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Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and *N*-Arylation Reactions

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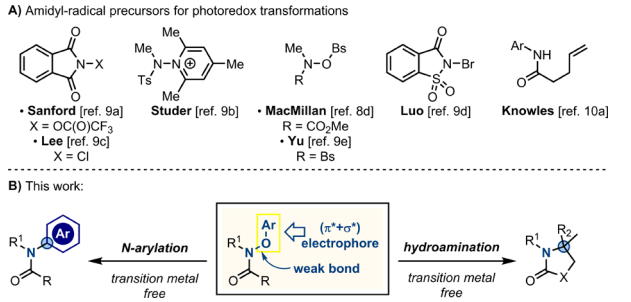
Supporting Information

ABSTRACT: The development of photoredox reactions of aryloxy-amides for the generation of amidyl radicals and their use in hydroamination−cyclization and *N*-arylation reactions is reported. Owing to the ease of single-electron-transfer reduction of the aryloxy-amides, the organic dye eosin Y was used as the photoredox catalyst, which results in fully transition-metal-free processes. These transformations exhibit a broad scope, are tolerant to several important functionalities, and have been used in the late-stage modification of complex and high-value N-containing molecules.

Nitrogen-containing compounds form the structural basis of almost all pharmaceuticals, agrochemicals, and materials.[1] As a result, the development of new methodologies that allow the selective formation of C−N bonds under mild conditions and in complex molecular settings is of great relevance. Amidyl radicals represent a very useful class of reactive intermediates with potentially broad applications in the preparation of amides and carbamates.[2] However, their implementation in synthesis is somewhat limited by (i) their available precursors, which are often difficult to make and highly reactive, and (ii) the reaction conditions required for their generation, which often preclude the presence of many functional groups.[2a] Pioneering studies from Ingold revealed that amidyl radicals display remarkably high electrophilic character, and this offers the advantage of an umpolung reactivity complementing the nucleophilic character of N-species in classical polar reaction modes.[3,4] However, as detailed by Newcomb, the amidyl radical electrophilicity also means that both inter- and intramolecular H-atom abstraction reactions are very favorable, and this frequently thwarts the development of C−N bond-forming processes.[5]

Recent progress toward the generation and use of N-radicals has employed photoredox catalysis[6] as an enabling tool for mild and selective single-electron-transfer (SET)[7] processes.[8] Of relevance to this work are the reports of Sanford,[9a] Studer,[9b] Lee,[9c] Luo,[9d] and Yu,[9e] which developed the photoredox generation of N-radicals and used them in *N*-arylation reactions. These methodologies involve the use and introduction of substrate-specific and difficult-to-modify N-groups. More recently, Knowles[10a] and Xu[10b] reported two elegant hydroamination reactions of amidyl radicals by using oxidative photoredox and electrochemical approaches, respectively (Scheme 1A). These processes require the use of *N*-aryl-amides and therefore cannot be used in a general sense for the synthesis of N-containing molecules.

Scheme 1. Amidyl Radicals



We have recently developed a transition-metal-free photoredox cyclization of iminyl radicals derived from aryloximes.[11] We decided to evaluate whether this activation mode could be applied to the generation of amidyl radicals and use it as a general platform for the synthesis of N-containing molecules. We reasoned that electron-poor aryloxy-amides would be ideal amidyl radical precursors owing to the aryloxy motif serving as a $(\pi^*+\sigma^*)$-electrophore[7b] that should facilitate a photoredox SET reduction−fragmentation cascade en route to the amidyl radical. We were particularly keen to explore whether this methodology had the potential to solve the challenge of generating *any* amidyl radical *independently from the nature of its N-substituents* and therefore decided to focus our attention on (i) substrates and substitution patterns that go far beyond the limits of current methodologies and (ii) providing access to highly functionalized, high-value N-containing compounds. In this Communication, we report the development of transition-metal-free photoredox hydroamination−cyclization and *N*-arylation reactions of amidyl radicals and their use in the late-stage functionalization of compounds with therapeutic applications.

Our proposed catalytic cycle for the photoredox cyclization of aryloxy-amides **A** is described in Scheme 2. We reasoned that SET reduction of the aryl unit of **A** would occur upon photocatalyst (PC) excitation by visible light irradiation,

