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RESEARCH ARTICLE

Tandem Photoredox Catalysis: Enabling Carbonylative Amidation of Aryl and Alkylhalides

José A. Forni[a]¥, Nenad Micic[a]¥, Timothy U. Connell[b], Geethika Weragoda[c] and Anastasios Polyzos*[a],[c]

[a] Mr J. A. Forni, Mr N. Micic and Dr A. Polyzos
School of Chemistry
The University of Melbourne
Victoria 3010, Australia.
E-mail: anastasios.polyzos@unimelb.edu.au
[b] Dr T. U. Connell
School of Science,
RMIT University
Melbourne, Victoria 3000, Australia.
[c] Dr G. Weragoda and A. Polyzos
CSIRO Manufacturing
Research Way, Clayton Victoria 3168, Australia.

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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 $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ 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 pharmaceutical 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

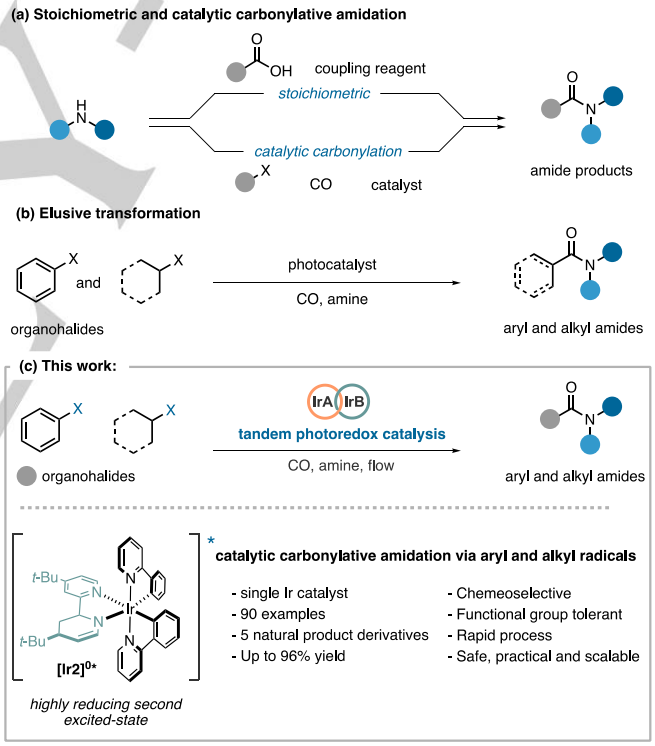


Figure 1. a) The classical generation of amide bonds via condensation reaction between a carboxylic acid, an amine and stoichiometric coupling agent (top) or a three-component transition metal catalyzed coupling of an organohalide, carbon monoxide (CO) and amine (bottom). b) A method for photocatalytic radical carbonylative amidation reaction of aryl *and* alkyl halides remains elusive. c) Our unified strategy for the carbonylative amidation of organohalides using tandem photoredox catalysis in continuous flow.

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

halides are incompatible owing to competitive beta-hydride elimination.[10]

Advances in radical protocols have addressed the limitations of transition metal catalyzed amidation.[11] 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 practicality of radical methods is impeded by hazardous reagents or high energy photochemistry.[11] To overcome these limitations, photoredox strategies have avoided reagents and conditions that complicate traditional radical chemistry.[12] However these are limited to alkyl substrates including alkyl iodides or alkyl organosilicates.[12] 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 (Figure 1b).

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.[13] Recently our group disclosed a method for the in-situ generation of a second highly reducing iridium photocatalyst from $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ via a 2-photon tandem photoredox cycle[14] (Figure 2a) and Nicewicz uncovered similar behaviour with organophotoredox catalysts.[15] This strategy has been successfully applied to the reductive protodehalogenation 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 1c). The tandem catalytic cycle of $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ 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 $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ $[Ir1]^+$ (Fig 2b). We envisioned that energy demanding organohalides could be engaged by the highly reducing second-excited $[Ir2]^{0*}$ ($E°([Ir2]^+/[Ir2]^{0*})$ -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.[16] The flow chemistry platform (Supplementary Fig S2) incorporates a tube-in-tube gas/liquid reactor[17] that permits the controlled and safe delivery of CO to the reaction solution,[18] particularly at the partial pressures necessary to overcome the reversibility of the radical carbonylation step.

