Organic Letters

Letter

Cite This: *Org. Lett.* 2019, 21, 3346−3351

pubs.acs.org/OrgLett

Deaminative Reductive Arylation Enabled by Nickel/Photoredox Dual Catalysis

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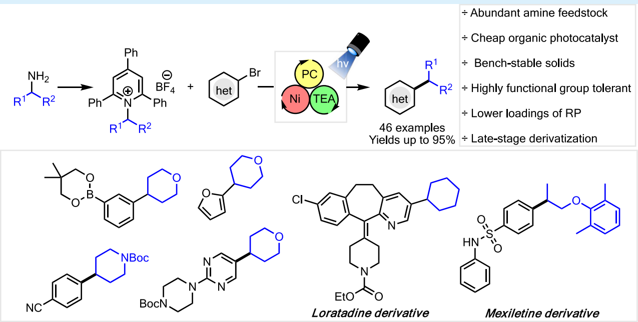
Supporting Information

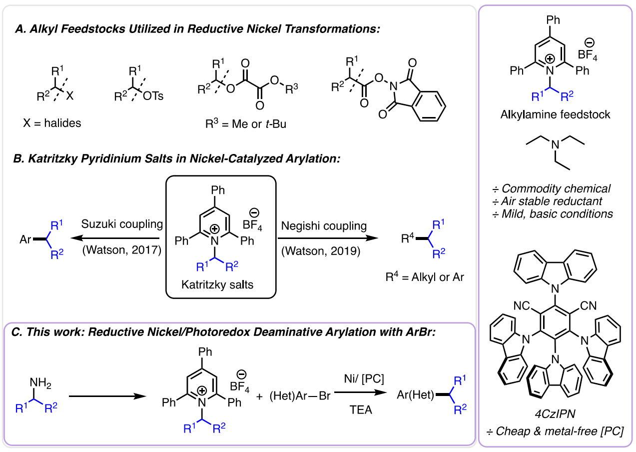
ABSTRACT: Described is a cross-electrophilic, deaminative coupling strategy harnessing Katritzky salts as a new species of electrophile in Ni/photoredox dual catalytic reductive cross-coupling reactions. Distinguishing features of this arylation protocol include its mild reaction conditions, high chemoselectivity, and adaptability to a variety of complex substrates [i.e., pyridinium salts derived from amines and partners derived from (hetero)aryl bromides].



Aliphatic primary amines are a privileged class of compounds prevalent in natural products, valued synthetic intermediates, and pharmaceutical drugs such as Tamiflu, Linagliptin, Amlodipine, and Sitagliptin.[1] In an elegant report, the Watson group recently demonstrated the use of Katritzky salts, formed via a simple condensation of the corresponding amines with a bench-stable, commercially available pyrylium salt, as alkyl radical precursors in cross-couplings with arylboronic acids.[2,3] Subsequently, Glorius, Aggarwal, Shi, Gryko, and Liu further demonstrated the utility of these redox-active amines in C−H arylation,[4] borylation,[5] alkynylation,[6] allylation,[7] and dicarbofunctionalization, respectively.[8] More recently, Watson and co-workers disclosed a deaminative alkyl−alkyl Negishi cross-coupling with alkylzinc halides.[9] The growing interest in this area highlights the challenges associated with C−N bond activation and presents new opportunities to address these limitations, in particular with regard to the development of cross-electrophilic, deaminative strategies to forge $C(sp^3)$-hybridized centers.

