Photoredox α -arylation of carbonyl compounds

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Abstract

The direct α -arylation of unactivated carbonyl compounds using aryl halides represents a powerful method to synthesize critical building blocks for diverse useful compounds. Numerous synthetic methods exist to forge C(sp²)-C(sp³) bonds, albeit metal free direct α -arylation of unactivated cyclic ketones has long been an elusive transformation. Herein, we report a green-light-mediated α -arylation of unactivated ketones from readily-available aryl halides via activation of a C(sp²)-X bond (X=I, Br, Cl) and an α -carbonyl C(sp³)-H bond in a single photocatalytic cycle. This approach is characterized by its mild reaction conditions, operational simplicity, and wide functional group tolerance. Importantly, the impressive outcome from multi-gram photocatalytic reaction underpins the strength of this method as a potentially practical and attractive approach for scale-up industrial purposes. The utility and scope of this reaction were further demonstrated by new syntheses of several feedstock chemicals that are commercially expensive but critical for synthesizing numerous pharmaceutical agents.

Introduction

Functionalization of C(sp³)-H bonds has evolved as a fundamental principle that underpins both academic and industrial importance in conceptualization and actualization of challenging organic

transformations¹. This ubiquitous but relatively inert bond, if converted to the more valuable C-C bond, can greatly accelerate the construction of molecules that are highly sought after in biomedical enterprises^{2,3}. Incorporation of aryl substituents at the α -position of carbonyl compounds is a powerful and attractive method to construct a C(sp²)-C(sp³) bond; and its coupling products, especially α -aryl cyclic ketones are significant structural motifs that are often encountered in biologically significant natural and pharmaceutical products (Fig. **1A**)⁴. A number of classical stoichiometric transformations have been developed for such a key transformation but many suffer from complications in scale-up, due to either a requirement for highly activated aryl halides, the use of stoichiometric amounts of toxic reagents or harsh reaction conditions (Fig. **1B**)⁵. Significant efforts have been directed towards the development of alternative synthetic routes for this important scaffold. With advances in metal-catalyzed transformations, palladium-catalyzed α -arylations of carbonyl compounds emerged as the most promising approach (Fig. **1B**). Extensive contributions to this reaction by Buchwald, Hartwig and Miura have made this approach one of the most attractive to date⁶⁻⁹. However, the high cost of transition metal catalysts and additives, as well as removal of trace metal moieties detract from the utility of this approach in the synthesis of pharmaceutical applications in particular. Given the profuse number of bioactive molecules containing such privileged scaffolds, a fresh but inexpensive, metal free, industry viable and environmentally benign synthetic approach is highly sought after.

Over the past several decades, visible light photoredox catalysis promises to be a powerful, clean and sustainable synthetic method in organic synthesis¹⁰. Accordingly, photoinduced electron transfer (PET) has emerged as an impressive technique to access previously inaccessible substrates, thereby fostering the use of abundant and inexpensive starting materials¹¹. Along with its advancement, numerous elegant visible-light-induced activation of the challenging C(sp²)-X

bond (X=I, Br, Cl) in aryl halides have been reported¹²⁻¹⁵. Concurrently, pioneering work of Nicewicz and Macmillan to activate the C-H bond α to aldehydes incepted the prospect of photoredox α -arylation of carbonyls¹⁶. Therefore, formation of α -arylated carbonyl compounds via a visible-light-mediated process using benchtop carbonyls and aryl halides appeared to be an appealing target. Notably, Macmillan and colleagues have demonstrated impressive progress in α -carbonyl functionalizations where aldehydes were mostly exemplified. However, so far α -arylation has only been accomplished with activated ketones such as α -chlorocarbonyls and α -phenylselenylketones (Fig. 1B)¹⁷⁻²². Despite the noteworthy advancements in photocatalysis to activate C(sp²)-X bonds and α -carbonyl C-H bonds, photoredox α -arylation of carbonyls using aryl halides and unactivated ketones remains elusive.