Aminocarbonylation of Aryl and Heteroaryl Halides

To initiate our study, we first examined the carbonylative amidation of methyl 4-iodobenzoate (**1**) (E_p^{red} = -1.78 vs SCE) as

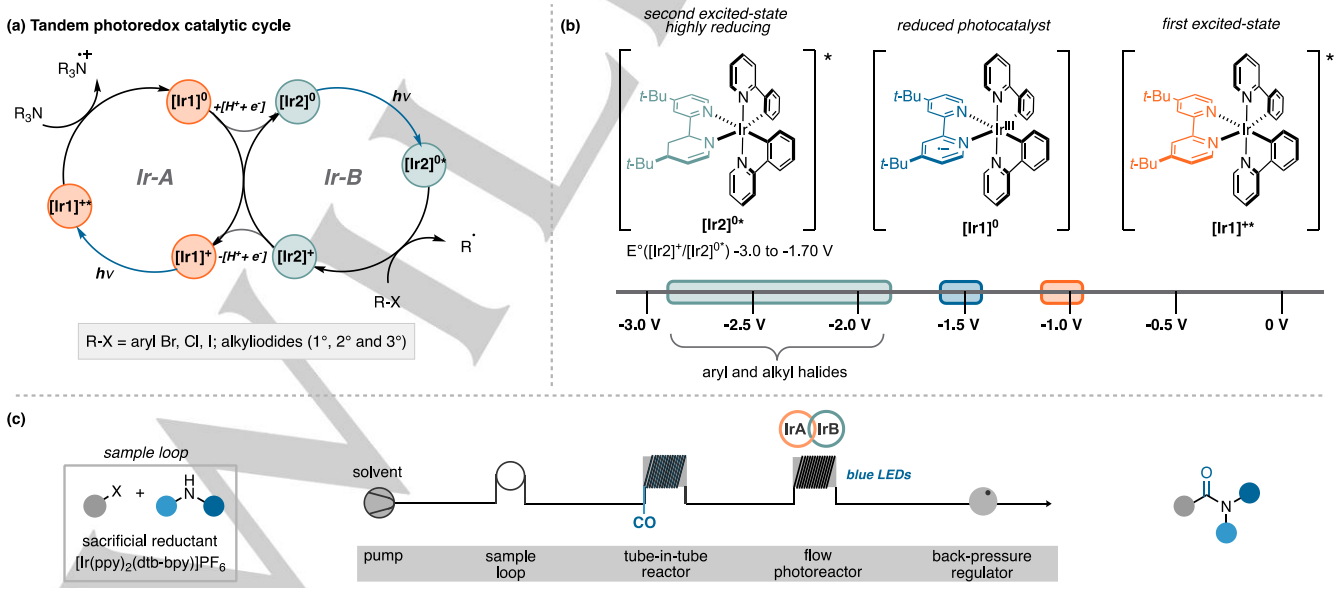
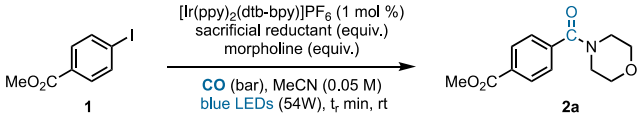


Figure 2. Design principle for the carbonylative amidation of aryl and alkyl halides. a) Tandem photoredox catalytic cycle of $[Ir(ppy)_2(dtb\text{-}bpy)]^+$; b) The highly reducing second excited state $[Ir2]^{0*}$; c) The flow chemistry platform.