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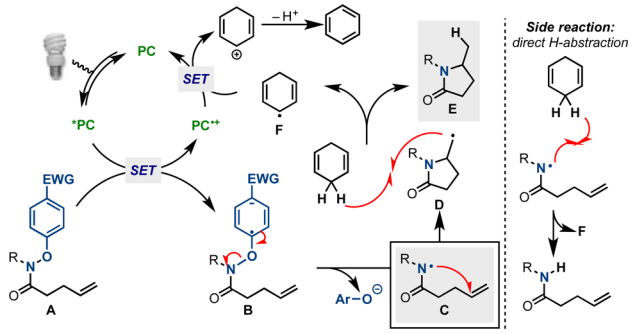
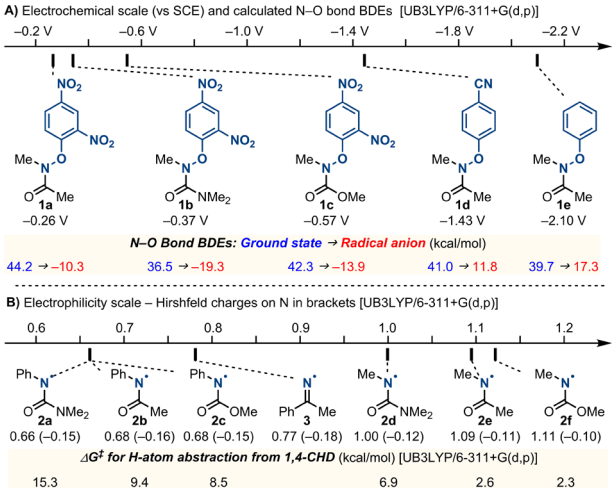
Scheme 2. Proposed Photoredox Cycle for the Hydroamination−Cyclization Reaction



delivering the radical anion **B** and $PC^{\bullet+}$. At this point, N−O bond fragmentation would form the amidyl radical **C**, which would produce **D** after 5-*exo*-*trig* cyclization. H-atom abstraction from 1,4-cyclohexadiene (1,4-CHD) would form the product **E** and generate the radical **F**, which would close the photoredox cycle by SET with $PC^{\bullet+}$. As aforementioned, a major element of concern was the high tendency of **C** to undergo preferential H-atom abstraction from 1,4-CHD over the desired 5-*exo*-*trig* cyclization.[12] This situation would be particularly problematic in our case, as (i) 1,4-CHD has a dual role as both a H-atom donor and SET reductant in two distinct but sequential events of the catalytic cycle and (ii) direct H-atom abstraction would form **F**, which would close the catalytic cycle and eventually consume **A**.

We started our investigation by performing cyclic voltammetry studies on model precursors **1a−e** (Scheme 3A). All of

Scheme 3. Electrochemical and DFT Studies



the substrates tested displayed irreversible reduction profiles, and the N-containing compounds (**1a−c**) fell well inside the range for SET reduction by the excited state of the organic dye eosin Y (EY) [$E^{red}_{1/2}$ = −1.11 V (vs SCE)].[13] DFT calculations aimed at evaluating the N−O bond dissociation energies (BDEs) revealed that all substrates **1a−e** have N−O BDEs of ∼40 kcal/mol. However, upon SET reduction, a dramatic weakening of the N−O bond takes place, which makes the fragmentation process thermodynamically driven and essentially immediate in the case of the NO_2-substituted derivatives **1a−c**.[14] Since a major element of concern in the development of our approach is the tendency of amidyl radicals to undergo H-atom abstraction, we were surprised by the high reactivity displayed by the *N*-Ar-amidyl radicals reported by Knowles[10a] and Xu.[10b] We performed further DFT studies to evaluate how the N-substitution pattern would impact the radical electrophilicity and, as a result, its ability to undergo H-atom abstraction. As described in Scheme 3B, local electrophilicity index values (ω^{+}_{rc})[15a] and Hirshfeld charges[15b] for various radicals were calculated. This study revealed a remarkable modulation of the radical electrophilicity that is offered by the *N*-Ar substituent. According to our scale, Ar-amidyl radicals (**2a−c**) are significantly less electrophilic than alkyl-amidyl radicals (**2d,e**). They are even less electrophilic than iminyl radicals (e.g., **3**), and this might be the reason for their low tendency to abstract H-atoms.[14] To further corroborate this scenario, we have calculated the barrier for H-atom abstraction ($\Delta G^{\ddagger}$) for the reaction between radicals **2a−f** and 1,4-CHD. As described in Scheme 3B, *N*-Ph-substituted radicals **2a−c** displayed higher barriers for H-abstraction compared with the more electrophilic *N*-alkyl radicals **2d−f**.[14] These results clearly show the relevance and challenges that are associated with the development of photoredox reactions of amidyl radicals with alkyl- and carbonyl-containing substitution patterns.