In recent years, nickel/photoredox dual catalysis has emerged as a powerful tool to construct C−C bonds via a single-electron transmetalation pathway.[10] In this context, the unique characteristics of this reaction manifold favor the formation of tetrahedral carbon centers without the need for harsh nucleophilic organometallic reagents or elevated temperature.[11] Given our and other groups'[12] longstanding interest in reductive nickel transformations and our deep understanding of photoredox catalysis,[13] we envisioned the application of Katritzky salts as a new species of alkyl radical precursors in a reductive, cross-electrophilic coupling with (hetero)aryl bromides, *representing one of the few synthetic methods employing a net reductive photoredox/Ni dual catalytic transformation* (Scheme 1).[14]

Scheme 1. Aliphatic Amines as Radical Precursors in Cross-Coupling

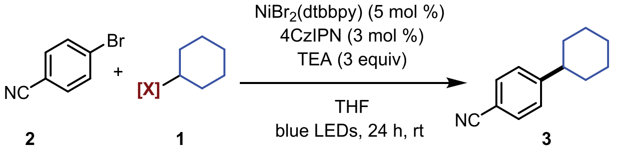


Given the accessible redox potential of Katritzky salts ($E_{1/2}$ = −0.93 V vs SCE),[7] the organic dye 4CzIPN (reduced photocatalyst $E_{1/2}$ = −1.21 V vs SCE) was examined and proved effective at delivering the desired coupled product (Table 1). Other photocatalysts were also tested (entries 2 and 3 in Table 1). Not surprisingly, $[Ir(dtbbpy)(ppy)_2]PF_6$

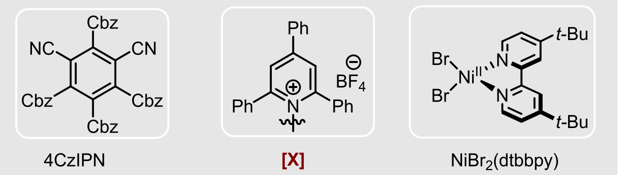
Received: March 28, 2019
Published: April 17, 2019

DOI: 10.1021/acs.orglett.9b01097
Org. Lett. 2019, 21, 3346−3351

Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	3 (%)[b]
1	**None**	**93 (86)**
2	[Ir{dF(CF$_3$)$_2$ppy}(dtbbpy)]PF$_6$	87
3	[Ir(dtbbpy)(ppy)$_2$]PF$_6$	99
4	3.0 equiv Hantzsch ester	33
5	CH$_3$CN	73
6	DMA	92
7	No light (dark)	0
8	No photocatalyst	0
9	No Ni catalyst	0
10	No amine	0



[a] **1** (0.45 mmol), **2** (0.3 mmol), 4CzIPN (3 mol %), and NiBr$_2$(dtbbpy) (5 mol %) in dry, degassed solvent (3.0 mL, 0.1 M) under blue LED irradiation for 24 h. [b] GCMS yield using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses.

provided quantitative conversion to the desired product, likely because of its strongly reductive nature ($E_{1/2}$ = −1.51 V vs SCE).[4,10b] Considering the low cost, ease of preparation, and excellent reactivity of 4CzIPN,[15] it was chosen as the photocatalyst of choice. Although DMA provided equally good results in this cross-coupling (entry 6 in Table 1), THF was chosen because of its low boiling point. However, it should be noted that the use of DMA for electron-rich substrates proved effective at times (see Supporting Information). As anticipated, control experiments proved that all components of the reaction were necessary for the dual catalytic system to proceed (entries 7−10). Finally, in an attempt to provide an easier reaction setup, the optimization was carried out using the precomplex NiBr$_2$·dtbbpy.

With suitable reaction conditions in hand, the scope of this deaminative cross-coupling was examined (Scheme 2). To this end, a wide array of aryl bromides bearing electron-withdrawing substituents at the *para*-position exhibited excellent reactivity (**3**−**10**, **16**). Electron-rich aryl bromides were also compatible substrates (**11** and **12**). Importantly, aryl bromides bearing an additional handle for further elaboration in Chan−Lam and Suzuki couplings, such as pinacol boronic ester (**17**) and aryl chlorides (**6** and **13**), reacted to afford the corresponding products in good yields.

