



## Communication

# Visible-light-initiated tandem synthesis of difluoromethylated oxindoles in 2-MeTHF under additive-, metal catalyst-, external photosensitizer-free and mild conditions

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## ABSTRACT

An efficient and eco-friendly protocol for synthesizing difluoromethylated oxindoles through a visible-light induced one-pot tandem reaction of *N*-arylacrylamides, difluoroacetic acid and  $\text{PhI}(\text{OAc})_2$  was developed. This reaction proceeded in the absence of any additive, base, metal-catalyst and external photosensitizer, using cheap and easily available  $\text{CHF}_2\text{CO}_2\text{H}$  as the difluoromethylation reagent and bulk biomass-derived 2-MeTHF as the sole solvent. 26 Examples of *N*-arylacrylamide substrates were investigated, and all of them successfully underwent difluoromethylation to deliver the target products in good to excellent yields.

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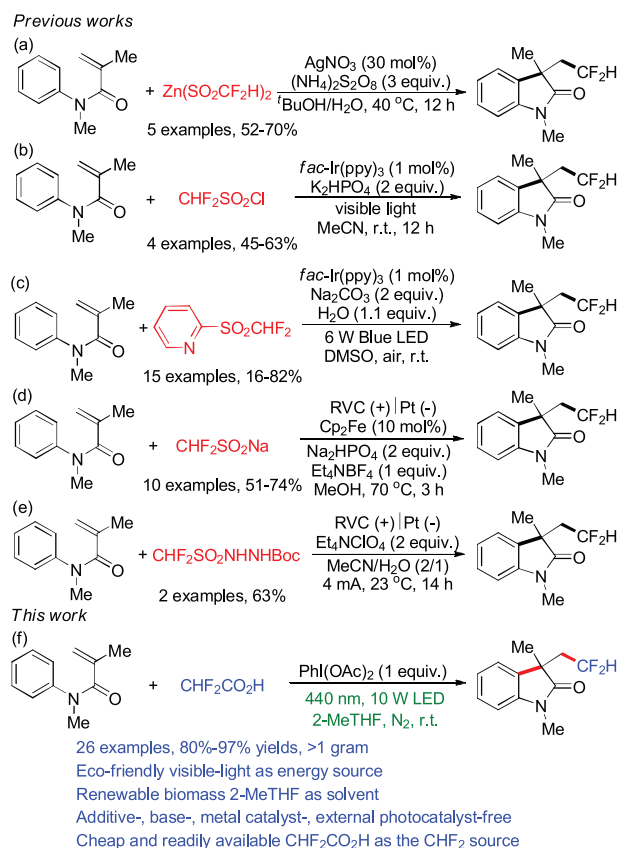
The primary goal of green chemistry is to make full use of renewable materials while minimizing the generation of chemical waste. For this reason, the development of a sustainable synthesis plan is of particular importance [1]. Much effort has been invested in developing green solvents over the decades [2]. Among these eco-friendly solvents, 2-MeTHF has received considerable attention [3], because it can be obtained from biomass feedstocks as a safe and innocuous solvent, and it is in line with the 3<sup>rd</sup>, 5<sup>th</sup> and 7<sup>th</sup> principles of Green Chemistry. Medical and synthetic chemistry require the construction of complex molecules with biological activity and diversity, for which tandem reaction is a powerful synthetic tool, because they can efficiently reduce the overall steps and minimize the generation of chemical waste [4]. On the other hand, visible light catalysis has attracted much attention in chemical and pharmaceutical industries [5]. However, most photocatalytic processes require precious metals and/or toxic transition metals or harmful organic photosensitizers, which not only generate waste, but also increase production costs, leading to cumbersome purification procedures and environmental problems. Therefore, an important goal of green chemistry is to develop

visible light-induced tandem reactions without external photosensitizers [6].

