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RESEARCH ARTICLE

Tandem Photoredox Catalysis: Enabling Carbonylative Amidation of Aryl and Alkyl Halides

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Abstract: We report a new visible light-mediated carbonylative amidation of aryl, heteroaryl and alkyl halides. A tandem catalytic cycle of [Ir(ppy)2(dtbbpy)]+ generates a potent iridium photoreductant via a second catalytic cycle in the presence of DIPEA which productively engages aryl bromides, iodides and even chlorides as well as primary, secondary and tertiary alkyl iodides. The versatility of the in-situ generated catalyst is illustrated by compatibility with aliphatic and aromatic amines, high functional group tolerance and the late-stage amidation of complex natural products.

Amide bond formation is fundamental to discoveries in the chemical and life sciences. The amide moiety is ubiquitous in natural and synthetic proteins and features prominently in versatile molecules including pharmaceuticals[1] synthetic polymers,[2] and agrochemicals.[3] Owing to the importance of amides, traditional synthetic approaches to amide bond formation are being challenged. Modern synthetic methods typically employ stoichiometric coupling reagents to mediate the condensation of a carboxylic acid and amine (Figure 1a).[4] These protocols liberate equivalents of toxic by-products and are generally incompatible with sterically congested amides.[5] Given the prevalence of the amide functionality in pharmaceuticals and agrochemicals, scaled processes are impeded by the expense associated with high molecular weight coupling reagents and the environmental impact of super-stoichiometric waste streams.[6]

With an increasing adoption of green chemistry principles by research and industrial laboratories, there is ongoing demand to develop a catalytic amide bond forming processes that are efficient, operationally simple, scalable and that reduce or eliminate the need for stoichiometric reagents.[1a],[7]

A key advance in catalytic amidation is the three-component coupling of an organohalide, carbon monoxide (CO) and amine (Figure 1a).[8] Transition metal catalyzed carbonylative amidation readily generates aryl and vinyl amides by reductive dehalogenation of corresponding organohalides. The high energy barrier to oxidative addition resulting from metal catalyst deactivation with CO coordination[9] imposes forcing conditions; high temperatures, extended reaction times and high CO pressure, which restricts application to activated substrates with insensitive functional groups. Furthermore, less activated alkyl...
Advances in radical protocols have addressed the limitations of transition metal catalyzed amidation. Free-radical carbonylative amidation proceeds by the single electron reduction or photoinduced homolysis of a carbon-halide bond to furnish a carbon-centered radical that traps CO to generate amides via an acyl radical and amine. Despite the synthetic potential, the practicability of radical methods is impeded by hazardous reagents or high energy photochemistry. To overcome these limitations, photoredox strategies have avoided reagents and conditions that complicate traditional radical chemistry. However, these are limited to alkyl substrates including alkyl iodides or alkyl organosilicates. Furthermore, the carbonylative amidation of aryl substrates with visible light photoredox catalysis remains unexplored. Consequently, a mild photocatalytic radical carbonylative amidation that engages aryl and alkyl substrates will solve an enduring challenge in synthetic chemistry.

We endeavored to develop a unified method for the carbonylative amidation of aryl and unactivated alkyl halides with photoredox catalysis. In doing so, valuable amides could be generated from the diverse and commercially available organohalide building blocks under mild conditions, thus unlocking the full potential of catalytic radical amidation. The photoredox carbonylative amidation of aryl and alkyl halides, however, is challenged by availability of photocatalysts that promote the photo-induced electron transfer (PET) induced reduction of unactivated C-(sp^2) and C-(sp^3) halogen bonds. Multiphoton excitation catalysis has emerged as new strategy to overcome the thermodynamic limitations of visible light photoredox catalysis to generate high energy photoreductants. Recently our group disclosed a method for the photoredox catalyzed carbonylative amidation of aryl and alkyl halides via a multiphoton initiated secondary catalytic cycle (Figure 2a) and Nicewicz uncovered similar behavoir with organophotoredox catalysts. This strategy has been successfully applied to the reductive photodhalogenation of unactivated organohalides and showcases the ability common photoredox catalysts to yield potent excited-state donors via multiphoton excitation.