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



Entry	Sacrificial reductant	Morpholine (equiv.)	Residence time, t_r (min)	CO (bar)	Conv. (%) [a]	Yield (%)[a]
1	TEA (1.2 equiv.)	2.0	5	35	50	39
2	DIPEA (1.2 equiv.)	2.0	5	35	97	70
3	DIPEA (1.2 equiv.)	1.05	5	35	92	71
4	DIPEA (1.05 equiv.)	1.05	5	35	89	74
5	DIPEA (1.05 equiv.)	1.05	5	25	88	55
6	DIPEA (1.05 equiv.)	1.05	5	50	90	75
7	DIPEA (1.05 equiv.)	1.05	15	35	>99	79 (74)
			Deviation from entry 7			
8		No DIPEA			<5	trace
9		No catalyst			<5	trace
10		No light			0	n.d.

[a] Determined by ^{1}H NMR analysis with 1,3,5-trimethylbenzene as the internal standard. Isolated yields are given in parentheses.

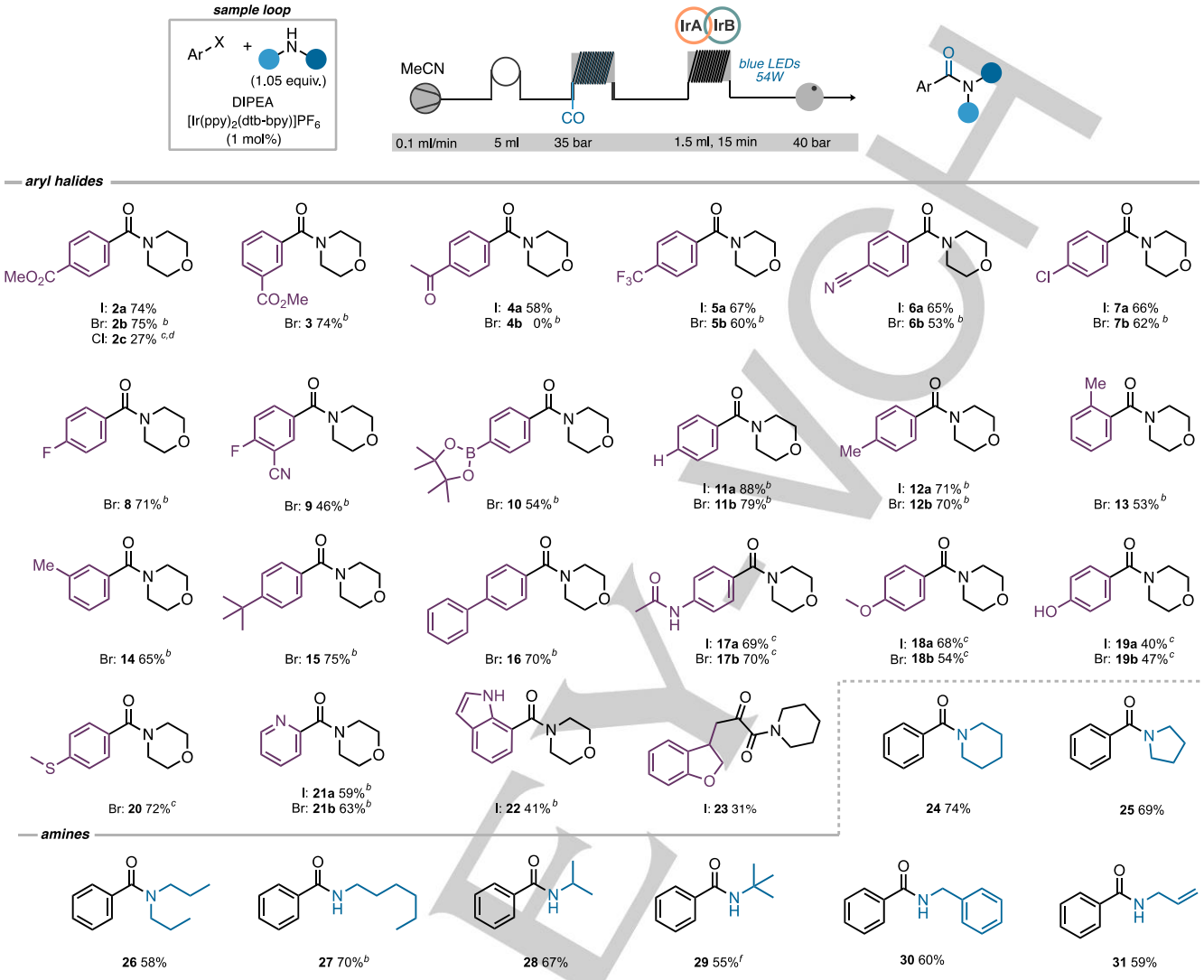
a representative substrate for the aryl halides (Table 1). We elected to use morpholine as the amine coupling partner with triethylamine (TEA) as sacrificial reductant and the catalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ on the basis of previously established conditions for the reduction of aryl halides 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_r = 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, organo-photoredox catalysts which are not expected to promote the generation a second highly reducing excite state equivalent to $[Ir2]^{0*}$ 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.[19] 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_p^{red} = -2.54 V vs SCE) was subjected to the same reaction conditions using *fac*-$Ir(ppy)_3$ *in lieu* of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, no conversion was observed. This ably demonstrates the greater potential of tandem