Given the mildly basic conditions of this protocol, a variety of sensitive functional groups, including lactone **15** and sulfonamide **16**, were compatible structural motifs. Substitution at the *meta*-position (**13**, **15**, **17**, and **18**) and *ortho*-position (**14** and **18**) was explored, whereby efficient cross-coupling events took place. Moreover, electron-deficient difluoroaryl bromide **18** and several heteroaryl systems (**19**−**30** and **36**) were successfully employed. Because of their notoriously unstable nature as the corresponding boronic acids (owing to protodeboronation under strongly basic conditions),[16] the analogous substructural partners had provided sluggish reactivity in previous reports.[2]

Given their importance in pharmaceutical settings,[17] a variety of nitrogen-containing heteroaryl bromides, including pyrimidine (**20** and **26**), quinoline (**23**, **27**, and **28**), isoquinoline **24**, pyridine (**25** and **29**), and indole (**30**) electrophiles were effectively incorporated under this reaction manifold. It is worth highlighting that heteroaromatics (**23** and **24**), previously well-behaved under photoinduced deamination/C−H arylation conditions,[3] reacted in a chemoselective manner. This highlights the complementary advantages of this protocol to existing Minisci transformations.[4,18]

Next, attention was turned to the scope of the alkylpyridinium salts, where a wide array of functional groups were tolerated. Katritzky salts bearing a free hydroxyl group (**39** and **40**) did not inhibit the reaction, presenting orthogonal reactivity to C−O bond formation previously reported by MacMillan.[19] Other pyridinium salts bearing an ester handle (**41**) and nitrogen heterocyclic structural motifs (**33** and **34**) afforded the desired products in excellent yields. It is worth noting that both cyclic (**31**−**36**, **39**−**42**) and acyclic (**37**, **38**, **43**, and **44**) alkylpyridinium salts reacted efficiently under the reaction conditions.

Finally, to demonstrate the applicability of this protocol to the synthesis of bioactive molecules, we prepared the corresponding alkylpyridinium salt from Mexiletine, a voltage-gated sodium channel blocker used as an antiarrhythmic.[20] Utilizing two different aryl bromides, success was achieved at delivering the cross-coupled products **43** and **44** in excellent yields. Finally, a complex aryl bromide derived from Loratadine,[21] used in the treatment of allergies, was compatible under the reaction conditions (**45**).

To highlight the benefits of employing 4CzIPN as an inexpensive organic photocatalyst [~\$5 mmol^{-1}], a transformation was successfully performed on gram scale, whereby the desired heteroaryl coupled product **27** was obtained in 90% yield (Scheme 3).

By taking further advantage of the inherent chemoselectivity of this cross-coupling as described earlier, the quinoline scaffold of **27** was further elaborated at the C2 position to obtain **46** and **47** in good yields, utilizing Minisci-type photoinduced deaminative and decarboxylative strategies previously reported by Glorius and Dhar, respectively.[4,18c] The ease with which a wide array of aryl and heteroaryl systems can be fashioned showcases the significant potential of deaminative-based C−C bond construction in industrial settings.

To probe the reaction pathway, we conducted a series of mechanistic experiments. In the presence of the radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl], the arylation was completely inhibited, with full recovery of the aryl bromide (Scheme 4A). This is suggestive of the involvement of radical species under this metallaphotoredox manifold. This hypothesis was further corroborated by isolation of **48**, a byproduct likely formed via a radical−radical coupling of the persistent dihydropyridine radical intermediate