Oxindole motifs exist widely in plenty of natural products, biologically active molecules and synthetic drugs [7]. It is of particular interest to build oxindoles with the difluoromethyl group ( $\text{CHF}_2$ ) [8], because  $\text{CHF}_2$  is a bioisostere of alcohol and thiol groups and may act as a lipophilic hydrogen donor *via* H-bonding. Accordingly, increasing research efforts have been made in the development of efficient methods for constructing difluoromethylated oxindoles [9]. In 2014, Tan and colleagues [10] pioneered the  $\text{AgNO}_3$ -catalyzed difluoromethylation of *N*-arylacrylamides with  $\text{Zn}(\text{CHF}_2\text{SO}_2)_2$  in the presence of  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  as the oxidant under heating conditions (Scheme 1a). Dolbier [11] and Liu [12] have, respectively, developed the visible-light-induced difluoromethylation of *N*-arylacrylamides by using different  $\text{CHF}_2$  sources ( $\text{CHF}_2\text{SO}_2\text{Cl}$  and 2-Py $\text{SO}_2\text{CHF}_2$ ) under alkaline conditions (Schemes 1b and c). The electrochemical difluoroalkylation reactions with  $\text{CHF}_2\text{SO}_2\text{Na}$  and  $\text{CHF}_2\text{SO}_2\text{NHNHBoc}$  under alkaline conditions have been reported by the groups of Xu [13], Ruan and Ackermann [14] (Schemes 1d and e). Despite significant achievements, however, the above-mentioned difluoromethylation reagents not only have limited commercial availability but also are highly costly and harmful. From an eco-friendly point of view, those procedures still suffer from some drawbacks, such as

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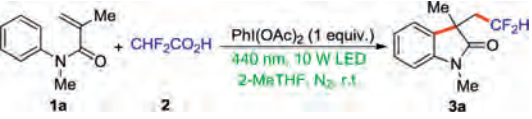
**Scheme 1.** Synthesis of difluoromethylated oxindoles.

employing expensive and/or harmful metal catalyst, excess chemical oxidants and base additives, toxic organic solvents as well as poor to moderate yields. Therefore, the exploration of environmentally friendly synthetic protocols for synthesizing difluoromethylated 2-oxindoles using cheap and readily available difluoromethylation reagents is of great importance and is highly desirable.

Difluoroacetic acid is a low-cost, simple-to-handle and easily available bulk chemical. The direct usage of CHF<sub>2</sub>CO<sub>2</sub>H as the difluoromethylation reagent to provide a CHF<sub>2</sub> motif is a preferable process [8h]. With our interests on developing green organic synthesis [15], we report herein an eco-friendly protocol for the construction of various difluoromethylated oxindoles *via* visible-light initiated (Principle 6<sup>th</sup>) one-pot tandem reaction (Principle 8<sup>th</sup>) of *N*-arylacrylamides, CHF<sub>2</sub>CO<sub>2</sub>H and PhI(OAc)<sub>2</sub> in biomass-derived 2-MeTHF (Principle 5<sup>th</sup>) under additive-, base-, metal catalyst-, external photosensitizer-free (Principle 1<sup>st</sup>) and mild conditions (Scheme 1f).

Initially, *N*-methyl-*N*-phenylmethacrylamide (**1a**), CHF<sub>2</sub>CO<sub>2</sub>H (**2**) and PhI(OAc)<sub>2</sub> were chosen as the template substrates to screen the reaction conditions (Table 1). Employing PhI(OAc)<sub>2</sub> as the promoter, and 2-MeTHF as the solvent, the desired product **3a** generated in 98% NMR yield under the irradiation of a 10 W LED (440 nm) at ambient temperature (Table 1, entry 1). We found that the irradiation wavelength of visible-light was of significant importance for the present transformation (entries 2–6), and the irradiation wavelength of 440 nm was the most suitable. Performing the reaction under solar irradiation led to the generation of polycyclic products **3a** in 32% yield (entry 7). Replacing 2-MeTHF with THF, MeCN, toluene, acetone, EtOAc or DCM provided a lower yield (entries 8–13). Performing the reaction under air atmosphere instead of nitrogen atmosphere led to a lower yield of **3a** (entry 14).

