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

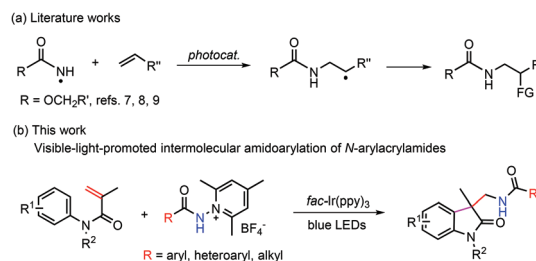
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A visible-light-promoted intermolecular radical amidation/cyclization of arylacrylamides was realized by using *N*-aminopyridinium salts as the source of amidyl radicals. The reaction exhibits a broad scope and good functional group tolerance, and 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, amidated 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

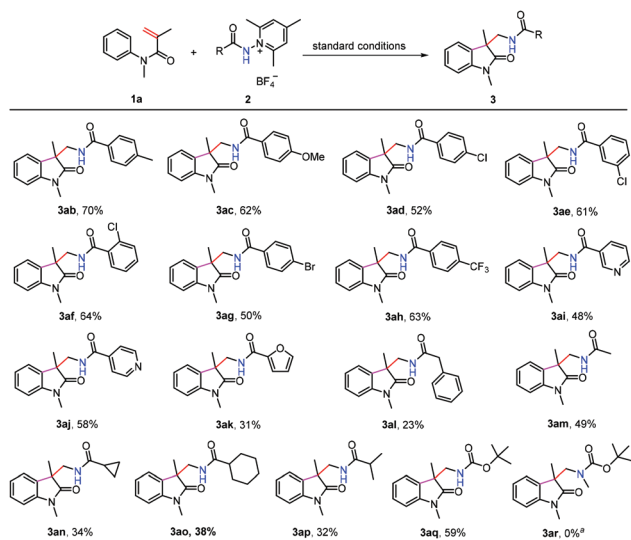


Scheme 1 Photochemical protocols for the intermolecular addition of primary amidyl radicals to alkenes.

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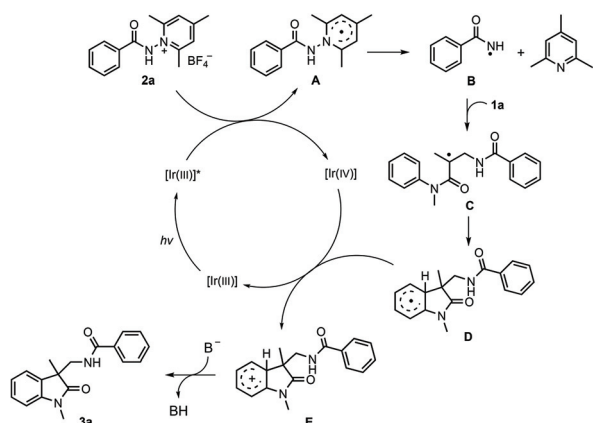
† Electronic supplementary information (ESI) available. CCDC 2122102. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2qo00127f



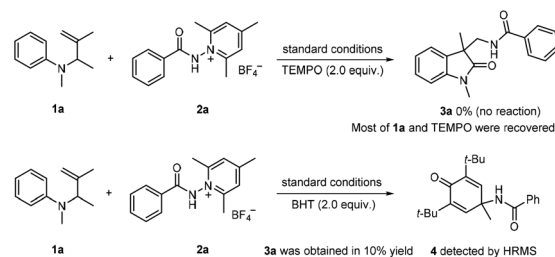
Scheme 3 Scope of aminopyridinium salts. The reactions were conducted at the 0.2 mmol scale. Isolated yields. * No reaction took place.

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 $[\text{Ir}(\text{III})]^*$, which generates radical A and $[\text{Ir}(\text{IV})]$. 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 $[\text{Ir}(\text{IV})]$ 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*- $\text{Ir}(\text{ppy})_3$ 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*- $\text{Ir}(\text{ppy})_3$ -catalyzed amidoarylation of arylacrylamides and *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.

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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.