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# Visible-light induced radical aryldifluoromethylation of *N*-arylacrylamides by [bis(difluoroacetoxy)iodo]benzene

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ABSTRACT

Visible light-induced radical aryldifluoromethylation of *N*-arylacrylamides using [bis(difluoroacetoxy)iodo]benzene as a difluoromethylation reagent is reported for the first time. The inexpensive and readily accessible reagents and the mild reaction conditions render this method an alternative and practical strategy for the synthesis of difluoromethyl substituted oxindoles.



## Introduction

The strategy of incorporating fluoroalkyl groups into organic molecules is widely employed in agrochemical, pharmaceutical, and materials science research as it can change the physicochemical properties and biological activities of compounds significantly [1]. Among the fluoroalkyl groups, the difluoromethyl group ($HCF_2$) has attracted particular attention in the field of drug discovery as it can be used as a lipophilic hydrogen donor and also because this group is an isostere of the hydroxyl, thiol, and amide groups [2]. However, unlike the well-developed trifluoromethylations [3,4], efficient and environmentally friendly methods for the corresponding difluoromethylations have not yet been developed considerably.

In the past decade, radical-based difluoromethylation has emerged as an advantageous synthetic strategy for introducing $HCF_2$ groups. Elegant work was performed by Baran et al. by using $Zn(SO_2CF_2H)_2$ as a novel difluoromethylating reagent that could generate a difluoromethyl radical with the aid of *tert*-butyl hydroperoxide [5]. Notably, the species generated upon the oxidation of sodium difluoromethanesulfinate ($NaSO_2CF_2H$) can also be used as a difluoromethyl radical precursor [6]. Besides, $NaSO_2CF_2H$, difluoromethanesulfonyl chloride [7], difluoromethylsulfone [8], difluoromethyl sulfoximine [9], and difluoromethylphosphonium salts [10] can be used as difluoromethyl radical sources in photoredox processes.

Oxindoles are important heterocyclic scaffolds found in a wide range of pharmaceuticals and bioactive natural products [11]. Thus, extensive efforts have been devoted to the synthesis of oxindole derivatives, especially to the synthesis of difluorinated 3,3-disubstituted 2-oxindoles (Scheme 1). In 2014, Tan's group reported a synthesis of difluoromethylated oxindoles through silver-catalyzed aryldifluoromethylation of *N*-arylacrylamides by using $Zn(SO_2CF_2H)_2$ as the difluoromethyl radical source and $(NH4)_2S_2O_8$ as oxidant [12]. Dolbier's group described a visible-light-induced difluoromethylation/cyclization of *N*-arylacrylamides with $HCF_2SO_2Cl$ for the synthesis of difluoromethylated oxindoles [13]. In 2019, Zhu and coworkers also realized this transformation by employing difluoromethyl benzo[*d*]-thiazol-2-yl sulfone as $CF_2H$ source [14]. Ruan and Ackermann reported a catalyst-free, direct electrochemical aryldifluoromethylation of *N*-arylacrylamides by $NaSO_2CF_2H$ [15]. In 2017, Maruoka and coworkers firstly employed [bis(difluoroacetoxy)iodo]benzene, which was prepared from the inexpensive and commercially available difluoroacetic acid, as a novel difluoromethyl radical source to realized the direct difluoromethylation of heteroarenes under visible-light irradiation [16]. In 2019, Gouverneur reported a hydrodifluoromethylation of alkenes by a *in situ* generated [bis(difluoroacetoxy)iodo]benzene [17]. Wang reported a Rhenium-catalyzed decarboxylative difluoromethylation of styrenes with [bis(difluoroacetoxy)iodo]benzene [18]. Due to our continued interest in