**Table 1**  
Optimization of reaction conditions.<sup>a</sup>



Entry	Variation from the standard conditions	Yield (%) <sup>b</sup>
1	None	98
2	405 nm instead 440 nm	84
3	430 nm instead 440 nm	89
4	435 nm instead 440 nm	92
5	445 nm instead 440 nm	88
6	460 nm instead 440 nm	82
7	Solar irradiation	32
8	THF instead of 2-MeTHF	54
9	MeCN instead of 2-MeTHF	80
10	Toluene instead of 2-MeTHF	65
11	Acetone instead of 2-MeTHF	56
12	EtOAc instead of 2-MeTHF	49
13	DCM instead of 2-MeTHF	22
14	Air instead of N <sub>2</sub>	76
15	Without PhI(OAc) <sub>2</sub>	N.R.
16	In dark	N.R.

<sup>a</sup> Conditions: **1a** (0.2 mmol), CHF<sub>2</sub>CO<sub>2</sub>H (0.4 mmol), PhI(OAc)<sub>2</sub> (0.2 mmol), solvent (1 mL), N<sub>2</sub>, 10 W LED, r.t., 4 h.

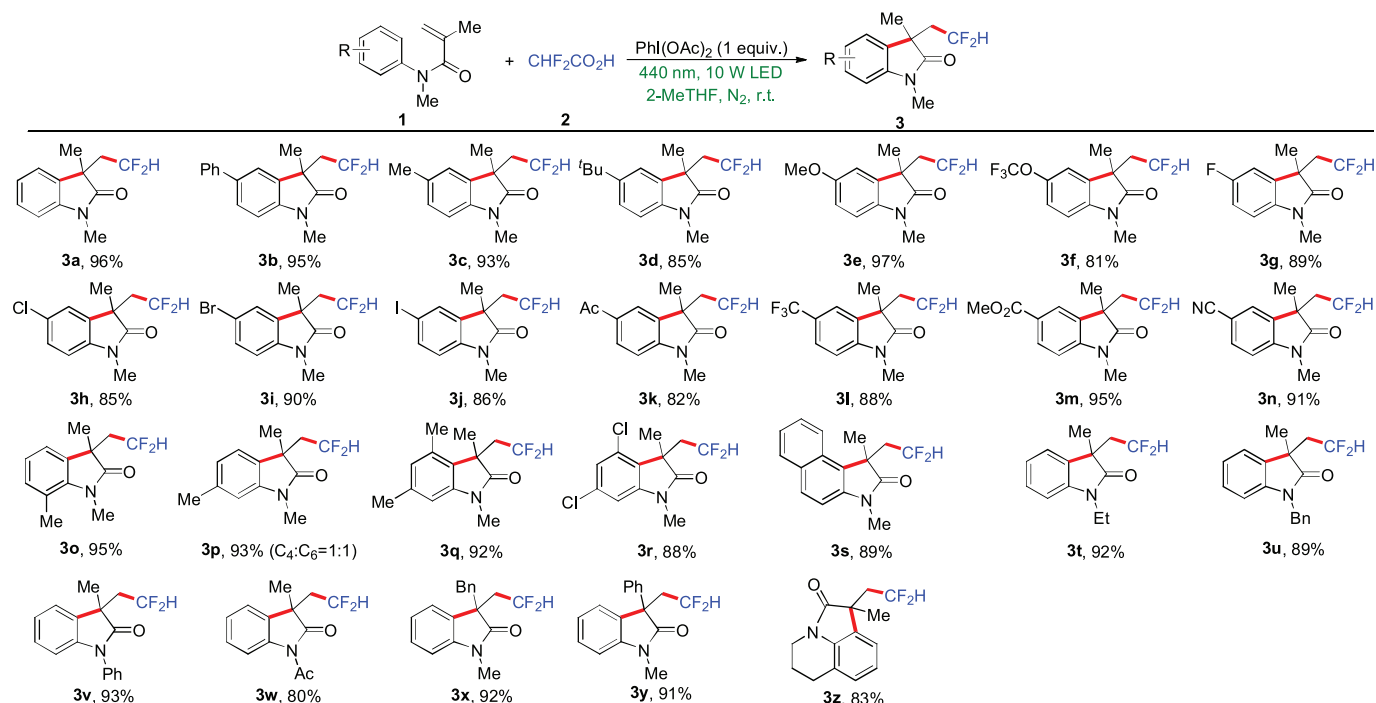
<sup>b</sup> Estimated by <sup>1</sup>H NMR using diethyl phthalate as internal reference.