Reported here is the first example of a general and practical strategy for the photoredox catalyzed carbonylative amidation of aryl, heteroaryl and alkyl halides. The platform harnesses a dual strategy of visible-light tandem photoredox catalysis and continuous flow chemistry (Figure 2c). The tandem catalytic cycle of [Ir(ppy)_2(dtbbpy)]^+ engages energy demanding aryl bromides, iodides and chlorides as well as primary, secondary and tertiary alkyl iodides via a multiphoton initiated secondary catalytic cycle. In combination with continuous flow processing, the strategy furnishes biologically relevant and diverse amides under mild reaction conditions with a broad substrate scope, atom economy, and scalability, offering a versatile reactivity mode for catalytic amide bond formation.

### Results and Discussion

The design plan for the carbonylative amidation of aryl and alkyl halides is shown in Figure 2. Central to this approach is the tandem photoredox cycle of [Ir(ppy)_2(dtbbpy)]PF_6 [Ir1]^+ (Fig 2b). We envisioned that energy demanding organohalides could be engaged by the highly reducing second excited [Ir2]^+ (E°([Ir2]^+/[Ir2]^0) = -1.70 V to -3.0 V) to generate the corresponding C-(sp^2) and C-(sp^3)-centered radicals (Fig 2c). Accordingly, the carbon-centered radical was proposed to react with excess CO to furnish the amide product. A key feature of the design plan is continuous flow chemistry. The flow chemistry platform (Supplementary Fig S2) incorporates a tube-in-tube gas/liquid reactor that permits the controlled and safe delivery of CO to the reaction solution particularly at the partial pressures necessary to overcome the reversibility of the radical carbynylation step.

### Aminocarbonylation of Aryl and Heteroaryl Halides

To initiate our study, we first examined the carbonylative amidation of methyl 4-iodobenzoate (1) (E^°(red) = -1.78 vs SCE) as...
a representative substrate for the aryl halides (Table 1). We elected to use morpholine as the amine coupling partner with triethylamine (TEA) as sacrificial reductant and the catalyst \([\text{Ir(ppy)}_2(\text{dtb-bpy})]\)PF$_6$ on the basis of previously established conditions for the reduction of aryl halides by the tandem photoredox system.\[^{14}\] A mixture of these reagents in acetonitrile was pumped through the gas–liquid reactor, enriched with CO at 35 bar, then irradiated inside the photoreactor with 54W blue LEDs. The photoreactor residence time was initially set to 5 min. The initial reaction conditions furnished the desired aminocarbonylation product 2a in 39% yield with incomplete consumption of the aryl halide (Table 1, entry 1).

Initial optimization of the reaction parameters with 1.05 equivalents of N,N-diisopropylethylamine (DIPEA), morpholine (2.0 equiv.), 35 bar CO gas pressure and 5 min residence time in the photoreactor furnished the amide 2a in 70% yield with quantitative conversion of the aryl halide (Table 1, entry 2). Competitive protodehalogenation was a secondary reaction pathway, with methyl benzoate accounting for the remainder of the mass balance. A reduction of the equivalents of DIPEA and morpholine was not markedly detrimental to yield (Table 1, entries 3–4). Attenuation of the CO pressure above 35 bar did not appreciably increase the yield of 2a (Table 1, entry 6) and pressure below 35 bar were detrimental to yield (Table 1, entry 5). An increased residence (t = 15 min) time gave optimal yields at 35 bar CO pressure (Table 1, entry 8). As expected, DIPEA, the Ir photocatalyst and blue light irradiation were essential for the transformation (Table 1, entry 8–10). Similarly, organophotoredox catalysts which are not expected to promote the generation a second highly reducing excite state equivalent to \([\text{Ir}^{2+}]^*\) were significantly less active (Supporting Information).

With the optimized reaction conditions in hand, we probed the reaction scope with respect to aryl halides (Table 2). Electron deficient aryl iodides and bromides afforded their corresponding amide products in good to excellent isolated yields (2a-11b). Aryl bromides and electron rich aryl halides required a slight increase in DIPEA (1.2 or 1.5 equiv.), morpholine (1.2 equiv.) and residence time (30 min) to achieve full conversion. To suppress protodehalogenation at elevated concentrations of DIPEA and morpholine, the CO pressure was raised to 45 bar. We rationalized that elevated pressures of CO would favor formation of the acyl radical instead of hydrogen atom abstraction by the aryl radical. 4-Bromoacetophenone did not furnish the amide functionalized acetophenone 4b, instead reduction of the carbonyl functional group was observed, with the amide functionalized α-methylbenzyl alcohol recovered as the isolated major product.