We envisioned that an organic photocatalyst that could activate both the challenging α -carbonyl C-H bond and C(sp²)-X bond in a single photocatalytic cycle resulting in a C-C bond union would be a synthetic transformation of broad interest. To that end, we have synthesized a new family of green light absorbing acridinium ions with a photoredox window wide enough to access both the C(sp²)-X bond of aryl halides and the α -carbonyl C-H bond in unactivated cyclic ketones. These newly developed acridinium ions are organic photocatalyst that can act as a photo-reductant involving an oxidative quenching process, which is rarely documented for the current existing acridinium photocatalyst families²³⁻²⁵. Herein, we report a new green-light-mediated acridinium-catalyzed direct α -arylation of unactivated ketones with aryl halides for the synthesis of α -aryl carbonyl compounds under mild reaction conditions (Fig. 1C). Furthermore, green light in the visible region is relatively low in energy and has better penetrability in reaction media promising smoother transition to scale-up reactions²⁶. Considering the ubiquity of α -aryl cyclocarbonyl structures as components of, and intermediates en route to bioactive and pharmaceutical

molecules, we envisaged this catalytic metal free method would be an attractive option for streamlining synthesis of pharmaceutical intermediates from abundantly available and inexpensive starting materials (Fig. 1D).

Fig.1 | Photoredox activation for the α -arylation of unactivated cyclic ketones. (A) Important bioactive natural products and drug molecules containing α -arylated cyclic ketone core. (B) Existing synthetic approaches for the α -arylation of cyclic ketones. (C) This work: direct photoredox α -arylation of unactivated cyclic ketones using novel green light acridinium as the photocatalyst. (D) Generation of complex value-added compounds from abundant feedstock.

Recently, acridinium ions (*e.g.*, 9-mesityl-10-methylacridinium) have been shown to be a powerful organic photocatalyst and their potential has been demonstrated in catalyzing a wide range of transformations under visible light²⁵. However, in most cases, they serve as photooxidants through reductive quenching processes, while only few examples of their use as photoreduction catalysts have been reported²³⁻²⁵. Based on our previous work on helicenium ion as photocatalyst, as well as recent reports on the structure/property relationship of acridinium ions, we deduced that introducing electron-donating groups in the *para* position of the aryl groups of tetramethoxy acridinium ions would promote their photoreductive ability^{23-25,27-28}. Thus, we report the synthesis of a series of electron-rich acridinium ions (**Acr 6-8**) from 1,3,5-trimethoxybenzene in only three steps (Fig. 2A).

Results and discussion

All three acridinium ions have been fully characterized, and the data for **Acr 7** are shown in Fig. 2 while the data for **Acr 6** and **Acr 8** are described in the supporting information. The structure of **Acr 7** has been unambiguously confirmed by its X-ray crystallographic analysis (Fig. 2B, CCDC 2085196, see the Supporting Information). Additionally, the UV-Vis absorption spectra of **Acr 6-8** showed a red shifted maximum absorption to the green light region ($\lambda_{\text{max}} = 494 \text{ nm}$) compared to reported acridinium ions (Fig. 2C and Fig. S1)²³⁻²⁵. Furthermore, electrochemical studies revealed a reversible reduction event at -1.28 V vs the saturated calomel electrode (SCE) on their cyclic voltammetric (CV) curves, with an additional reversible oxidation event at +0.58 V (Fig. 2D and Fig. S2), which renders our assumption of applying them in photoreduction catalysis involving oxidative quenching process feasible in theory. Based on the reported literature protocol¹¹, we calculated that the estimated excited-state oxidation ($E_{1/2}(\text{C}^{*+}/\text{C}^{++})$) and reduction

potential ($E_{1/2}$ (C^{+*}/C^*)) for this acridinium series, which are at -1.85 V and +1.15 V vs. SCE, respectively (Supplementary table 1, see details in the Supporting Information).

Fig.2 | Development of the photoreducing acridiniums. (A) Three step synthetic route to acridiniums. (B) Molecular structure of **Acr 7**, hydrogen atoms are omitted for clarity. (C) Photophysical properties of **Acr 7**. (D) Cyclic voltammogram of **Acr 7**, only the reversible events are shown for clarity. (E) Lifetime spectrum of **Acr 7**.