DOI: 10.1021/acs.orglett.9b01097
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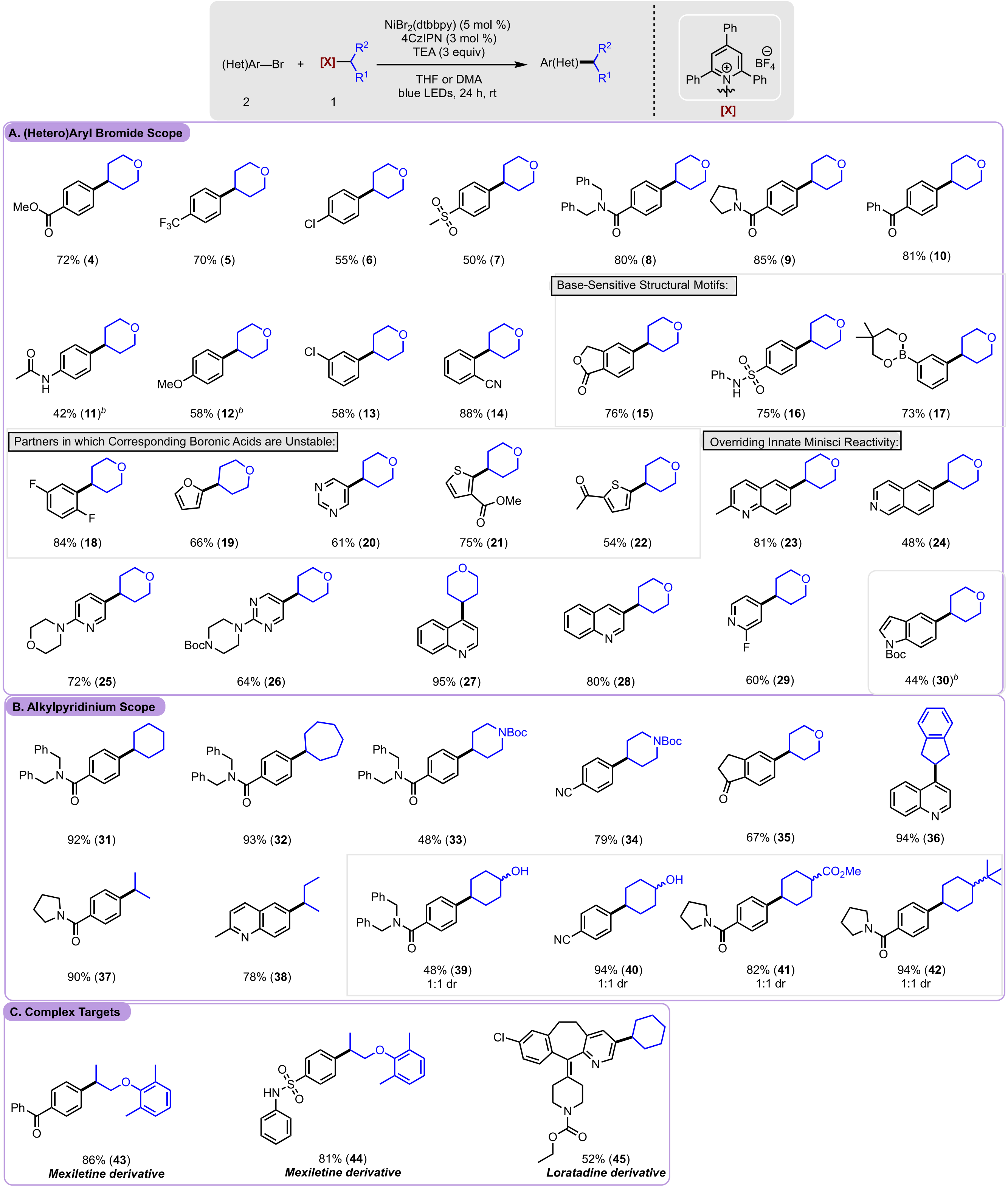
Scheme 2. Scope of (Hetero)aryl Bromides and Alkylpyridinium Salts[a]

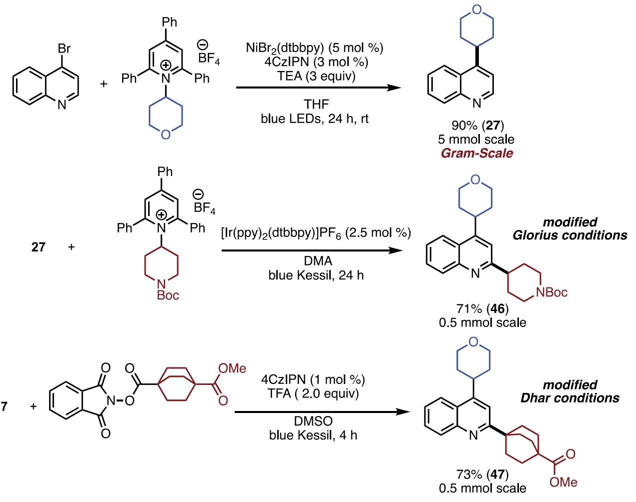


[a]As in Table 1 (entry 1), 0.5 mmol scale. [b]Using DMA as a solvent, 48 h.