Significantly, aryl bromides could be selectively carbonylated in the presence of boronates (10), demonstrating exquisite orthogonality to Pd-catalyzed carbonylative amidation where the Suzuki coupling typically dominates.\[^{15}\] Deactivated substrates bearing electron donating substitution were well tolerated (12a-20) and steric sensitivity to ortho-methyl substituent was generally not observed (12-14). Under the developed reaction conditions, full conversion of the starting aryl halide was achieved for each example. Notably, when 4-bromothioanisole (E$_{\text{E}\text{nd}}$ = -2.54 V vs SCE) was subjected to the same reaction conditions using fac-[Ir(pppy)$_2$] in lieu of [Ir(ppy)$_2$(dtb-bpy)]PF$_6$, no conversion was observed. This ably demonstrates the greater potential of tandem

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### Table 1. Selected optimization and control experiments for the carbonylative amidation of aryl iodide 1 in flow

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sacrificial reductant</th>
<th>Morpholine (equiv.)</th>
<th>Residence time, t (min)</th>
<th>CO (bar)</th>
<th>Conv. (%)$^{[a]}$</th>
<th>Yield (%)$^{[a]}$</th>
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<tbody>
<tr>
<td>1</td>
<td>TEA (1.2 equiv.)</td>
<td>2.0</td>
<td>5</td>
<td>35</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>DIPEA (1.2 equiv.)</td>
<td>2.0</td>
<td>5</td>
<td>35</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (1.2 equiv.)</td>
<td>1.05</td>
<td>5</td>
<td>35</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA (1.05 equiv.)</td>
<td>1.05</td>
<td>5</td>
<td>35</td>
<td>89</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>DIPEA (1.05 equiv.)</td>
<td>1.05</td>
<td>5</td>
<td>25</td>
<td>88</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>DIPEA (1.05 equiv.)</td>
<td>1.05</td>
<td>5</td>
<td>50</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>DIPEA (1.05 equiv.)</td>
<td>1.05</td>
<td>15</td>
<td>35</td>
<td>&gt;99</td>
<td>79 (74)</td>
</tr>
</tbody>
</table>

**Deviation from entry 7**

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>No DIPEA</td>
<td>&lt;5</td>
<td>trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>No catalyst</td>
<td>&lt;5</td>
<td>trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>No light</td>
<td>0</td>
<td>n.d.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Determined by $^1$H NMR analysis with 1,3,5-trimethylbenzene as the internal standard. Isolated yields are given in parentheses.
visible light photoredox catalysis to engage energy demanding substrates beyond the capabilities of a conventional photoredox cycle. The reaction was extended to the ambient temperature amidation of methyl 4-chlorobenzoate which generated the amide (2c) in 27% yield. Although sluggish via this method, the carbonylation of aryl chlorides at ambient temperature via conventional transition metal catalysis has not been realized due to the high energy barrier for oxidative addition of the transition metal catalyst to aryl chloride. We are currently investigating conditions to accelerate the reduction of aryl chlorides using tandem photoredox catalysis. Notably, the method was compatible with electron-rich and deficient heteroaryl halides (21a-22).

We next examined the generality of amines in the carbonylative amidation of bromobenzene (Table 2). The method afforded the corresponding aryl amide products in good to excellent yield (55 - 79%) with a strong preference for secondary aliphatic cyclic amines (11b, 24-25) and secondary acyclic amines (26). Primary aliphatic amines were tolerated (27-30) although an increase of equivalents of n-hexyl amine and tert-butyl amine (27, 29) was necessary to achieve full conversion. Allyl amine, containing a terminal alkene that is susceptible to radical addition by aryl (21) and alkyl (22) radical, gave 31 without unwanted substitution or polymerization by-products. The developed reaction was further applied to a radical addition/aminocarbonylation cascade reaction. The bis-carbonylated α-keto amide 23 was the dominant reaction product. Synthetic access to the methylene α-keto amide motif is not readily accessible by Pd-catalyzed carbonylative methodology owing to the uncontrollable generation of carbonylated by-products. Finally, we demonstrate the straightforward scalability of the method by processing 10 mmol of...
bromobenzene to afford 1.8 g of 2a in 72% isolated yield (see supplementary information).