Notably, the different pendant arms within this system "Pr for **Acr 6**, (CH₂)₂Py for **Acr 7**, and (CH₂)₂NMe₂ for **Acr 8** have very little influence on their electrochemical properties. Moreover, the excited-state lifetime (Fig. 2E and Fig. S3, $\tau = 3.85$, 4.10, 2.65 ns for **Acr 6**, **7** and **8**,

respectively) is also comparable to the values of other common organic photocatalysts (2–20 ns in general)¹¹. Therefore, we envisioned that **Acr 6-8** should be able to reduce the aryl halides with the reduction potential <-1.85 V vs SCE to generate the corresponding aryl radicals through oxidative quenching under visible light. As enamines can show very low oxidation potentials ($\sim+0.5$ V vs SCE) and can be generated *in situ* by reacting cyclic ketone with secondary amine, we hypothesized that the oxidative quenching process of **Acr 6-8** ($E_{1/2}(C^{*++}/C^+) = +0.58$ V vs SCE) is compatible with enamines²⁹. Therefore, **Acr 6-8** acridinium family should be competent to act as an efficient organic photocatalyst for catalyzing the direct α -arylation of cyclic ketones with aryl halides in the presence of a secondary amine under green light, which allows for a general and practical access to α -aryl carbonyl compounds under mild conditions.

Reaction optimization. Towards the development of this photocatalytic reaction protocol, we focused our initial investigations on 4-iodobenzonitrile **9** and cyclohexanone **10** (Fig. 3A). The initial reaction attempt proceeded smoothly in acetonitrile (MeCN) under green light ($\lambda_{\text{max}} = 518$ nm) in presence of **Acr 7** (5 mol%) by using pyrrolidine **14** to generate the enamine *in situ*, which afforded the desired product **11** in 70% NMR yield. Running the reaction under blue ($\lambda_{\text{max}} = 467$ nm) or white light (23 W) produced **11** in 70% and 60% NMR yield, respectively (Fig. 3B). Thus, the follow-up optimizations were conducted under green light ($\lambda_{\text{max}} = 518$ nm), which also has a relatively low energy and higher penetration depth. The investigation of various amines showed that the reaction with pyrrolidine **14** resulted in the highest NMR yield (75%) among the different cyclic and acyclic secondary amines evaluated (Fig. 3B). Thus, **14** was chosen as the amine for further optimizations. Evaluation of catalyst loading of **Acr 7** informed us that 0.2 mol% and 0.5 mol% both yielded **11** in 75% NMR yield (Fig. 3C). Employing **Acr 6** or **8** as the photocatalyst demonstrated similar outcomes compared to **Acr 7**, which is not surprising since all the three

acridiniums share almost indistinguishable photophysical and electrochemical properties. It should be noted that, some dehalogenated product was observed as byproduct in the crude ^1H NMR spectra, which decreased with lower catalyst loading improving the overall yield for the desired α -arylated product (Supplementary table 2). Thus, employing MeCN as solvent, pyrrolidine **14** as the amine, 0.2 mol% **Acr 7** as the photocatalyst, and green light ($\lambda_{\text{max}} = 518 \text{ nm}$) as the light source are the optimized reaction conditions.

Fig.3 | Realization of a photocatalytic α -arylation of unactivated ketones. (A) Optimization reaction with different light sources, amines and photocatalysts. (B) Crystal structure of the α -arylated ketone product **11**. (C) Comparison of light sources and amines. (D) Evaluation and optimization of the photocatalysts for the photoredox α -arylation of cyclic ketones. Yields are calculated from crude ^1H NMR spectra using 1,3,5-trimethoxy benzene as internal standard. ¹Reactions were run with 5 equiv pyrrolidine and 0.2 mol% **Acr 7**. ²Reactions were run with 5 equiv of amine and 0.2 mol% **Acr 7** under 518 nm green light. ³Reactions were run with 5 equiv pyrrolidine under 518 nm green light. LED, light emitting diode. More detailed reaction optimizations can be found in the supporting information.

