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Visible-light-promoted radical amidoarylation of arylacrylamides towards amidated oxindoles†

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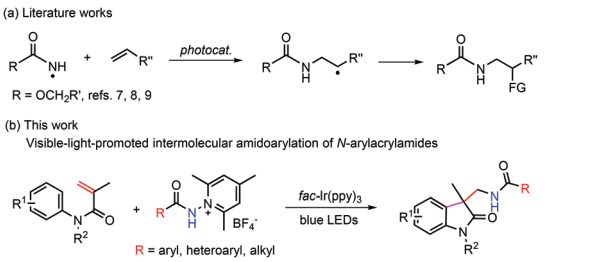
A visible-light-promoted intermolecular radical amidation/cyclization of arylacrylamides was realized by using *N*-aminopyridinium salts as the source of amidyl radicals. The reaction exhibits a broad scope and good functional group tolerance, and a variety of amide-tethered-oxindoles were prepared in this way in moderate to good yields.

C–N bond-forming reactions have drawn persistent interest from chemists because of the importance of nitrogen-containing compounds in materials science and in medicinal chemistry. Among the various strategies used for the construction of C–N bonds, those mediated by nitrogen-centered radicals have been gaining prominence, with accumulating studies showing that the high reactivity of N-radicals can be exploited to tackle a number of challenging synthetic problems.[1] Multiple methods have been developed for the generation of N-radicals under mild conditions, which greatly enhances their usefulness in organic synthesis.[2]

The radical amination of alkenes constitutes a highly valuable type of reaction for the preparation of nitrogen-containing compounds.[3] Significant progress has been made over the past few years, which is to a great extent attributable to the employment of visible-light photoredox catalysis.[4] For instance, excellent protocols have been reported for the anti-Markovnikov hydroamination[2f,5,6] and amination/difunctionalization (Scheme 1a).[7–10] It is noteworthy that primary amidyl radicals, which have been sparingly employed to react with alkenes because of a lack of an effective means of generation, have begun to be used for the construction of the C–N bond.[6–9] Despite this advancement, most of the investigations in this line have focused on protected amidyl radicals, and intermolecular olefin amidation with aryl and alkyl-attached primary amidyl radicals has been much less explored. In view of the great synthetic potential of amidyl radicals as well as the structural importance of amides, it would be highly desirable to broadly investigate the reactivity and efficacy of common amidyl radicals towards the addition of alkenes.

Oxindoles represent an important class of naturally occurring heterocycles that show highly effective biological and physiological activities.[11] Oxindoles can be efficiently prepared from *N*-phenylacrylamides *via* radical addition/intramolecular aromatic substitution.[12] Our previous study shows that by reacting aminium radicals with *N*-phenylacrylamides, aminated oxindoles can be accessed readily in good yields.[13] Considering the significance of the amidyl group in medicinal chemistry, it would be desirable to incorporate the amidyl group into oxindoles by this strategy. Chang *et al.* reported an effective photochemical protocol for the preparation of amidated oxindoles through the reaction of benzoyl azides with *N*-phenylacrylamides.[14] We envisioned that by reacting amidyl radicals with *N*-phenylacrylamides, the scope of the reaction could be expanded. *N*-Aminopyridinium salts have recently been demonstrated to be highly efficient precursors toward N-centered radicals (Scheme 1b);[15,16] they were expected to fulfill our need to deliver the primary aryl and alkyl amidyl radicals under mild conditions. Indeed, our results verified the viability of our design, and the reaction of *N*-phenylacrylamides with *N*-aminopyridinium salts was performed under blue light irradiation with *fac*-Ir(ppy)$_3$ as the photocatalyst (Scheme 1b). It is worth noting that the reaction



Scheme 1 Photochemical protocols for the intermolecular addition of primary amidyl radicals to alkenes.

