

## RESEARCH ARTICLE

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Acridine/Lewis acid photocatalysis enables  $\alpha$ -amidyl radical cyclizationsSaurav Joshi,<sup>†a</sup> Dillon R. L. Rickertsen,<sup>†a</sup> Emma N. George,<sup>a</sup> Ion Ghiviriga<sup>ib</sup> and Daniel Seidel<sup>ib</sup> \*<sup>a</sup>

A Lewis acid-activated acridine photocatalytic platform is reported that enables intramolecular Giese-type cyclizations of  $\alpha$ -amidyl radicals under mild photochemical conditions. This approach addresses long-standing challenges associated with  $\alpha$ -amidyl radical reactivity and provides direct access to bicyclic and polycyclic nitrogen frameworks, including izidinones, izidines, and indoloquinolizidines. The method displays broad substrate scope and enables the efficient construction of annulated azacycles that are difficult to access using existing radical or ionic strategies. The synthetic utility of the protocol is demonstrated through formal syntheses of the indoloquinolizidine alkaloids ( $\pm$ )-eburnaminol and ( $\pm$ )-larutensine, underscoring its value for the rapid assembly of a structurally complex, medicinally relevant polycyclic ring system.

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## Introduction

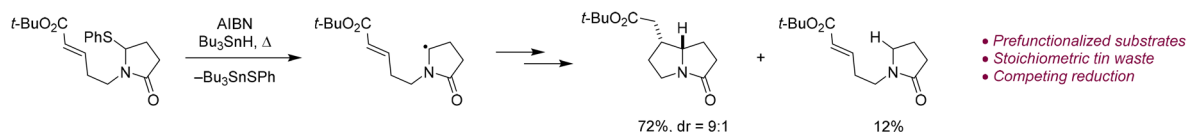
The prevalence of saturated nitrogen heterocycles as ubiquitous motifs in pharmaceuticals, bioactive molecules, and natural products has continually inspired strategies for direct C–H functionalization of azacycles.<sup>1</sup> A recent analysis revealed that 82% of small-molecule drugs approved by the FDA between 2013 and 2023 contain at least one nitrogen heterocycle, highlighting their central role in medicinal chemistry.<sup>2</sup> Although synthetic studies often focus on the most frequently encountered nitrogen heterocycles in FDA-approved drugs or other privileged scaffolds,<sup>3</sup> numerous other bicyclic nitrogen frameworks beyond these leading motifs hold significant potential to provide unique insights and stimulate future research. One such example is the *izidinone* core, a bicyclic lactam present in diverse biologically active molecules.<sup>4</sup> Reduction of the *izidinone* scaffold provides the corresponding *izidine* framework, a prevalent motif widely represented in natural products and biologically active compounds.<sup>5</sup> Herein, we report an intramolecular  $\alpha$ -amidyl radical cyclization enabled by a Lewis acid activated acridine photocatalytic platform that provides access to polycyclic nitrogen heterocycles.

As an intriguing approach to construct bicyclic nitrogen scaffolds,  $\alpha$ -amino radicals have been shown to undergo intramolecular addition to pendent olefins to afford annulated

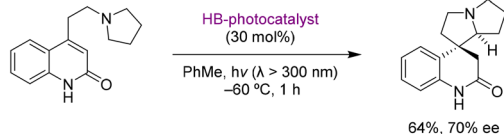
structures. Traditionally, such transformations have relied on  $\text{Bu}_3\text{SnH}$ -mediated processes and prefunctionalized substrates (Scheme 1a).<sup>6</sup> However, concerns over tin toxicity and challenging removal, limited functional group tolerance, and competing reduction processes,<sup>6a</sup> have prompted the search for alternative approaches. In recent years, visible-light photocatalysis has emerged as a versatile approach to generate  $\alpha$ -amino radicals under mild conditions,<sup>7</sup> and their frequent use in Giese reactions<sup>8</sup> is well documented. In a landmark study employing transition-metal polypyridyl photocatalysts, Nishibayashi *et al.* demonstrated the visible-light mediated generation of  $\alpha$ -amino radicals from tertiary amines, enabling their intermolecular addition to electron-deficient alkenes.<sup>9</sup> While intermolecular Giese additions of  $\alpha$ -amino radicals and related species are extremely common, intramolecular variants are exceedingly rare and essentially unknown for amine derivatives with high oxidation potentials (Scheme 1b).<sup>10</sup> Seminal work by Bach and coworkers accessed a spirocyclic Giese product in enantioenriched form.<sup>10a</sup> The requisite  $\alpha$ -amino radical was generated *via* an intermolecular hydrogen atom transfer (HAT) process involving the excited state of a chiral diaryl ketone photocatalyst containing a lactam to enable hydrogen bonding interactions with the substrate. Other examples include a study by Reiser and coworkers, who reported on the cyclization of oxidatively generated  $\alpha$ -amino radicals derived from *N*-aryl tetrahydroisoquinolines containing a pendent conjugate acceptor.<sup>10b</sup> Here, a subsequent further oxidation process ultimately generates ring-fused indoles in moderate yields. A related study by Xie/Zhu *et al.* accessed *N*-aryl pyrrolidines from the corresponding linear precursors.<sup>10c</sup> A rare example of a Giese cyclization of an