Aryl halide scope. With optimized conditions identified, we set out to explore the scope of this new green-light-mediated direct α -arylation protocol. Using cyclohexanone as the model ketone substrate, different aryl halides were investigated. As shown in Fig. 4A, a range of diversely substituted aryl iodides were found to be excellent substrates and were successfully converted into their corresponding α -arylcyclohexanone products. Diverse 4-aryl substituents were well tolerated (**21** to **28**, 57 to 70% yield), as was parent iodobenzene (**29**, 61% yield). Heteroaryl iodides also performed well, smoothly furnishing the desired α -arylated products with different heteroaromatic rings such as pyridine (**30** and **31**, 57 and 74% yield), indole (**32**, 62% yield) and thiophene (**33**, 45% yield). Additionally, aryl bromides bearing a variety of functional groups such as cyano (**11**, X = Br, 56% yield), ester (**21**, X = Br, 51% yield), ketone (**25** and **34**, X = Br, 40% and 50% yield), and 9-phenanthrene (**35**, 33% yield) were well-tolerated, giving rise to the expected α -aryl ketones, albeit in slightly lower yields compared to aryl iodides. Moreover, we also evaluated the competence of 4-chlorobenzophenone. The corresponding α -arylcyclohexanone was indeed formed although in low yield (**34**, X = Cl, 27% yield), presumably due to the stronger bond dissociation energy of the C(sp²)-Cl bond (C(sp²)-Cl > C(sp²)-Br > C(sp²)-I)³⁰. Nevertheless, the utility of this method was further strengthened by three complex chiral aryl iodide substrates that have been synthesized from (+)- α -tocopherol, (-)-menthol, and (-)-borneol accordingly. These aryl iodides from natural products were demonstrated to be excellent substrates for this protocol (**36** to **38**, 66 to 70% yield). It is noteworthy to mention that a wide range of useful functional groups including cyano (**11**), ester (**21**), halide (**22**, **23**), ketone (**25**, **34**), tosylamine (**26**), amide (**27**) and carboxylic acid (**28**) proved to be compatible with this reaction manifesting the versatility and practicability of this photoredox protocol.

Fig. 4 | Reaction scope of photocatalytic α-arylation of unactivated ketones. (A) Substrate scope of aryl halides, isolated yield. (B) Substrate scope of ketones, isolated yield. ¹2 mol% Acr 7 was used. ²Reaction was run in 50 °C. See supplementary materials for specific reaction details. Et, ethyl; Ts, *p*-toluenesulfonyl; Me, methyl; *t*-Bu, tertiary butyl.

Ketone scope. Next, we turned our attention to expand the ketone reaction scope. We evaluated a myriad of cyclohexanone derivatives with 4-iodobenzonitrile as the aryl halide. Cyclohexanones with different electron-donating or electron-withdrawing groups at 4-position performed well, smoothly furnishing the corresponding α -aryl cyclic ketone with a useful *cis*-diastereocontrol (**39** to **43**; 64% to 81% yield with 6.5:1 to 9:1 d.r.). Additionally, disubstitutions at the 4-position such as *gem*-dimethyl (**44**; 64% yield) and ketal (**45**; 62% yield) were also well tolerated. However, elevated temperature (50 °C) was required to synthesize **45**, presumably due to the slow formation of intermediate enamine at room temperature³¹. The reactions for these 4-substituted cyclohexanones were performed with 2 mol% catalyst loading which afforded the products in higher yields. Interestingly, 2-methyl cyclohexanone formed the desired α -arylated product with excellent *cis*-diastereoselectivity, albeit in a compromised yield possibly due to steric effect (**46**; 32% yield, >20:1 d.r.). Moreover, when 3-methylcyclohexanone **48** was evaluated under optimal condition, two regio-isomeric products were isolated with good diastereoselectivity (**49** and **50**; 52% yield, 11.5:1 d.r. and 22% yield, >20:1 d.r.). Heterocyclic ketones such as tetrahydro-4H-thiopyran-4-one was also demonstrated to be compatible, affording the corresponding product in good yield (**47**; 65% yield). Finally, cyclopentanone also engaged productively with iodobenzene, 4-iodobenzotrifluoride (**51** and **52**; 62% and 63% yield), and even for sterically hindered aryl ester (**53**, 65% yield).