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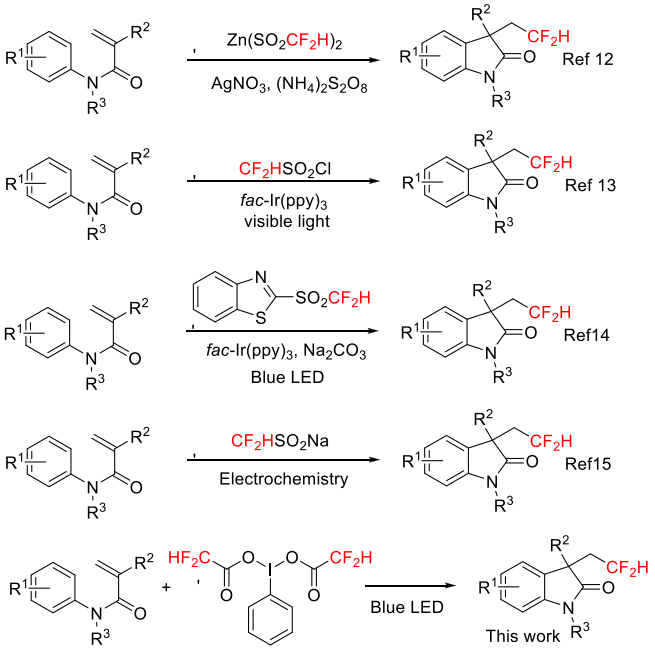



**Scheme 1.** Aryldifluoromethylation of *N*-Arylacrylamides with different difluoromethylation reagents.

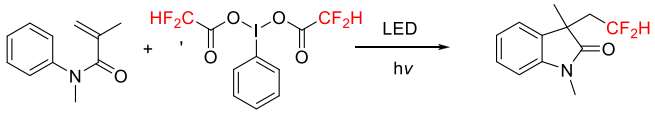
the fluoroalkylation of alkenes [19], We report herein the visible light-induced radical aryldifluoromethylation of *N*-arylacrylamides by [bis(difluoroacetoxy)iodo]benzene to construct fluorinated 3,3-disubstituted 2-oxindoles.

## Results and discussion

We began our investigation by treating *N*-methyl-*N*-phenylmethacrylamide (**1a**) with [bis(difluoroacetoxy)iodo]benzene (**2**) in tetrahydrofuran (THF) under 18 W blue LED irradiation. Fortunately, the desired aryldifluoromethylation product **3a** was obtained in 62% yield. Various solvents were screened to improve the yield (Table 1, entries 2–7), and the maximum yield (80%) was obtained in 1,4-dioxane. Following this, the reaction was conducted in 1,4-dioxane in different types of visible light. Decreasing the power of the light to 15 W diminished the yield slightly (78%), while increasing the power to 21 W increased the yield to 86%. Further increasing the power to 24 W increased the yield to 90%. While the use of white or purple LEDs decreased the yield, a green LED did not give the desired product. Finally, loading of the difluoromethylation reagent was examined. Decreasing the loading of **2** to 1.4 equiv. diminished the yield, while increasing the loading of **2** to 1.8 equiv gave 98% yield. Notably, when reaction was carried out in dark, no desired product was observed. Thus, the optimised reaction conditions for the aryldifluoromethylation of **1a** were as follows—**1a**: 0.30 mmol, **2**: 0.54 mmol, and solvent: 1,4-dioxane (2 mL) under 24 W blue LED irradiation at 40 °C.