The control experiments showed that no reaction took place when this reaction was performed in the absence of PhI(OAc)<sub>2</sub> or visible-light irradiation (entries 15 and 16).

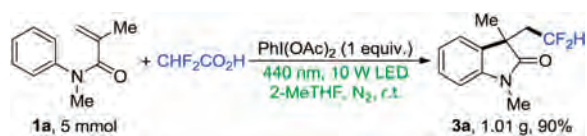
With the optimized procedure developed (Table 1, entry 1), the generality of the visible-light-initiated tandem reaction was then investigated (Scheme 2). A variety of substituted *N*-arylacrylamides with electron-neutral, electron-donating or electron-withdrawing groups at the *para* position of phenyl ring were subjected to the present reaction, providing the desired products in excellent yields. Notably, a wide range of valuable functional-groups such as phenyl (**3b**), alkyl (**3c** and **3d**), alkoxy (**3e** and **3f**), halogens (**3g–3j**), acetyl (**3k**), trifluoromethyl (**3l**), ester (**3m**) and nitrile (**3n**) were all tolerated in this approach. *N*-arylacrylamide substrates containing functional groups at various positions of the phenyl ring were well compatible and provided the target products (**3c**, **3o–3r**) in high yields. When *meta*-substituted substrate **1p** was subjected to the reaction, a 1:1 mixture of two regioisomers **3p** and **3p'** was obtained. The naphthyl substrate was also suitable substrates for this transformation (**3s**). Among them, products containing halogens, esters and nitriles may be further functionalized to construct more complex molecules. *N*-Arylacrylamides containing alkyl, phenyl and acetyl groups at the nitrogen atom underwent the reaction smoothly and provided the corresponding products (**3t–3w**) in excellent yields. The substrates modified with alkyl and phenyl substituents on the  $\alpha$ -position of vinyl group delivered the target products (**3x** and **3y**) in good yields. When *N*-phenylmethacrylamide was used as the reaction substrate, no desired product was detected. This reaction could also be carried out in the presence of a tetrahydroquinoline moiety, generating the tricyclic oxindole (**3z**) in 83% yield. No reaction occurred when 2,2-difluoro-2-phenylacetic acid was instead of difluoroacetic acid.

To investigate the practical applicability of this protocol, the tandem reaction was performed on a gram scale (5 mmol). As expected, the yield of **3a** (90%) was similar to that from the small-scale synthesis (Scheme 3).

To gain insight into the mechanism of the present tandem reaction, we conducted a series of control experiments. When the model reaction of **1a**, **2** and PhI(OAc)<sub>2</sub> was performed, we observed the formation of [bis(difluoroacetoxy)iodo]benzene (**4**) [16]. We

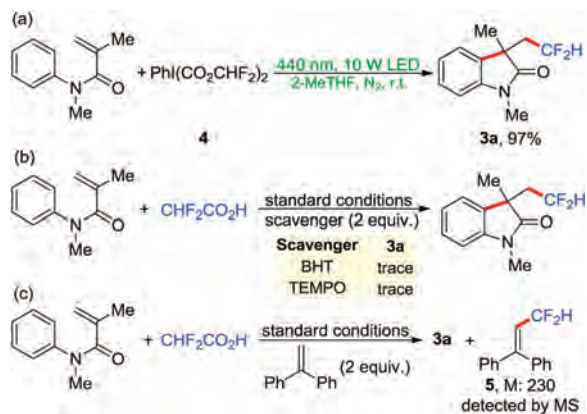


**Scheme 2.** Reaction scope. Conditions: **1** (0.3 mmol),  $\text{CHF}_2\text{CO}_2\text{H}$  (0.6 mmol),  $\text{PhI}(\text{OAc})_2$  (0.3 mmol), 2-MeTHF (1.5 mL),  $\text{N}_2$ , 10 W LED, r.t. 4 h.