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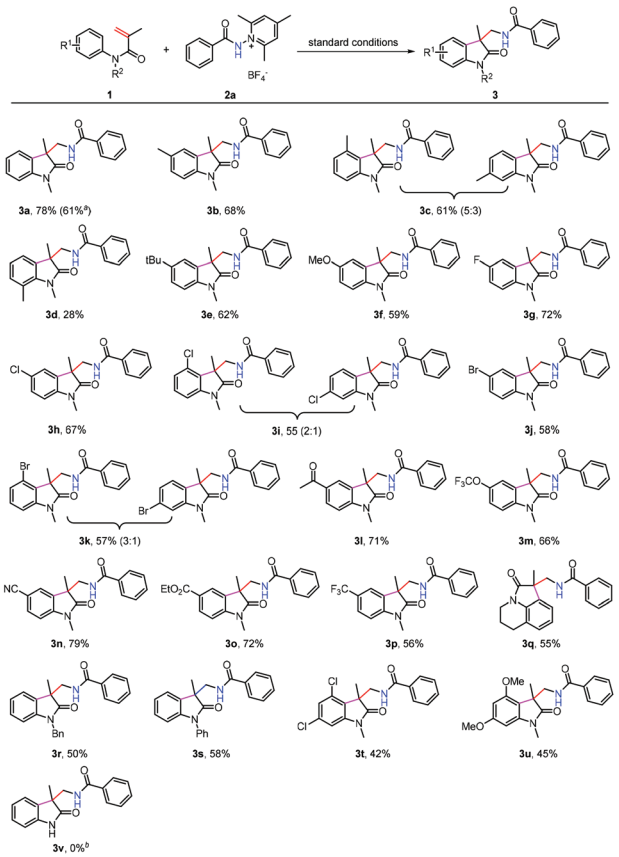
exhibited good functional tolerance, and the alkyl-substituted amido group can be introduced into the oxindole motif as well as the aryl and heteroaryl-substituted amido group.

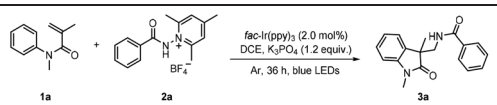
Initially, we selected *N*-phenylacrylamide **1a** and *N*-aminopyridinium salt **2a** as the model substrates to investigate the feasibility of the reaction under visible-light irradiation (40 W Kessil blue LEDs, 50% intensity) in the presence of a photocatalyst (Table 1). A systematic survey of the reaction conditions with variation in the photocatalyst, solvent and base revealed the optimum conditions to be: *fac*-Ir(ppy)$_3$ as the photocatalyst, K_3PO_4 as the base in 1,2-dichloroethane (DCE) at room temperature, and blue-light irradiation for 36 h. Under these conditions, the desired product **3a** was isolated in good yield (with **2a** as the limiting substrate). The structure of **3a** was confirmed by X-ray crystallographic analysis (CCDC no. 2122102†).[17] Other catalysts, such as Cu(dap)$_2$Cl and eosin Y, were ineffective under the current conditions (Table 1, entries 2 and 3). Replacing DCE with MeCN, dichloromethane (DCM), or $CHCl_3$ resulted in lower yields (entries 4–6). Additionally, the yield was diminished when K_2CO_3 or Et_3N was used as the base or in the absence of a base (entries 7–9). Control experiments indicate that both photocatalyst and light irradiation are necessary for the reaction to take place (entries 10 and 11).

To test the generality of this reaction, the scope of arylacrylamides **1** was investigated, and the results are shown in Scheme 2. Both electron-donating and electron-withdrawing groups on the *N*-phenyl ring were well tolerated, and the corresponding products were obtained in moderate to good yields. Notably, a broad range of functional groups such as the halo (**3g–3k**) and cyano (**3n**) groups were well tolerated, which offers the potential for further transformations. This protocol



Scheme 2 Scope of arylacrylamides. The reactions were conducted at the 0.2 mmol scale. Isolated yield. [a] **1a** (6.0 mmol, 1.5 equiv.), **2a** (4.0 mmol, 1.0 equiv.), base (4.8 mmol, 1.2 equiv.), *fac*-Ir(ppy)$_3$ (2.0 mol%), DCE (30 mL), 40 W Kessil blue LEDs (100% intensity), room temperature, 42 h, under argon atmosphere. [b] A complex mixture was generated.