We started the optimization of our proposed process using the di-NO_2-substituted amide **4a** due to its synergistic (i) ease of synthesis, (ii) ease of SET reduction, and (iii) very favorable N−O bond fragmentation (Scheme 4).[11] Our optimized reaction conditions required the use of EY as the PC, 1,4-CHD as the H-atom source, and K_2CO_3 as the base. Acetone was found to be the best reaction medium, and in terms of the light source, we found that green LEDs (λ = 530 nm) gave the best results. Under these reaction conditions **7a** was obtained in 78% yield.[14] With these optimized reaction conditions in hand, we evaluated the scope of this photoredox cyclization reaction. Pleasingly, our protocol enabled the generation and use of amidyl radicals with broad N-substitution patterns, as shown by the use of a primary alkyl group (**7b,c**) as well as the hindered cyclohexyl (**7d**) and a redox-active sulfone[16]-containing heterocycle (**7e**). More remarkably, we were able to generate and implement *N*-Boc- and *N*-Cbz-protected amidyl radicals (**7f,g**). The success of these cyclizations is noteworthy owing to the high electrophilicity of these radicals (ω^{+}_{rc} = 1.3).[14] To the best of our knowledge, the generation and use of these amidyl radicals have not been reported in the literature.

We then showcased our method by preparing more-complex products, including **7i**, which contained a sugar-like moiety as N-substituent, and bicyclic (**7j,k,n**), tricyclic (**7o**), and spirocyclic (**7l**) molecules. Cyclization to form a fully substituted carbon center was possible (**7p**), and we succeeded in using a trifluoro-substituted olefin substrate (**7q**). We then extended this chemistry to the synthesis of cyclic carbamates. However, in this case the reaction conditions had to be adjusted because the competing H-atom abstraction became significantly more problematic owing to the increased radical electrophilicity (see Scheme 3B). Nevertheless, we were able to use a range of differentially substituted substrates without the need for a stabilizing N-aromatic group (**8a−f**). We then used our methodology for the modification of the terpenes (−)-linalool (**8g**) and (−)-myrtenol (**8h**) as well as performing a cyclization that produced a cyclic thiocarbamate (**9**). Finally, as many therapeutic molecules contain alkyl-substituted amino groups, we showcased the applicability of our methodology with the late-stage modification of the blockbuster drugs mexiletine and rimantadine, which gave **7r** and **7s** in high yields.

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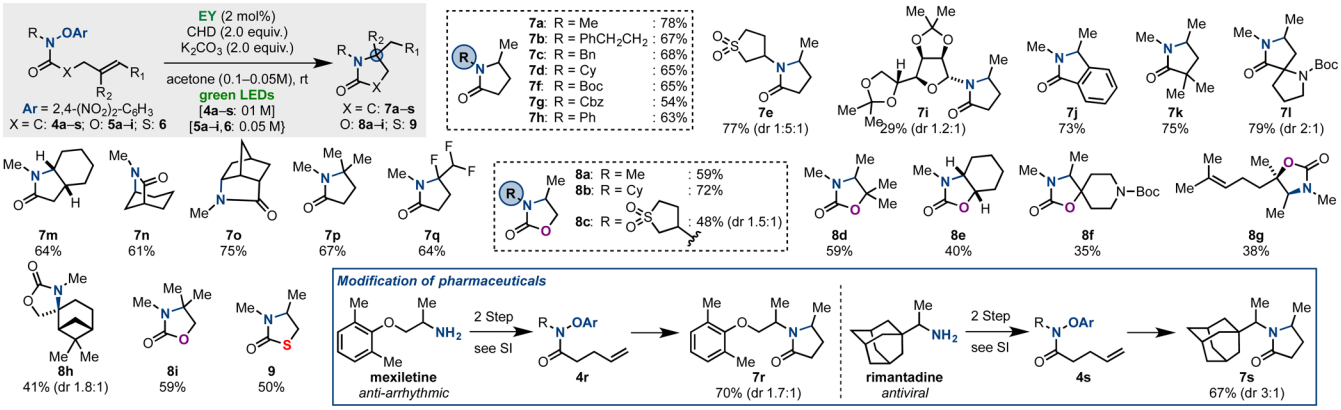
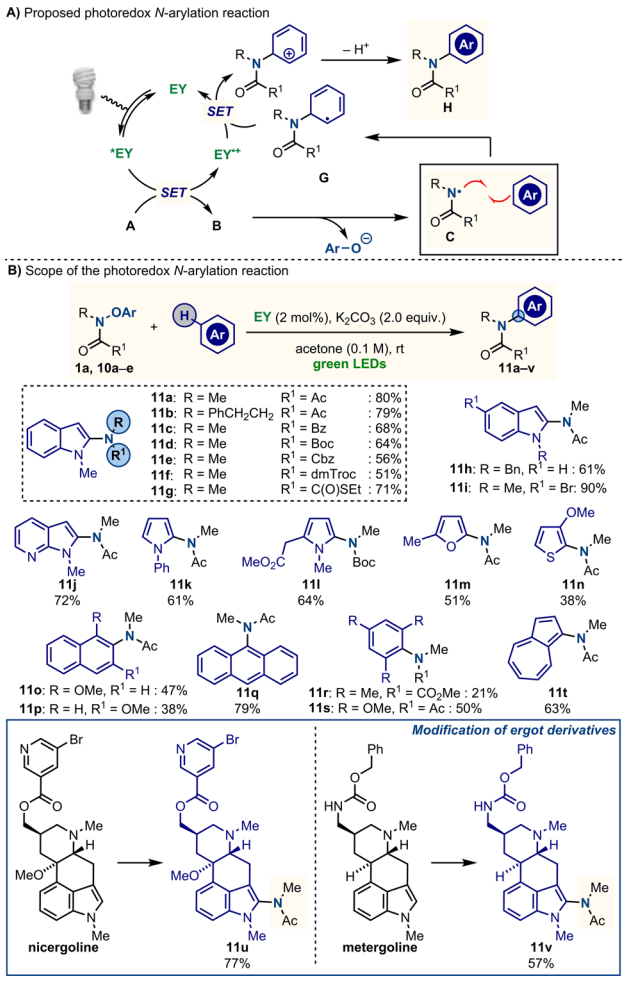
Scheme 4. Scope of the Photoredox Hydroamination–Cyclization Reaction