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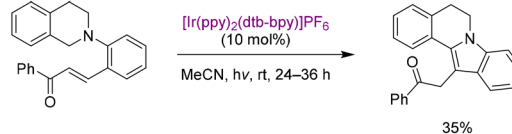
## a) Traditional radical-based approach to annulated nitrogen heterocycles

b) Photochemical Giese cyclizations of  $\alpha$ -amino radicals via C–H functionalization

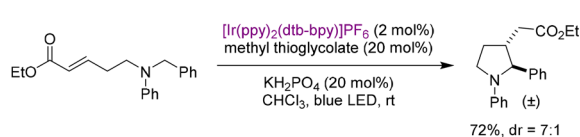
Bach (2005)



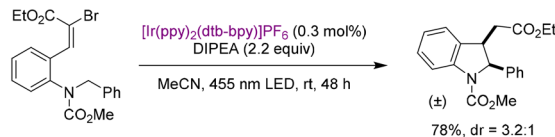
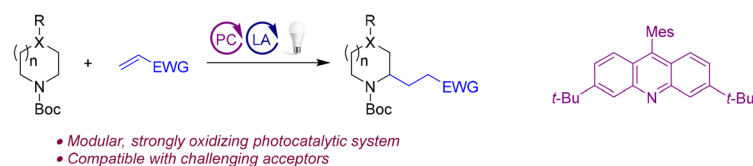
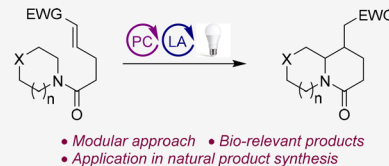
Reiser (2012)



Xie, Zhu (2017)



Reiser (2017)

c) Intermolecular Giese reactions of  $\alpha$ -carbonyl radicals (our previous work)d) Giese cyclizations of  $\alpha$ -amidyl radicals (this work)

Scheme 1 Overview and current work.

$\alpha$ -carbonyl radical was reported by Reiser and coworkers.<sup>10f</sup> Their strategy involves the oxidative transformation of a prefunctionalized conjugate acceptor to generate a vinyl radical that subsequently engages in an intramolecular 1,6-HAT process to furnish the requisite  $\alpha$ -carbonyl radical. Interestingly, all known Giese cyclizations of  $\alpha$ -aminoalkyl radicals generated *via* C–H functionalization appear to be limited to the formation of five-membered fused rings.<sup>11</sup>  $\alpha$ -Amino radicals that undergo Giese cyclizations have also been generated by photomediated decarboxylation<sup>12</sup> and through the reduction of imines (not shown).<sup>13</sup>

The utility of strong photooxidants in enabling challenging bond constructions under mild conditions has been exemplified by the development of acridinium-based photoredox catalysis.<sup>14</sup> Seminal contributions from Nicewicz and co-workers established the ability of *N*-aryl acridinium photocatalysts to generate  $\alpha$ -carbonyl radicals through the oxidation/deprotonation of simple *N*-Boc amines.<sup>15</sup> At least in part inspired by these findings, acridine/Lewis acid complexes have emerged as highly oxidizing, and modular visible-light photocatalysts, providing complementary reactivity to acridine photocatalysis which has largely centered on PCET processes.<sup>16</sup> Following seminal work by Fukuzumi and coworkers,<sup>17</sup> Sanford *et al.* demonstrated that acridine/Lewis acid complexes function as potent photoactive species, enabling demanding arene C–H

amination.<sup>18</sup> Concurrently, our group established related complexes as powerful catalysts for the  $\alpha$ -functionalization of Boc-protected secondary amines, engaging oxidatively generated  $\alpha$ -carbonyl radicals in intermolecular Giese reactions with broad acceptor scope (Scheme 1c).<sup>19</sup> Building on this development of Lewis acid activated acridines as strongly oxidizing photocatalysts, we envisioned that this platform could enable direct access to challenging radical manifolds and unlock intramolecular  $\alpha$ -amidyl radical Giese additions, providing a modular entry into annulated nitrogen heterocycles (Scheme 1d).<sup>20</sup>

## Results and discussion

We began our investigation of the proposed Giese cyclization with model substrate **1a**. Gratifyingly, acridine **3a**, used in combination with triflic acid, delivered product **2a** in 54% yield (entry 1). The use of boron trifluoride etherate provided **2a** in reduced yield (entry 2). Systematic evaluation of Lewis acids revealed that Sc(OTf)<sub>3</sub> provided substantial improvements in yield, consistent with a trend correlating higher charge density with enhanced reactivity (see the SI for details). Increasing Sc(OTf)<sub>3</sub> loadings led to progressive yield improvements (entries 3–5), possibly due to increased substrate acti-