Synthetic applications. We envisioned to take advantage of the low energy green light, as it has better penetrability into the reaction media over blue light, by showcasing our method on a multigram scale²⁶. For this demonstration, we selected **11** as our target α -arylated ketone, a synthetic precursor for a selective β_3 -adrenergic agonist (Fig. **5A**)³². The synthesis of **11** from 4-iodobenzonitrile and cyclohexanone, on a 50 mmol scale under standard reaction conditions

resulted in near identical outcome as was observed for the 1 mmol scale reaction (**11**, 70% and 71% yield in 50 mmol and 1 mmol respectively). This example highlights the synthetic strength of this photoredox method to form α -arylated cyclocarbonyl in a single step from inexpensive, readily-accessible starting materials. Additionally, we synthesized the precursor for the cyclopentane variant of this same selective β_3 -adrenergic agonist in good yield (**55**, 72% yield, **Fig 5A**)³².

Inspired by the success of this scale up demonstration, we expanded the scope of this photocatalytic method in the formal syntheses of bioactive and drug molecules. We first evaluated streamlining a route to the naturally occurring alkaloid (+)-epibatidine that has garnered a lot of interest as an nAChR agonist (**Fig. 5B**)³³. Not surprisingly, multiple synthetic approaches have been reported^{34,35}. Nevertheless, the work of Aggarwal and colleagues stands out as one of the efficient ones due to their single step synthesis of α -arylated ketone precursor **58**³⁶. We synthesized the same scaffold using our new reaction conditions which delivered the product in similar yield (**58**, 75% yield). Next, we investigated ketamine, which is an FDA approved general anesthetic. Many of the published ketamine route proceed via the α -arylated cyclohexanone precursor **60**, which in most cases requires multiple steps to synthesize^{37,38}. We performed a gram scale reaction starting from readily available 2-iodochlorobenzene **59** and cyclohexanone **10**, which led to the isolation of the ketamine precursor in moderate yield (**60**, 51% yield, **Fig. 5B**). The simplistic nature of this reaction, efficiency and ease of operation were further confirmed through its application in the syntheses of two critical feedstock chemicals for clinical candidates (**Fig. 5C**). We employed 4-iodobenzotrifluoride **61** and cyclohexanone **10** using our standard reaction conditions, which furnished the target α -arylated ketone in good yield (**62**, 68% yield). Significantly, **62** is central to the synthesis of a family of CNS active molecules that are under study by Hoffmann La Roche^{39,40}.

Fig. 5 | Synthetic applications. (A) Large scale reaction demonstration. (B) Application to the synthesis of pharmaceutical intermediates for bioactive and drug molecules. (C) Target application examples using cheap feedstock.

Finally, 2-(4-fluorophenyl)cyclopentanone **64** was synthesized from benchtop reagents such as, 4-fluoriodobenzene **63** and cyclopentanone **54** following the same general method (**64**, 67% yield). It is a critical feedstock chemical to synthesize BMS-932481 a γ -secretase modulator that is also a clinical candidate for the treatment of Alzheimer's disease^{41,42}. Unsurprisingly, both of these privileged scaffolds **62** and **64** are commercially available, but are prohibitively expensive (**62**, \$623 per gram; **64**, \$628 per gram)⁴³⁻⁴⁸. Our green-light-mediated acridinium-catalyzed α -arylation to the cyclic ketones offers a new approach for expediently assembling value-added chemical scaffolds from abundant starting materials.