Table 2. Aryl halide and amine scope[a]



Aryl halides: [a] Unless otherwise noted, reactions carried out with aryl halide (0.25 mmol), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol %), DIPEA (1.05 equiv.), morpholine (1.05 equiv.), MeCN (5 mL), CO (35 bar), 54 W blue LED irradiation, room temperature, 15 min photoreactor residence time. Isolated yields are given. (b) DIPEA (1.2 equiv.), morpholine (1.2 equiv.), CO (45 bar). (c) DIPEA (1.5 equiv.), morpholine (1.2 equiv.), 30 min, CO (45 bar). (d) 43% conversion. Amines: (e) Unless otherwise noted, reactions carried out with bromobenzene (0.25 mmol), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol %), DIPEA (1.2 equiv.), amine (1.2 equiv.), MeCN (5 mL), CO (45 bar), 54 W blue LED irradiation, room temperature, 15 min photoreactor residence time. (f) amine (5.0 equiv.). Isolated yields are given.

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.[20] We are currently investigation 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] acyl radicals, 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.[23] Finally, we demonstrate the straightforward scalability of the method by processing 10 mmol of

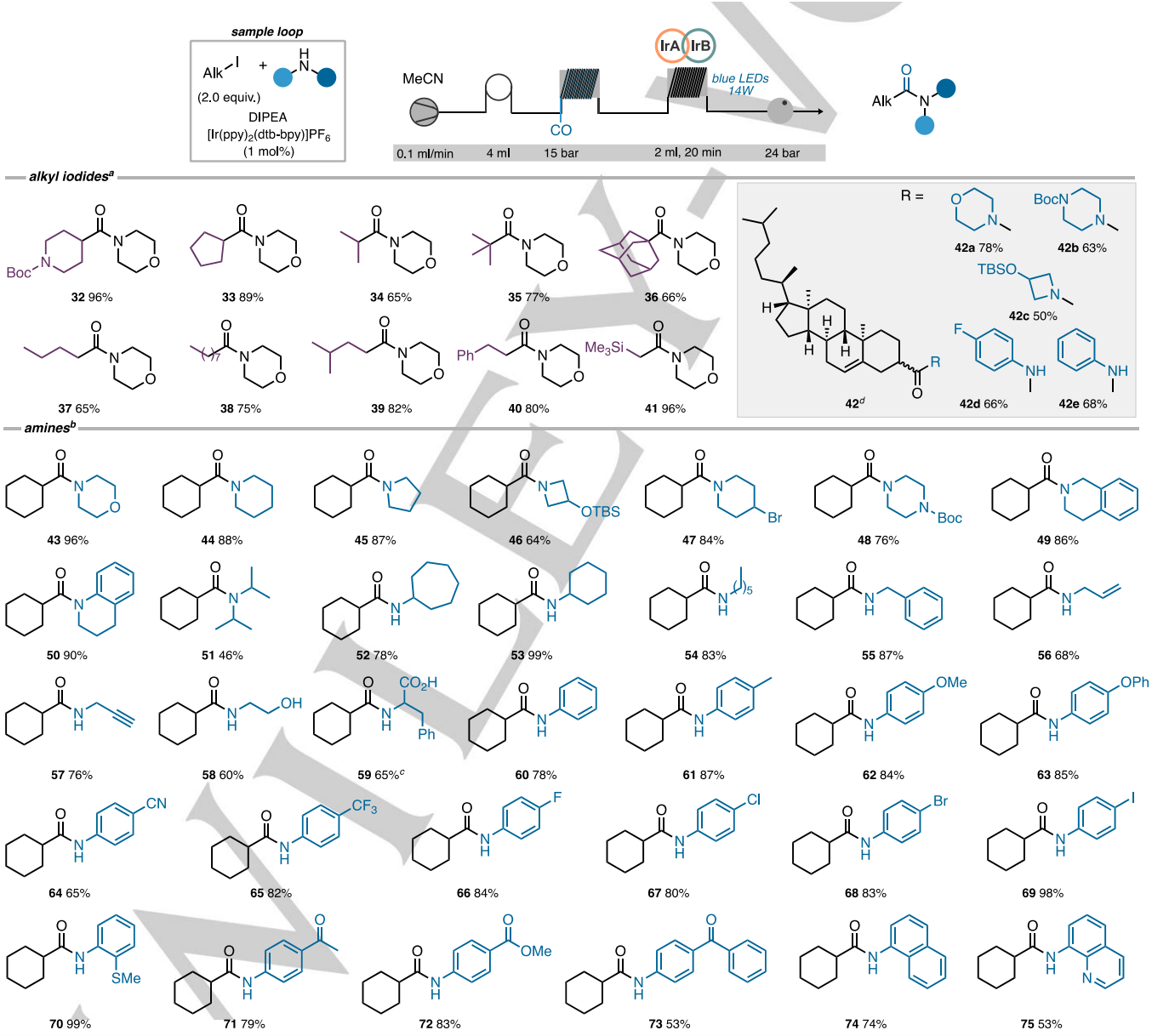
bromobenzene to afford 1.8 g of **2a** in 72% isolated yield (see supplementary information).

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 assembled 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_p^{red} = -2.15 V vs SCE)[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 $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ 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[a]

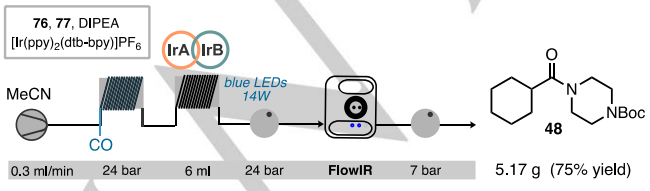