Aminocarbonylation of Alkylhalides

We next turned our attention to the carbonylative amidation of alkyl iodides. For this study, we assembled a bespoke flow platform from commercially available components to demonstrate how non-specialist laboratories can access flow methodology as a strategy for photochemical carbonylation. The flow chemistry platform consists of a Knauer® Smartline pump (although any syringe or HPLC pump capable of high pressure handling can be deployed), an Upchurch® 6 port injection valve, a tube-in-tube gas/liquid reactor and bespoke flow photoreactor fabricated in our laboratory (Supplementary Fig S3 and Fig S4).

The method was re-optimized for the carbonylative amidation of alkyl iodides and the synthesis of cyclohexylamide (43) using iodocyclohexane (E°\text{red} = -2.15 V vs SCE)\textsuperscript{14} as a representative alkyl iodide substrate. In line with the aryl halides, we selected morpholine as the amine coupling partner, DIPEA as sacrificial reductant and the [Ir(ppy)\textsubscript{2}(dtb-bpy)]PF\textsubscript{6} photocatalyst. Optimization of the reaction parameters required 1.05 equivalents of DIPEA, 2 equivalents of the alkyl iodide, 15 bar CO gas pressure and 20 min residence time (in the photoreactor) to afford amide 43 in 96% yield (see supplementary information).

Next, we focused attention on the generality of the carbonylative amidation of alkyl iodides. As shown in Table 3,

Table 3: Scope of alkyl iodide and amines\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Alkyl iodides\textsuperscript{a}</th>
<th>Amine\textsuperscript{b}</th>
<th>R</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boc\textsuperscript{N}</td>
<td>N</td>
<td>R = O, Boc\textsuperscript{N}</td>
<td>43%</td>
</tr>
<tr>
<td>32%</td>
<td>33%</td>
<td>34%</td>
<td>36%</td>
</tr>
<tr>
<td>37%</td>
<td>38%</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>42%</td>
<td>43%</td>
<td>44%</td>
<td>45%</td>
</tr>
<tr>
<td>50%</td>
<td>51%</td>
<td>52%</td>
<td>53%</td>
</tr>
<tr>
<td>61%</td>
<td>62%</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>72%</td>
<td>73%</td>
<td>74%</td>
<td>75%</td>
</tr>
</tbody>
</table>

[a] Unless otherwise noted, reactions carried out with alkyl halide (2.0 equiv.), [Ir(ppy)\textsubscript{2}(dtb-bpy)]PF\textsubscript{6} (1 mol%), DIPEA (1.05 equiv.), amine (0.40 mmol), MeCN (4 mL), CO (15 bar), 14W blue LED irradiation, room temperature, 20 min photoreactor residence time. Isolated yields are given. a) Conditions for primary alkyl iodides: alkyl iodide (2.5 equiv.), DIPEA (3.0 equiv.), 40 min (4 mL reactor volume). b) DIPEA (3.0 equiv. for 60-75). c) MeOH/H\textsubscript{2}O (9:1) solvent system, DIPEA (3.0 equiv.), 0.05 M concentration, 40 min (4 mL reactor volume).
tertiary morpholinoamides are obtained in excellent yields for tertiary, secondary, and primary iodides. A notable feature of this method is the tolerance of primary alkyl iodides, which can be difficult to reduce via Pd catalyzed amidation of amides were obtained in 1:1 dr and orthogonality of the tandem photoredox reaction to Pd protodehalogenation under similar conditions. The desired product (Scheme 1) without erosion of yield. The standard conditions were used with two minor adjustments; the reactor volume was increased to 6 mL and a FlowIR® unit was used to monitor the reaction. The reaction was run continuously giving 5.17 g of the desired in 75% yield, based on steady state collection.

Mechanistic Studies
Experimental and theoretical approaches were utilized to study the reaction mechanism. Firstly, we probed the mechanism of the photocatalytic cycle with aryl halides. Control experiments established in the optimization studies support the operation of a photocatalytic process through dependence on the [Ir(ppy)2(dtbbpy)]PF6 photocatalyst and blue light irradiation (Table 1, entry 8-10). The control experiments further support the operation of a tandem photoredox cycle where the generation of the second excited-state [Ir2]red is dependent on the addition of a tertiary amine reductant with labile α-hydrogens (Supplementary, S4 Table A(ii)).