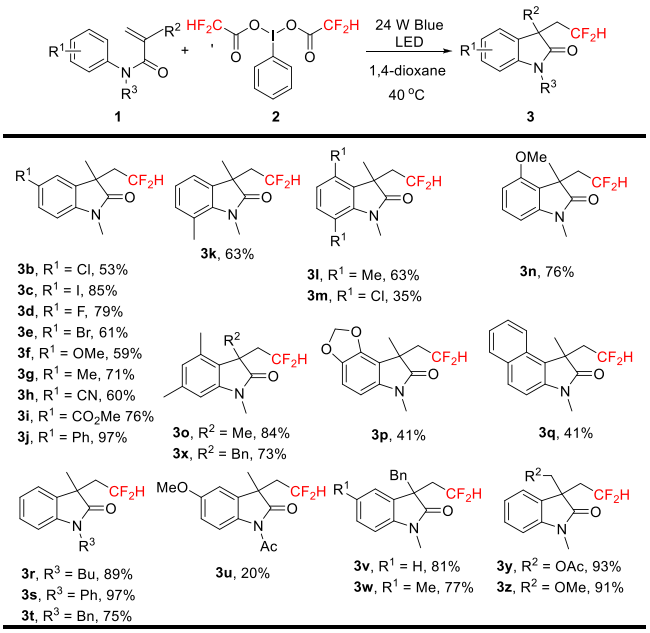
With the optimized reaction conditions in hand, we examined the substrate scope of this reaction using a series of *N*-Arylacrylamides (**1b**–**1z**). The results are summarised in Scheme 2. *N*-Methyl-*N*-phenylmethacrylamides bearing electron-donating or electron-withdrawing substituents in the *ortho*-, *meta*-, and *para*-positions of the aniline ring (**1b**–**1p**) could be smoothly transformed to the corresponding oxindoles in moderate to good yields. Notably, when *N*-methyl-*N*-naphthylmethacrylamide **1o** was employed as the substrate, the desired product **3q** was obtained in a moderate yield. Other *N*-substitutes-*N*-phenylmethacrylamides (**1r**–**1u**) gave the desired aryldifluoromethylation products in good yields. *N*-Acetyl-*N*-phenylmethacryl amide **1u** was an exception, which gave **3u** in 20% yield due to the electron-withdrawing property of the acyl group. Examination of the α-substituted acrylamides (**1v**–**1z**) revealed that benzyl, acetoxy, and methoxy substituents were well-tolerated and could afford the desired products (**3v**–**3z**) in good yields.

**Table 1**
Optimization of the aryldifluoromethylation of **1a** by [bis(difluoroacetoxy)iodo]benzene (**2**).[a]




| Entry | **2**/equiv. | Light Source (LED) | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 1.6 | Blue 18 W | THF | 62 |
| 2 | 1.6 | Blue 18 W | DCE | 9 |
| 3 | 1.6 | Blue 18 W | DCM | 49 |
| 4 | 1.6 | Blue 18 W | MeCN | 31 |
| 5 | 1.6 | Blue 18 W | MeOH | Trace |
| 6 | 1.6 | Blue 18 W | DMF | 75 |
| 7 | 1.6 | Blue 18 W | DMSO | 22 |
| 8 | 1.6 | Blue 18 W | Toluene | Trace |
| 9 | 1.6 | Blue 18 W | 1,4-dioxane | 80 |
| 10 | 1.6 | Blue 15 W | 1,4-dioxane | 78 |
| 11 | 1.6 | Blue 21 W | 1,4-dioxane | 86 |
| 12 | 1.6 | Blue 24 W | 1,4-dioxane | 90 |
| 13 | 1.6 | White 24 W | 1,4-dioxane | 88 |
| 14 | 1.6 | Purple 24 W | 1,4-dioxane | 83 |
| 15 | 1.6 | Green 24 W | 1,4-dioxane | 0 |
| 16 | 1.4 | Blue 24 W | 1,4-dioxane | 86 |
| 17 | 1.8 | Blue 24 W | 1,4-dioxane | 98 |
| 18 | 1.8 | In dark | 1,4-dioxane | 0 |

[a] **1a** (0.30 mmol), **2** (0.42–0.54 mmol), solvent (2 mL) under LED irradiation for 12 h at 40 °C.
[b] Isolated yield.



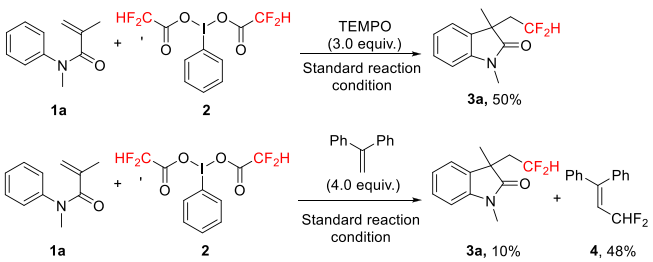

Reaction conditions: **1** (0.30 mmol), **2** (0.54 mmol), 1,4-dioxane(2 mL) under 24 W blue LED irradiation for 12 h at 40 °C. The yield reported is isolated yield.

