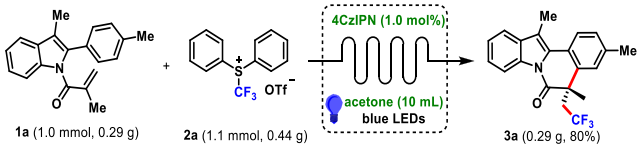
Scheme 4. Scale-Up Experiment[a,b]

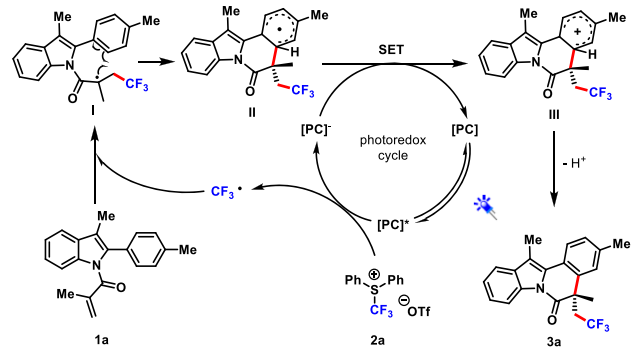


[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), 4CzIPN (1.0 mol %), and acetone as the solvent (10.0 mL) in a PFA tube (ID = 600 μm, volume = 1.0 mL) at a flow rate of 100 μL/min under 50 W blue LED irradiation at room temperature. [b]The isolated yield of recrystallized product was calculated on the basis of **1a**.

continuous-flow technology was also suitable for the scale-up reaction.

On the basis of related literature reports[11,29] and the above-mentioned observations, we proposed a possible mechanism for this photocatalyzed fluoroalkylation/cyclization reaction (Scheme 5). Initially, photocatalyst PC (4CzIPN) excited by

Scheme 5. Possible Mechanism



visible light irradiation (**PC***) reduced Ph_2SCF_3OTf generate a CF_3 radical by way of a single electron transfer (SET) process. Then, the $CF_3^{\bullet}$ radical added to the C=C bond of the indole derivative (**1a**) to give a new carbon radical intermediate **I**, which underwent an intramolecular cyclization to give the radical intermediate **II**. Subsequently, **II** interacted with PC^- to form the cation **III** via a single electron transfer (SET) process. At last, the deprotonation of carbocation III to afford the cyclization product **3a**.

In summary, we have developed a photocatalyzed fluoroalkylation/cyclization reaction under mild conditions in continuous flow. A vast array of tri- or difluoromethylated indole[2,1-*a*]isoquinoline derivatives were obtained in moderate to good yields by using readily accessible Ph_2SCF_3OTf or $Ph_2SCF_2HBF_4$ reagents as the CF_3/CF_2H sources. Detailed mechanistic studies provided strong support for the radical fluoroalkylation/cyclization sequence. It is particularly worthy of note that the robustness of the strategy involving photocatalysis and continuous flow was shown for this reaction to clearly outperform the batch performance (83% vs 0%). Moreover, this radical sequence provides a highly valuable methodology for fluorinated diketone synthesis and could be further extended for use in industrial applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00476.

FAIR data, including the primary NMR FID files, for compounds **3a−3r**, **4a−4p**, and **6a−6e** (ZIP)

Experimental procedures, more optimization of reaction conditions, the equipment of the reaction, X-ray crystallography structure of compound **3e**, characterization data, copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for the products (PDF)

Accession Codes

CCDC 2039357 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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