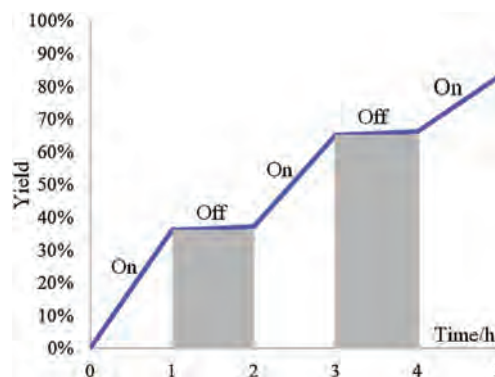


**Scheme 3.** Large scale experiment.

envisioned that this reaction probably proceeded *via* a ligand exchange and a tandem difluoromethylation reaction to provide the product **3a**. To prove our hypothesis, we treated **1a** and compound **4** in 2-MeTHF under the irradiation of a 10 W LED (440 nm). As expected, the desired product **3a** was formed in 97% NMR yield (Scheme 4a). This result suggested that compound **4** was the key intermediate for the present reaction. When 2 equiv. of a radical scavenger (TEMPO or BHT) was added to the reaction system, the desired reaction was seriously inhibited (Scheme 4b). The free-radical capturing adduct (diphenylethylene- $\text{CHF}_2$ , **5**) was also detected by GC-MS (Scheme 4c). The On/Off light illumination revealed that this transformation was fully suppressed in the

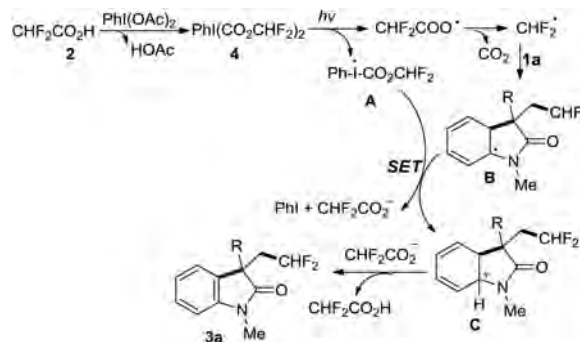


**Scheme 4.** Control experiments.



**Fig. 1.** On/Off light illumination experiment.

absence of light irradiation (Fig. 1). The UV–vis absorption experiments revealed that compound **4** could absorb ultraviolet-visible light and serve as the photosensitizer in the present reaction. These results demonstrated that the continuous visible-light illumination is necessary for the developed photocatalytic reaction.



**Scheme 5.** Plausible reaction mechanism.

On the basis of the above mentioned results and previously reported literatures [7d,16,17], a plausible mechanism is proposed (Scheme 5). The ligand exchange between the  $\text{CHF}_2\text{CO}_2\text{H}$  (**2**) and  $\text{PhI}(\text{OAc})_2$  first occurred, leading to the formation of bis(difluoroacetoxy)iodobenzene (**4**). The intermediate **4** was subsequently excited by visible-light (440 nm) to generate an iodanyl radical **A** and a difluoroacetic acid radical. The decarboxylation of difluoroacetic acid radical would provide a  $\text{CHF}_2$  radical, which reacted with substrate **1a** to form a carbon-centered radical **B**. Next, a single-electron-transfer (SET) process occurred between the radical **A** and the radical **B**, resulting in the generation of cationic intermediate **C**, difluoro-acetate anion and  $\text{PhI}$ . Finally, the difluoroacetate anion promoted the deprotonation of the intermediate **C**, which would provide the target product **3a** and  $\text{CHF}_2\text{CO}_2\text{H}$ .

In summary, we have developed the first example of visible-light induced one-pot tandem reaction of *N*-arylacrylamides,  $\text{CHF}_2\text{CO}_2\text{H}$  and  $\text{PhI}(\text{OAc})_2$ , providing an eco-friendly and practical method to access various difluoromethylated oxindoles. In contrast to the previous reported protocol, this reaction is promoted by visible light in the absence of any additive, base, metal or external photosensitizer, employing cheap and easily available  $\text{CHF}_2\text{CO}_2\text{H}$  as the difluoromethylation reagent and bulk biomass-derived 2-MeTHF as the reaction medium. Owing to the easily-obtained and low cost starting materials, clean and mild conditions, simple operation procedure and excellent reaction efficiency, this process is expected to be an ideal strategy for preparing  $\text{CHF}_2$ -containing molecules

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2021.01.021>.

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