Table 1 Optimization of the reaction conditions[a]

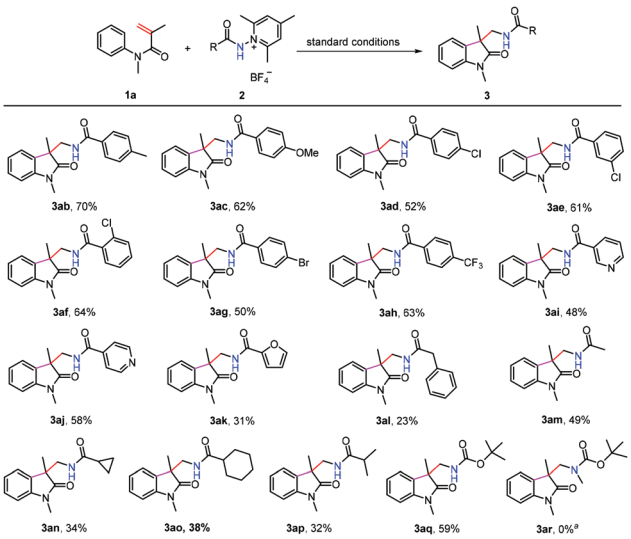


Entry	Deviation from the standard conditions	Yield[b] (%)
1	Standard conditions	81 (78[c])
2	Eosin Y instead of Ir(ppy)$_3$	Trace[d]
3	Cu(dap)$_2$Cl instead of Ir(ppy)$_3$	N.R.
4	MeCN instead of DCE	56
5	DCM instead of DCE	74
6	$CHCl_3$ instead of DCE	64
7	K_2CO_3 instead of K_3PO_4	64
8	Et_3N instead of K_3PO_4	41
9	No base	61
10	In the dark	N.R.
11	No photocatalyst	N.R.

[a] Reaction conditions: **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol, 1.0 equiv.), K_3PO_4 (0.12 mmol, 1.2 equiv.), *fac*-Ir(ppy)$_3$ (2.0 mol%), DCE (1.0 mL), 40 W Kessil blue LEDs (50% intensity), room temperature, 36 h, under an argon atmosphere. [b] Isolated yields. [c] The reaction was conducted at the 0.2 mmol scale. [d] Reaction time was 24 h. Detailed information concerning the screening of the reaction conditions is presented in Tables S1–S5 in the ESI.†

is applicable to gram-scale preparation. As such, **3a** was obtained in 61% yield upon isolation when the reaction was performed at the 4.0 mmol scale. However, the expected product **3v** was not obtained when the *N*-unprotected acrylamide was used as the substrate. In this case, the reaction only delivered a complex mixture.

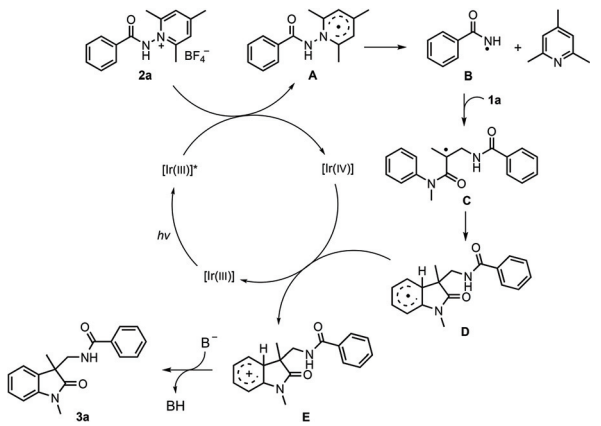
We next turned our attention to examine the scope of *N*-aminopyridinium salts **2** under the standard conditions (Scheme 3). It can be seen that a range of substrates bearing electron-donating and electron withdrawing groups on the phenyl ring of pyridinium salts can be converted to the expected products (**3ab–3ah**), and heteroaryl aminopyridinium salts such as pyridine (**3ai** and **3aj**) and furan (**3ak**) were also suitable substrates for the present reaction. Moreover, alkyl and alkyloxyl-substituted amidyl groups can be introduced into the oxindole motif as well, although the yields of **3al–3ap** were considerably lower than those obtained using their aryl-substituted counterparts. The lower yields of **3al–3ap** might be attributed to the presence of competitive pathways (C–H abstraction from the solvent, for example) that *N*-alkyl amidyl radicals are liable to undergo. This method did not work for