[a] Unless otherwise noted, reactions carried out with alkyl halide (2.0 equiv.), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol %), DIPEA (1.05 equiv.), amine (0.40 mmol), MeCN (4 mL), CO (15 bar), 14W blue LED irradiation, room temperature, 20 min photoreactor residence time. Isolated yields are given. a) Conditions for primary alkyl iodides: alkyl iodide (2.5 equiv.), DIPEA (3.0 equiv.), 40 min t_r (4 mL reactor volume). b) DIPEA (3.0 equiv. for 60-75). c) MeOH/H_2O (9:1) solvent system, DIPEA (3.0 equiv.). d) solvent: toluene/MeCN (3:2), DIPEA (1.05 equiv. for **42a**, **42** and **42c**; 3.0 equiv. for **42d** and **42e**), 0.05 M concentration, 40 min t_r (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 PET via conventional Ir photocatalysts owing to their negative redox potential ($E_{n\text{-}Bul}$ = -2.33 V vs SCE)[24] and the intrinsic reactivity between primary alkyl iodides and amines in a S_N2 reaction.[12a, 12b] Exceptional selectivity for carbonylative amidation of primary alkyl iodides is observed using this tandem photoredox method, affording the corresponding desired amide products in yields up to 96% (**41**). The compatibility of amines in this transformation was next investigated (Table 3). Firstly, a series of aliphatic amines were examined. Saturated cyclic secondary amines smoothly furnished the corresponding amides in excellent yield (**44**-**50**), although acyclic amines are sensitive to steric hinderance (**51**). Primary amines were all competent including amines appended to cyclic and acyclic hydrocarbons (**52**-**54**) as well as allylic, propargylic and benzylamines (**55**-**57**). Interestingly, ethanolamine afforded the amide (**58**) exclusively without competitive esterification. Furthermore, the amino acid derived amide (**59**) was furnished smoothly demonstrating the potential application in challenging carbonylative peptide synthesis.[12a]