Mechanistic investigations. Subsequent efforts were directed towards understanding the mechanism of this new photoredox activated reaction (Fig. 6). Initial control experiments showed that in absence of a light source no reaction was observed (Supplementary Table 6). Furthermore, exclusion of either photocatalyst **Acr 7** or additive pyrrolidine **14** also failed to promote α -arylation of ketone (Fig. 6A). Since enamine is assumed to be generated *in situ* by the corresponding ketone and pyrrolidine **14**, we treated ethyl-4-iodobenzoate **65** with commercially available enamine 1-pyrrolidino-1-cyclohexene **66** under standard reaction condition (Fig. 6B left). The desired product **21** was isolated with 75% yield, which supports our hypothesis of the importance of the enamine intermediate. Meanwhile, we carried out the same experiment with 4-iodotoluene **67** instead of ethyl-4-iodobenzoate **65**. In this case, the desired α -arylated cyclohexanone product **68** was not observed (Fig. 6A right, 5% of dehalogenated byproduct was detected while rest of the starting material **67** remained intact). These results are in line with the reduction potential of **67** ($E_{\text{red}} = -2.12$ V vs SCE), which is beyond the reach of **Acr 7** ($E_{1/2}(\text{C}^{*+}/\text{C}^{+*}) = -1.85$ V vs. SCE), while the reduction potential of **65** ($E_{\text{red}} = -1.87$ V vs SCE) is a close match to the excited-state oxidation potential of **Acr 7**³⁰. This observation suggests the presence of a single electron transfer (SET) to

the aryl halide, via an oxidative quenching step. However, recent reports from Leonori and colleagues suggest that radical chain propagation pathway, initiated from halogen atom transfer (XAT) by an α -aminoalkyl radical formed during a reductive quenching step, is a viable mechanism^{14,49}. The involvement of such radical chain propagation mechanism cannot be ruled out at this point, despite the result from the alternating light/dark experiment that showed no activity in absence of light (Supplementary Fig. S4)⁵⁰. To further probe the mechanism, we attempted the photo-Arbuzov reaction with two different aryl halides (4-iodobenzonitrile **9** and 4-iodotoluene **67**), triethyl phosphite **69** and **Acr 7** under 518 nm green LED in absence of pyrrolidine and enamine (Fig. 6C). According to the work of König and colleagues, triethyl phosphite is a fast coupling partner for *in situ* formed aryl radical in photo-Arbuzov reaction⁵¹. In case of 4-iodobenzonitrile, 45% yield of the aryl-phosphite adduct **70** was observed, despite the lack of pyrrolidine or enamine, which substantiates the hypothesis of an aryl radical generation via single electron transfer (SET) from the excited state photocatalyst to the aryl halide. However, 10% tolyl-phosphite adduct **71** was also detected when 4-iodotoluene **67** was used. Since the reduction potential of **67** is no match to **Acr 7**, it can be assumed that the peripheral dimethyl amine groups on **Acr 7** can initiate XAT to some extent. From our understanding, these observations suggest that the SET and XAT mechanistic pathways can contribute to this transformation concurrently, with SET pathway being predominant with our photocatalyst **Acr 7** (Fig. S5 and S6).

Fig. 6 | Mechanistic insight of the photoredox α -arylation of ketone. (A) Control experiment in absence of pyrrolidine (left) and in absence of photocatalyst **Acr 7** (right). (B) Evaluation of excited state redox potentials of **Acr 7** with enamine and different aryl iodides. (C) Photo-arbuzov reaction to trap the aryl radical. (D) Proposed mechanistic pathway. See supplementary materials for specific reaction details. ¹Yield was calculated from ³¹P NMR spectroscopy.