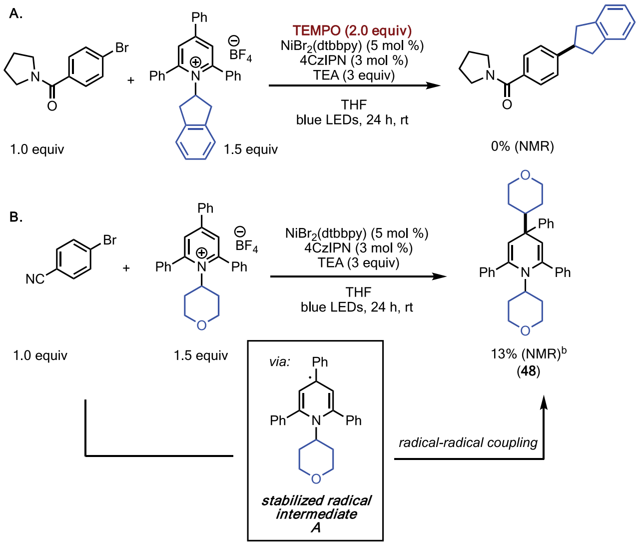
A with a transient secondary alkyl radical during the course of the reaction[6] (Scheme 4B).

To gain further understanding of the role of the photocatalyst, fluorescence quenching studies were performed (Figure 1). As anticipated, the Stern–Volmer relationship confirmed that the photoexcited 4CzIPN was quenched by both triethylamine and the Katritzky salt. Although these results could support an operative single-electron-transfer (SET) reduction of the alkylpyridinium salt by the photocatalyst, we cannot rule out the possibility of a direct SET

Scheme 3. Sequential Gram-Scale Deaminative Cross-Coupling and Minisci C−H Arylation



Scheme 4. Support for Involvement of Radical Intermediates



[a]As in Table 1 (entry 1), 0.3 mmol scale. [b]NMR yield was calculated based on the alkylpyridinium reagent (theoretical yield of 0.225 mmol).

event from a low-valent nickel intermediate as proposed by Watson and Lei.[2,14a]

Based on these results and precedented literature reports detailing the reductive cleavage of Katritzky salts,[2−8] a plausible mechanism is depicted in Scheme 5. First, visible-light irradiation of 4CzIPN generates a potent excited-state oxidant ($E_{1/2}$ = +1.35 V vs SCE),[22] which is sufficiently quenched by triethylamine **D** ($E_{1/2}$ = +1.0 V vs SCE),[10b] thus forming the reduced state of the photocatalyst. Upon generation of alkyl radical **IV** from the Katritzky salt ($E_{1/2}$ = −0.93 V vs SCE)[7] via SET from the photoexcited 4CzIPN or a low-valent nickel intermediate, the radical is intercepted by a ligated Ni(0) complex **V** to afford a Ni(I) intermediate. Subsequently, **VI** undergoes oxidative addition with the (hetero)aryl bromide to afford the corresponding high-valent Ni(III) complex **VII**. Reductive elimination would then occur to yield the desired coupled product **3** and Ni−Br species **VIII**.