For a more detailed exploration of the mechanism, spectroscopic measurements of key intermediates were performed (Supplementary Fig S9 to S15). Spectroscopy experiments with LED irradiation (λ = 445 nm) of a solution containing 0.1 mM [Ir1]0 and 50 mM DIPEA resulted in the rapid formation of [Ir1]3+ (λabs = 530 nm)[14] followed by exponential decay and the concomitant increase in emission intensity attributable to [Ir2]red (λem = 510 nm)[14] and consonant with the characterization of [Ir2]red under similar reaction conditions (Scheme 2b(i)). When the measurements were repeated with the addition of methyl 4-iodobenzoate (1) (Ered = -1.78 V vs SCE), absorption or emission attributable to either intermediate was not observed, suggesting rapid oxidation of [Ir1]0 to [Ir1]3+ via electron transfer to methyl 4-iodobenzoate (Supplementary Fig S12 and S13). Substituting 1 for 4-bromothioanisole S4 (Ered = -2.54 vs SCE), formation of [Ir1]3+ was observed along with emission assigned to [Ir2]red, albeit with a significantly lower intensity as [Ir1]3+ is not quenched by the more difficult to reduce bromide substrate (Supplementary Fig S14 and S15). We further confirmed this interaction between 4-bromothioanisole (S4) and [Ir2]red using steady state emission quenching experiments (Supplementary Fig S17). In line with the aryl halides, spectroscopic measurements show that the addition of iodocyclohexane (Ered = -2.15 V vs SCE)[14] reduced the emission intensity of excited-state [Ir2]red (λem = 510 nm)[14] suggesting electron transfer to the alkyl iodide (Scheme 2b(ii)). Furthermore, absorption for [Ir1]3+ (λabs = 530 nm)[14] was observed concurrent to emission assigned to [Ir2]red, with the addition of iodocyclohexane and that evidences reduction from [Ir2]red and not directly from [Ir1]3+ (Scheme 2b(iii)). This electron transfer pathway was further confirmed by Stern-Volmer quenching studies of [Ir2]red with iodocyclohexane (Scheme 2b(iv)).

A plausible mechanism for the generation of aryl and alkyl radicals from organohalides by visible light tandem photoredox catalysis is shown in Scheme 2. Visible light excitation of [Ir1]0 generates excited-state [Ir1]red and reductive quenching with DIPEA generates the reductant [Ir1]2+ and DIPEA−. In the presence of energy demanding organohalides, electron transfer from [Ir1]2+ is thermodynamically unfavorable and hydrogen atom transfer (HAT) from DIPEA− to [Ir1]2+ dominates. The resulting HAT generates [Ir2]red containing a semi-saturated (dtb-bpy) ligand and initiates the second Ir photocatalytic cycle (Ir-B).
Scheme 2. a) Single electron reduction of aryl and alkyl halides by the tandem photoredox cycle of [(ppy)Ir(dbpy)]+.

b) Spectroscopic studies: (i) absorbance of [Ir1]0 and emission of [Ir2]0* in the absence of the organohalide quencher, monitored at 530 nm and at 510 nm, respectively. (ii) Emission of [Ir2]0* in the absence, and presence of iodocyclohexane. (iii) Absorbance of [Ir1]0 in the absence and presence of iodocyclohexane. (iv) Quenching experiments of [Ir2]0* by iodocyclohexane.

c) Plausible reaction pathways for conversion of the acyl radical into the amide product.