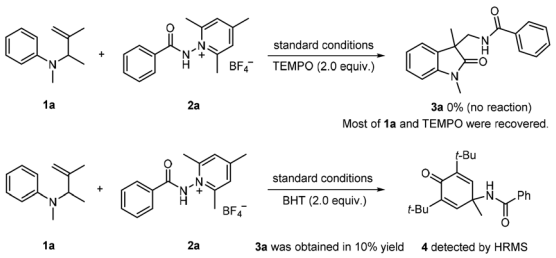
Scheme 3 Scope of aminopyridinium salts. The reactions were conducted at the 0.2 mmol scale. Isolated yields. [a] No reaction took place.

the *N*-disubstituted aminopyridinium salt **2r**, possibly as a result of steric hindrance caused by the *N*-methyl group.

The present reactions are believed to take place following the radical pathway shown in Scheme 4. Taking the reaction of **1a** with **2a** as an example, it can be seen that the reaction is initiated by the single electron transfer between the *N*-aminopyridinium salt **2a** and the excited [Ir(III)]*, which generates radical **A** and [Ir(IV)]. Radical **A** then undergoes fragmentation to give the amidyl radical **B**, which is subsequently trapped by **1a** to produce the radical intermediate **C**. The latter undergoes cyclization to afford radical **D**. Oxidation by [Ir(IV)] converts **D** to the carbocation **E**, from which **3a** is finally generated by deprotonation. K_3PO_4 has a beneficial effect on the reaction, probably because it can enhance the basicity of the system to make the deprotonation easier. This radical mechanism was supported by the inhibition experiment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 5). The reaction of **1a** and **2a** was



Scheme 4 Proposed mechanism.



Scheme 5 Inhibition experiment.

completely inhibited in the presence of 2.0 equiv. of TEMPO, and the yield of **3a** was significantly decreased when 2.0 equiv. of BHT was added into the reaction vessel. In the latter case, the BHT-trapped product **4** was also detected by HRMS. That the reaction could not take place without *fac*-Ir(ppy)$_3$ and light irradiation (Table 1, entries 10 and 11) reveals the necessity of photoexcitation of the catalyst during the reaction.

In summary, we have developed an effective protocol for the preparation of amidyl-attached oxindoles *via* photoinduced and *fac*-Ir(ppy)$_3$-catalyzed amidoarylation of arylacrylamides with *N*-aminopyridinium salts as the amidyl radical precursors. This method allows a variety of substituted arylacrylamides and *N*-aminopyridinium salts to be converted to the desired products in moderate to good yields. Further attempts to expand the synthetic scope of the intermolecular radical amidation of unactivated olefins are ongoing in our laboratory.

Author contributions

Y.-Z. Wang and W. Yu contributed to the conceptualization of this study. Y.-Z. Wang carried out all the experimental work. Y.-Z. Wang and W. Yu wrote the manuscript. Y.-Z. Wang, W.-J. Lin, H.-C. Liu and W. Yu reviewed the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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17 CCDC 2122102† (*N*-((1,3-dimethyl-2-oxoindolin-3-yl) methyl)benzamide, **3a**) contains the supplementary crystallographic data for this paper.