The next phase of the study investigated the compatibility of anilines as the amine component. Optimal yields were obtained with an increased equivalent of DIPEA. In general, the yields were insensitive to the presence of electron withdrawing or donating substituents, however electron rich anilines marginally improved yield (**60**-**65**). The aryl amines with extended conjugation, 1-aminonaphthyl (**74**) and 8-aminoquinoline (**75**), were tolerated with the latter establishing a simple approach to access novel 8-aminoquinoline derivatives relevant to auxiliary directed C-H activation strategies.[25] Importantly, across all of these examples, the aryl and alkyl halides were reliably reduced by (**Ir2***) in the presence of other functional groups capable of undergoing single electron reduction. Notably, the halogenated substrates afforded the desired product (**66**-**69**) in excellent yields and with exceptional chemoselectivity despite propensity for protodehalogenation under similar conditions.[26] Importantly, the orthogonality of the tandem photoredox reaction to Pd-catalyzed carbonylative amidation is highlighted by the unreactivity of the halides for substrates (**66**-**69**).

A further demonstration of synthetic utility is demonstrated through the preparation of cholesterol amides (**42**) in good to excellent yields via the iodinated cholesterol (Table 3). The amides were obtained in 1:1 dr and **42c**-**e** were isolated as the enantiopure diastereoisomers following chromatographic purification. The operational simplicity and practicality of the method is exemplified through the scaled up carbonylative amidation of **48** (Scheme 1) without erosion of yield. The standard



Scheme 1: Reaction scale-up. Conditions: 1-Boc-piperazine **76** (0.1M) iodocyclohexane **77** (2 equiv.), DIPEA (1.05 equiv.), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol %).