d) Mechanistic investigations: (i) DFT determination of the redox potential of aryl and alkyl acyl radicals. (ii) Control experiment with an alcohol nucleophile. (iii) DFT determination of reaction enthalpies for the radical chain propagation step.
Absorption of blue light by [Ir2]® produces the highly reducing excited state catalyst [Ir2]®*, which has a reduction potential (E°([Ir2]®*/[Ir2]®) = -3.00 to -1.70 V vs SCE), below [Ir1]®* and [Ir1]. The energy demanding organohalides are substantially reduced by [Ir2]®* via electron transfer to generate an aryl or alkyl radical and [Ir2]. The catalytic cycle is closed by the reduction of [Ir2]* by [Ir1]® or DIPEA* (via DIPEA*). Finally, [Ir1]®* may be regenerated following hydrogen atom transfer from [Ir2]* to acceptors such as aryl and alkyl radicals or the acyl radical (80). We next considered the fate of the acyl radicals which are converted to the product via three possible pathways (Scheme 2c). In Path A, single electron oxidation of the acyl radical by the oxidized photocatalyst [Ir2]* (E°([Ir2]*/*[Ir2]) = +0.88 V vs SCE) results in the formation of the electrophilic acylum ion 81.18a, 27 For aryl derived radicals, the calculated DFT (B3LYP/6-31+G(d,p)) oxidation potentials of the resulting acyl radical were estimated to be -0.11 to +0.36 V vs SCE (Supplementary Table S1) depending on substitution on the aromatic ring, suggesting electron transfer is thermodynamically favorable. Similarly, the DFT estimated oxidation potentials of aryl radicals is approximately 0.0 V vs SCE suggesting generation of acylum ion (81) from the alkyl iodoide is also favorable (Scheme 2c(i)). Subsequent reaction of the electrophilic acylum ion with the amine affords the amide. In Path B halogen atom abstraction by the acyl radical (80) to form an acyl halide11a128 is followed by nucleophilic addition of the amine. In Path A and B, the generation of an electrophilic acylum ion 81 or acyl halide (82) is necessary to promote nucleophilic addition of the amine. However, with the replacement of an amine with alcohol nucleophiles, low yields of the ester were observed for both aryl and alkyl halides (Scheme 2c(iii)). The insensitivity to alcohol nucleophiles suggests that paths A and B are not the dominant processes in this carbonylative amidation. A third mechanism, Path C proceeds via nucleophilic addition of the amine to the acyl radical giving the acyloxy radical 83 via amine-assisted intermolecular proton transfer.29 Formation of the acyl radical proceeds via oxidation of α-hydroxy radical (83) by the [Ir2]®* catalyst or by radical chain propagation. The oxidation potential of a series of hydroxybenzyl and hydroxyalkyl radical species (83) was estimated by DFT calculations (Supplementary Table S14) and the oxidation of these intermediates by [Ir2]®* catalyst is thermodynamically feasible. Ryu and co-workers have reported that hydroxybenzyl radical species (83) undergo radical chain propagation with the aryl iodides that is accompanied with a highly endothermic (ΔH = 12.6 kcal/mol) SET to the aryl halide.30 However, net amide formation is largely exothermic and predicted to be spontaneous (ΔH = -19.3 kcal/mol),30 demonstrating that formation of the strong amide bond is the driving force for this process. Within the context of alkyl halides, our DFT studies support spontaneous electron transfer from α-hydroxyalkyl radical (83) to the alkyl iodide (ΔG = -43 kcal/mol, ΔH = -42 kcal/mol; Scheme 2c (iii)). On the basis of these mechanistic studies reported herein, we assign formation of the amide product via the radical propagation sequence in Path C.

Conclusion

In summary, we have developed a new light-mediated protocol for the carbonylative amidation of energy demanding organohalides.

This transformation exploits the unique tandem photocatalytic cycle of [Ir(ppy)2(dbtt-bpy)]®, which enganges aryl bromides, iodides and chlorides as well alkyl iodides to generate aryl, heteroaryl and alkyl amides using carbon monoxide as C1 building block. The versatility of the method is demonstrated by compatibility with primary, secondary and tertiary amines in addition to high functional group tolerance, enabling the generation of synthetically useful and pharmaceutically relevant amides, and the late stage functionalization of complex biologically active compounds. The application of continuous flow processing affords an operational ease, safety and scalability suitable for integration in both academic and industrial laboratories.

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Keywords: photoredox • tandem photoredox • carbonylation • amides • flow chemistry

Twice the shine: A photoredox catalyzed radical carbonylative amidation of aryl, heteroaryl and alkyl halides has been developed. The tandem catalytic cycle of [Ir(ppy)$_2$(dtb-bpy)]$^+$ engages aryl bromides, iodides and chlorides as well as primary, secondary and tertiary alkyl iodides via a multiphoton initiated secondary catalytic cycle. In combination with continuous flow processing, the protocol furnishes diverse amides with mild reaction conditions.

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