Although the full mechanistic details of the α -arylation reaction remain to be elucidated, a prospective mechanism involving oxidative quenching is proposed based on the mechanistic insights gained and previous reports (Fig. **6D**). First, it is proposed that in presence of a green light source ($\lambda=518$ nm) the **Acr 7** accepts a photon to populate the excited state (**Acr 7***) as it has a strong absorption cross section in the green light region of the visible light spectrum. Given that, **Acr 7*** is a strong reductant [$E_{1/2}(\text{C}^{++}/\text{C}^{+*}) = -1.85$ V vs SCE in CH_3CN], we hypothesize that the high energy state intermediate would undergo single-electron transfer with the aryl halide **72** [$(E_{1/2}^{\text{red}}) \leq -1.85$ V vs SCE in CH_3CN] to afford the aryl radical **73** and the oxidized acridinium photocatalyst **Acr 7⁺**. Concurrent with this photoredox step, pyrrolidine **14** can condense with cyclic ketone substrate **74** to form the electron-rich enamine **75**. The electron deficient **Acr 7⁺** dication [$(E_{1/2}^{\text{red}}) = +0.58$ V vs SCE in CH_3CN] can readily accept an electron from the electron-rich enamine **74** [$(E_{1/2}^{\text{ox}}) \leq +0.58$ V vs SCE in CH_3CN] to generate the enaminy radical cation **76** and thereby completing the photoredox cycle. We hypothesize that, this enaminy radical cation **76**, or its resonance structure iminium radical cation, can undergo radical-radical coupling with the aryl radical species **73** to forge a new $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)$ bond. Upon hydrolysis of the iminium intermediate **77**, we can expect the regeneration of the ketone functional group via the removal of the amine to furnish the final desired product **78**.

Conclusion

In summary, a versatile acridinium family has been developed with a highly reducing nature under low energy green light. Potential utility of this acridinium family has been demonstrated by a newly developed photoredox protocol for α -arylation of unactivated ketones. The metal free photoredox α -arylation of ketones developed here is broad in scope and tolerant of variety of functional groups. The transformation is proven to be significantly powerful and clean on a multi-gram scale reaction.

Importantly, its utility was exemplified in the synthesis of several economically important building blocks for diverse array of bioactive and pharmaceutical agents. Given the versatility and operational simplicity of this approach, we expect that this method will provide a new but clean reaction platform to attain a sustainable and practical synthetic field.

Methods

General procedure for the synthesis of acridiniums (Acr 6-8). A 100 ml pressure vessel equipped with a magnetic stir bar was charged with compound **5** (1.0 mmol, 1.0 equiv) and corresponding primary amine (10.0 mmol, 10.0 equiv) in 10 mL pyridine. Then the vessel was tightly closed with a stopper and the solution was stirred for 24 h at 90 °C. The color of the reaction mixture changed from dark blue to orange-brown indicating the full consumption of compound **5**. Then the reaction mixture was allowed to cool to room temperature and added dropwise to excess Et₂O (500 ml) while stirring. Immediately, an orange precipitate was observed and filtered using gravity filtration. The orange solid was then recrystallized using slow evaporation in CH₂Cl₂/hexanes or MeCN/Et₂O. The title compound was obtained as fine crystals of green-orange color (88-91% overall yield).

General procedure for the photoredox α -arylation of cyclic ketone. Inside a N₂ glovebox, an oven-dried 10 mL schlenk flask equipped with a magnetic stir bar was charged with **Acr 7** (0.002 equiv or 0.02 equiv, 0.2 mol% or 2.0 mol%), corresponding aryl halide (1.0 equiv), corresponding ketone (5.0 equiv), pyrrolidine (5.0 equiv) and dry MeCN (0.1 M). Then the Schlenk flask was placed in a water bath approximately 5 cm away from a Kessil 518 nm Green LED lamp. After completion (6-72 h), the reaction mixture was evaporated under vacuum. To neutralize the crude reaction mixture 1.0 N HCl was added and then the aqueous layer was extracted by 3 portions of Et₂O. Combined organic layer was washed with brine, dried using Na₂SO₄, concentrated under

vacuum and purified by flash chromatography to afford the corresponding pure α -arylated ketone product.

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Author contribution

T.L.G. conceived the idea and supervised the work. M.H. performed the synthesis of Acr 6-8, their characterization and the catalytic reaction condition optimizations. M.H. and A.C.S. synthesized the starting materials, performed the catalytic transformations, and characterized the products formed. A.C.S. performed the life-time measurements, and M.H. performed the absorption and emission measurements. J.M. conducted the CV and XRD measurements. M.H. and T.L.G. prepared the manuscript for publication.

Data and materials availability

All data is available in the manuscript or the supplementary materials.

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