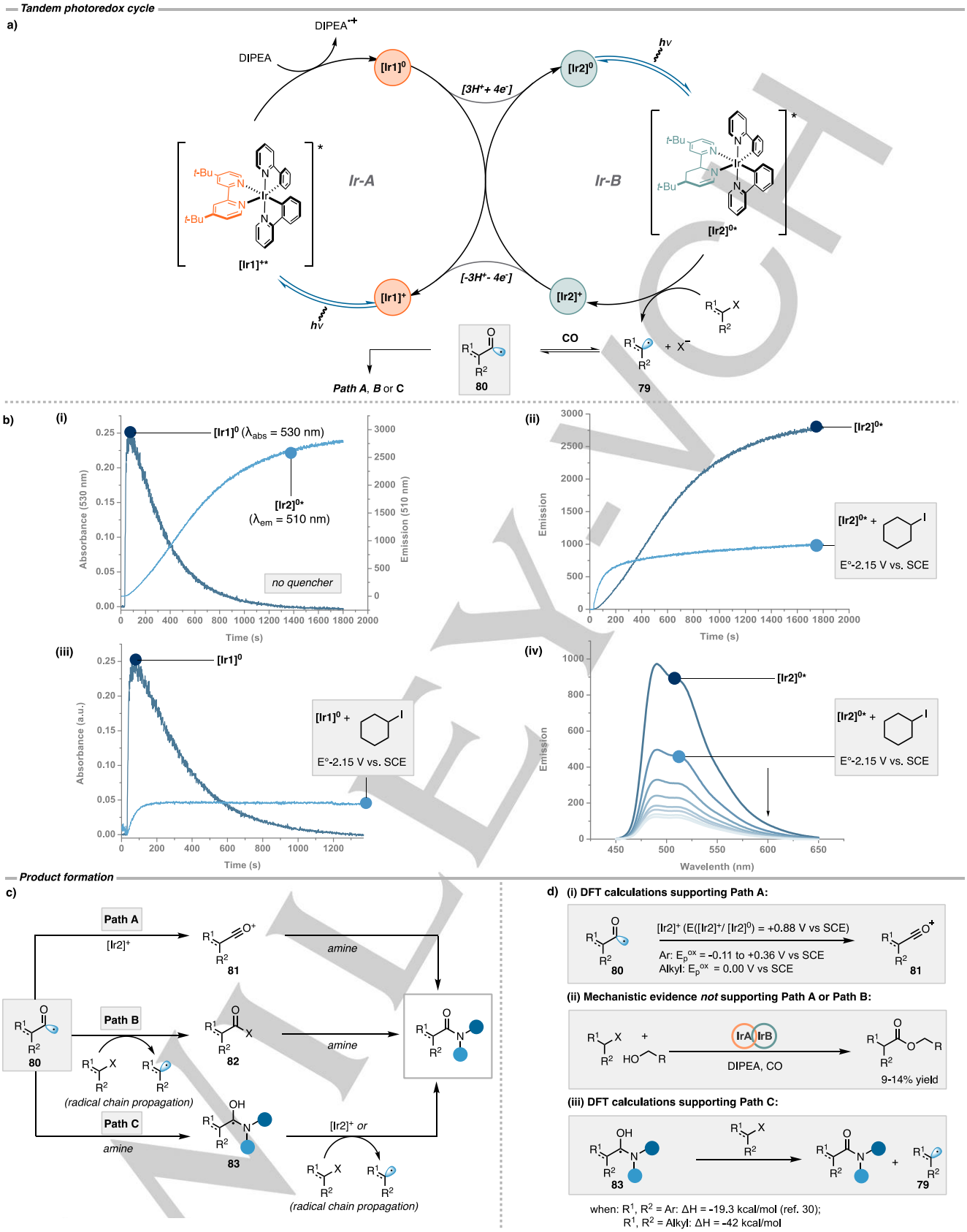
conditions were used with two minor adjustments; the reactor volume was increased to 6 mL and a FlowIR® unit was used to monitor the reaction. The reaction was run continuously giving 5.17 g of the desired in 75% yield, based on steady state collection.

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 $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ 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 $[Ir2]^{0*}$ is dependent on the addition of a tertiary amine reductant with labile α-hydrogens (Supplementary, S4 Table A(ii)).[14]