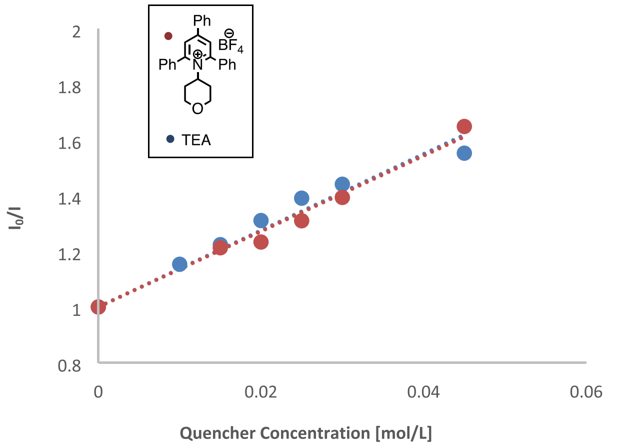
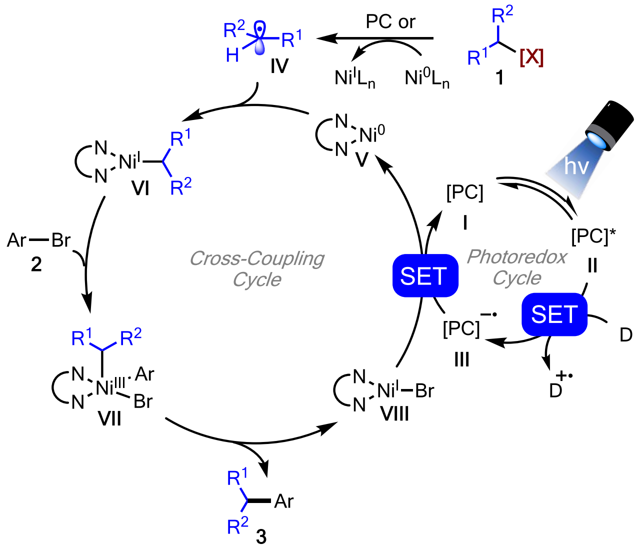


Figure 1. Stern−Volmer Fluorescence Quenching Studies of 4CzIPN (*c* = 2.0 M) in THF.

Scheme 5. Reductive Nickel/Photoredox Dual Catalysis: Mechanistic Rationale



Reduction of **VIII** by the ground state of the reduced photocatalyst **III** ($E_{1/2}$ = −1.21 V vs SCE) concurrently completes both catalytic cycles.

The developed arylation protocol does exhibit a limitation owing to the inherent stability of the dihydropyridine radical intermediate **A** generated (Scheme 5). Thus, primary alkylpyridinium salts preferentially undergo reoxidation to deliver the corresponding pyridine byproduct.[6] Considering the sheer number of existing, complementary cross-coupling approaches for primary alkyl radicals developed by our group and others,[22] we foresee the current work as an important, complementary approach to the challenges associated with the activation of inert C−N bonds in recently described systems that appear restricted to aryl iodides and use excess metal reductants at elevated temperatures.[23]

In conclusion, a cross-electrophilic, reductive deaminative arylation protocol under photoredox conditions has been developed, using triethylamine as the terminal reductant. By eliminating the need for stoichiometric metal reductants, elevated temperatures, and/or strong bases, an exceptional array of functional groups and complex structural scaffolds can be incorporated, including those from bioactive molecules. This arylation protocol is scalable, operationally simple, and utilizes alkylamines as abundant feedstocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01097.

General procedures; fluorescence quenching studies; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support provided by the NSF (CHE-1664818) and the NIGMS (R01 GM 113878 to G.M.). J.Y. acknowledges funding from the National Natural Science Foundation of China (Grant No. 21602017), the Natural Science Foundation of Jiangsu Province (Grant No. BK20160405), the University Science Research Project of Jiangsu Province (16KJB150001), and China Scholarship Council (201708320115). M.R. acknowledges support from the Ministerio de Educación, Cultura y Deporte, Subprograma Estatal de Movilidad and Fulbright grant visiting scholar program. We thank Mr. Shuai Zheng (UPenn) for stimulating discussions. We thank Dr. Charles W. Ross, III (UPenn) for his assistance in obtaining HRMS data. Kessil is acknowledged for providing the lights used in this study.

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