Having developed a photoredox transition-metal-free hydroamination process, we decided to evaluate whether our method could be used to achieve intermolecular *N*-arylation reactions (Scheme 5A).[17] Mechanistically, we envisaged that, upon photoredox amidyl radical generation (**A** → **C**) and in the presence of an electron-rich aromatic partner, an intermolecular reaction[18] would take place to forge the C–N bond in **G**. This species would then close the photoredox cycle and provide the product **H**. Related reactions have been reported in the literature (Scheme 2A);[9] however, they do not allow structural modification of the N-radical, and they require a large excess of the aromatic partner (normally 5–10-fold excess). We hoped that our substrates and activation mode would address these two major limitations and provide a general platform for the arylation of N-molecules. As described in Scheme 5B, by simply exposing **1a** to *N*-Me-indole (2.0 equiv), EY, and K_2CO_3 in acetone under green LEDs irradiation, the coupled product **11a** was obtained in high yield.[14] Gratifyingly, our approach enabled us to easily modify the N-substitution pattern, as shown by the implementation of substrates that contain an *N*-alkyl chain (**11b**), an *N*-Bz (**11c**), the most commonly used N-protecting groups, *N*-Boc (**11d**), *N*-Cbz (**11e**), and *N*-dimethyl-Troc (**11f**), and a thiocarbamate (**11g**). The compatibility of the *N*-dimethyl-Troc group is noteworthy, as the X–CCl_3 motif is frequently used as photoredox SET acceptor.

Scheme 5. Photoredox *N*-Arylation Reaction



We then looked at the aromatic unit and extended the scope of this reaction to *N*-Bn- and 5-Br-*N*-Me-indole (**11h,i**), azaindole (**11j**), pyrroles (**11k,l**), furan (**11m**), thiophene (**11n**), naphthalenes (**11o,p**), anthracene (**11q**), mesitylene (**1r**), trimethoxybenzene (**1s**), and azulene (**11t**). As electron-rich heteroaromatics constitute the core of many natural products and pharmaceutical agents,[1] we decided to evaluate whether our method could be used as a late-stage amination protocol. We were intrigued by the idea of modifying the core structure of lysergic acid, a molecule that has been a source of interest and imagination in both chemistry and popular culture.[19] We were delighted to see that, upon exposure of the therapeutically active ergot derivatives nicergoline and metergoline to our reaction conditions, the C-2 amino-functionalized products **11u** and **11v** were obtained in good yields. We believe that these examples showcase the power of our arylation manifold owing to the high structural complexity and the number of functional groups that are tolerated, which includes an unprotected carbamate. In fact, the excited state of a photoredox catalyst could potentially oxidize the piperidine ring N-atom and reduce the electron-poor pyridine ring. As an example, when the reaction on nicergoline was repeated by using $Ir(ppy)_3$ as the PC, we obtained a complex mixture, possibly due to the stronger redox properties of its excited state.

In conclusion, we have identified a class of easy-to-make and highly reactive aryloxy-amides that were used in the first photoredox transition-metal-free generation of amidyl radicals. This activation mode represents a general strategy for the implementation of intramolecular hydroamination reactions as well as intermolecular *N*-arylation processes. The methodology reported here displays high functional group tolerance, which is

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illustrated by the late-stage modification of terpenes, blockbuster drugs, and complex ergot derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04920.

Experimental procedures, ^{1}H and ^{13}C NMR spectra, and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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