For a more detailed exploration of the mechanism, spectroscopic measurements of key intermediates were performed (Supplementary Fig S9 to S15). Spectroscopy measurements with LED irradiation (λ = 445 nm) of a solution containing 0.1 mM $[Ir1]^+$ and 50 mM DIPEA resulted in the rapid formation of $[Ir1]^0$ (λ_{abs} = 530 nm)[14] followed by exponential decay and the concomitant increase in emission intensity attributable to $[Ir2]^{0*}$ (λ_{em} = 510 nm)[14] and consonant with the characterization of $[Ir2]^{0*}$ under similar reaction conditions (Scheme 2b(i)). When the measurements were repeated with the addition of methyl 4-iodobenzoate (**1**) (E_p^{red} = -1.78 V vs SCE), absorption or emission attributable to either intermediate was not observed, suggesting rapid oxidation of $[Ir1]^0$ to $[Ir1]^+$ via electron transfer to methyl 4-iodobenzoate (Supplementary Fig S12 and S13). Substituting **1** for 4-bromothioanisole S4 (E_p^{red} = -2.54 vs SCE), formation of $[Ir1]^0$ was observed along with emission assigned to $[Ir2]^{0*}$, albeit with a significantly lower intensity as $[Ir1]^0$ 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 $[Ir2]^{0*}$ using steady state emission quenching experiments (Supplementary Fig S17). In line with the aryl halides, spectroscopic measurements show that the addition of iodocyclohexane (E_p^{red} = -2.15 V vs SCE)[14] reduced the emission intensity of excited-state $[Ir2]^{0*}$ (λ_{em} = 510 nm)[14] suggesting electron transfer to the alkyl iodide (Scheme 2b(ii)). Furthermore, absorption for $[Ir1]^0$ (λ_{abs} = 530 nm)[14] was observed concurrent to emission assigned to $[Ir2]^{0*}$, with the addition of iodocyclohexane and that evidences reduction from $[Ir2]^{0*}$ and not directly from $[Ir1]^0$ (Scheme 2b(iii)). This electron transfer pathway was further confirmed by Stern-Volmer quenching studies of $[Ir2]^{0*}$ 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 $[Ir1]^+$ generates excited-state $[Ir1]^{+*}$ and reductive quenching with DIPEA generates the reductant $[Ir1]^0$ and $DIPEA^{\bullet+}$. In the presence of energy demanding organohalides, electron transfer from $[Ir1]^0$ is thermodynamically unfavorable and hydrogen atom transfer (HAT) from $DIPEA^{\bullet+}$ to $[Ir1]^0$ dominates. The resulting HAT generates $[Ir2]^0$ 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 $[Ir(ppy)_2(dtb\text{-}ppy)]^+$. 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 $[Ir2]^0$ produces the highly reducing excited state catalyst $[Ir2]^{0*}$, which has a reduction potential ($E°([Ir2]^+/ [Ir2]^{0*})$ = -3.00 to -1.70 V vs SCE), below $[Ir1]^{+*}$ and $[Ir1]^+$. The energy demanding organohalides are subsequently reduced by $[Ir2]^{0*}$ via electron transfer to generate an aryl or alkyl radical and $[Ir2]^0$. The catalytic cycle is closed by the reduction of $[Ir2]^+$ by $[Ir1]^0$ or DIPEA$^{\bullet}$ (via DIPEA$^{\bullet+}$). 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 $[Ir2]^+$ ($E_{½}([Ir2]^+/ [Ir2]^0)$ = +0.88 V vs SCE) results in the formation of the electrophilic acylium ion **81**.[18a, 27] For arene derived radicals, the calculated DFT (B3LYP/6-311+G(g,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 alkyl acyl radicals is approximately 0.0 V vs SCE suggesting generation of acylium ion (**81**) from the alkyl iodides is also favorable (Scheme 2c(i)). Subsequent reaction of the electrophilic acylium ion with the amine affords the amide. In Path B halogen atom abstraction by the acyl radical (**80**) to form an acyl halide[11a],[28] is followed by nucleophilic addition of the amine. In path A and B, the generation of an electrophilic acylium 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 2 c(ii)). 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 α-hydroxy radical **83** via amine-assisted intermolecular proton transfer.[29] Formation of the amide 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 2 c(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 $[Ir(ppy)_2(dtb\text{-}bpy)]^+$, which engages 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

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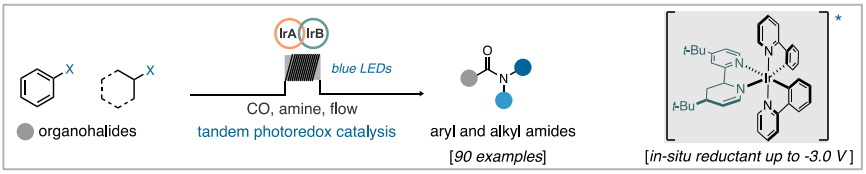

Twice the shine: A photoredox catalyzed radical carbonylative amidation of aryl, heteroaryl and alkyl halides has been developed. The tandem catalytic cycle of $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ engages aryl bromides, iodides and chlorides as well as primary, secondary and tertiary alkyl iodides via a multiphoton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

Institute and/or researcher Twitter usernames: @PolyzosLab

Author/s:
Forni, JA;Micic, N;Connell, TU;Weragoda, G;Polyzos, A

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