**Scheme 2.** Scope of aryldifluoromethylation of *N*-Arylacrylamides.

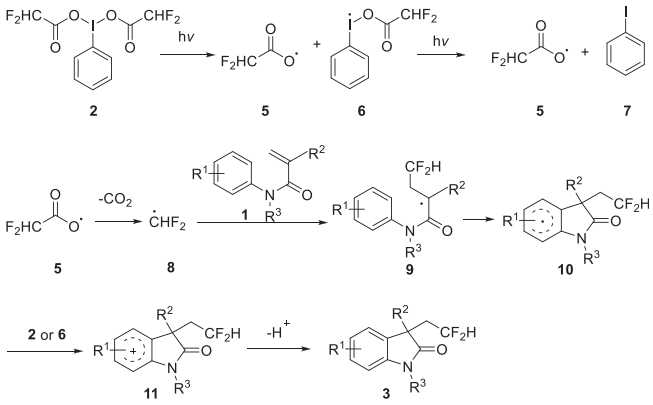
Based on literature [16,20], we speculated that difluoromethyl radicals might be the key intermediates in this reaction. Two radical trapping experiments were carried out under the optimised reaction conditions to detect the presence of such an intermediate (Scheme 3). When radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 3 equiv) or 1,1-diphenylethylene (4 equiv) was added to the reaction mixture under the optimised conditions, the yield of **3a** decreased to 50% and 10%, respectively. Furthermore, (3,3-difluoroprop-1-ene-1,1-diyl)dibenzene (**4**) was obtained in 48% yield when 1,1-diphenylethylene was used as a radical scavenger, thus confirming the formation of an intermediate free radical species in this transformation.

Based on literature and the abovementioned results [16,20], we proposed a plausible mechanism for this transformation (Scheme 4). First, the photolysis of [bis(difluoroacetoxy)iodo]benzene **2** generated difluoromethyl carboxyl radical **5** and iodanyl radical **6**, which degraded to **5** and iodobenzene **7**. Following this, decarboxylation of **5** afforded difluoromethyl radical **8**, which reacted with *N*-Arylacrylamide **1** to give alkyl radical intermediate **9**. Intermediate **9** could cyclise to form aryl radical **10**. Finally, oxidation of **10** by **2** or **6**, followed by deprotonation, afforded the desired product **3**.

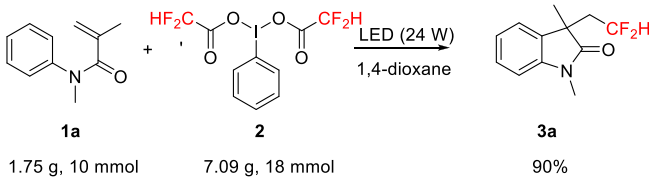
Finally, to illustrate the possible practical application of this transformation, a gram-scale aryldifluoromethylation reaction of **1a** was conducted (Scheme 5). To our delight, the desired product **3a** was obtained in 90% yield.




**Scheme 3.** Additional reactions for investigating the mechanism.




**Scheme 4.** Possible reaction mechanism.




**Scheme 5.** Scale up of the aryldifluoromethylation reaction.

## Conclusion

In summary, we developed the visible light-induced radical aryldifluoromethylation of *N*-Arylacrylamides to synthesise difluoromethyl-substituted oxindoles using [bis(difluoroacetoxy)iodo] benzene as a difluoromethylation reagent. The inexpensive and readily accessible reagents and the mild reaction conditions render this reaction an alternative and practical strategy for the synthesis of difluoromethyl-substituted oxindoles. Investigations on difluoromethylation of other organic compounds with [bis(difluoroacetoxy)iodo]benzene are currently underway in our laboratory.

## 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.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152864.

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