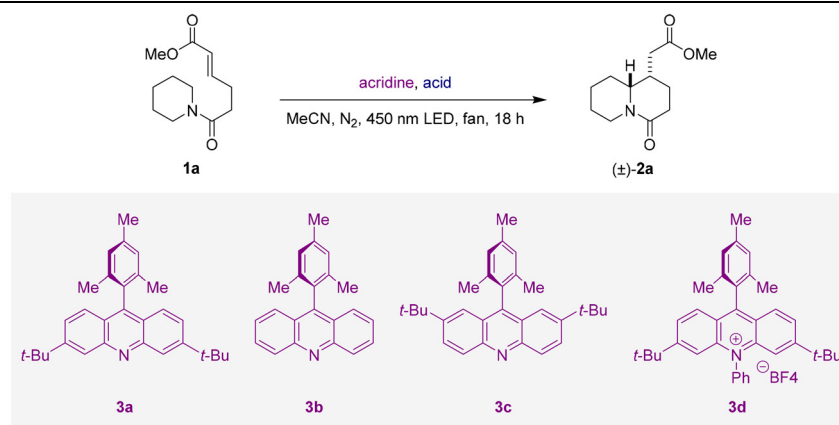
vation. Acridines **3b** and **3c** were also examined. Catalyst **3c** delivered competent reactivity (entry 7), whereas **3b** gave <10% yield (entry 6). Consistent with our prior findings, the acridinium photocatalyst **3d** also promoted the reaction, albeit less efficiently than the acridine/Sc(OTf)<sub>3</sub> system (entry 8). However, adding Sc(OTf)<sub>3</sub> to acridinium **3d** enhanced the yield relative to acridinium alone (entry 9). This suggests a beneficial role for Lewis acid coordination in substrate activation and/or in facilitating the rate-limiting reduction of the carbon-centered radical intermediate formed after the Giese addition step.<sup>19a</sup> Notably, doubling the reaction concentration in the presence of 20 mol% of Sc(OTf)<sub>3</sub> furnished **2a** in 84% yield (entry 10). Importantly, the reaction remained highly efficient with lower photocatalyst loadings: 5 mol% **3a** provided 84% yield (entry 11), while 2.5 mol% resulted in a comparable yield of 79% (entry 12), underscoring the robustness of the catalytic system. The reaction still proceeded in the absence of a Lewis acid, albeit in diminished 19% yield (entry 13). Control experiments confirmed that both light and photocatalyst are essential (entries 14 and 15) (Table 1).

With the optimal conditions in hand, the scope of the transformation was evaluated (Scheme 2). Cyclic amines spanning several ring sizes (**2b–2f**) underwent smooth annulation

to furnish the corresponding products in good yields. For morpholine,  $\alpha$ -C–H functionalization adjacent to nitrogen occurred selectively to give **2g** in 54% yield. Substituted piperidines, including 4-substituted (**2i**, **2j**) and 2-substituted (**2k**) derivatives, showed good reactivity. In contrast, the 2-phenylpiperidine derivative (**2l**) exhibited sluggish reactivity. Functional groups such as ketals and alkenes (**2m**, **2n**) were compatible, although electron-withdrawing substitution attenuated the nucleophilicity of the  $\alpha$ -amidyl radical, resulting in diminished yields in the case of ketal. Linear amines also reacted to give **2o** and **2p**. Product **2q** was obtained as a mixture of regioisomers. Other nitrogen heterocycles such as tetrahydroisoquinoline (**2r**) and tetrahydro- $\beta$ -carboline (**2s**) were viable substrates. A number of substrates containing different acrylate acceptors furnished products in good to excellent yields (**2t–2w**), exhibiting tolerance for halogens and easy-to-oxidize electron-rich heterocycles such as thiophene. Acrylonitrile (**2x**) and vinyl ketone (**2y**) acceptors were also viable. A substrate containing a trisubstituted alkene also participated in the reaction (**2z**).

In the process of tailoring the method to individual substrates, we observed that heating under irradiation (80 °C, blue LEDs) significantly improved yields for certain low-

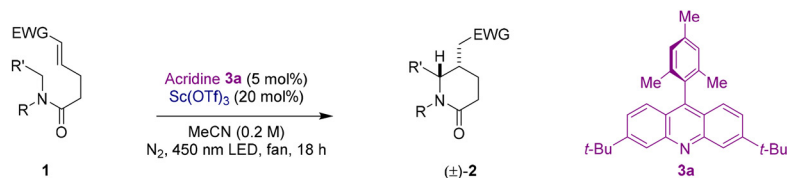
Table 1 Optimization of reaction conditions



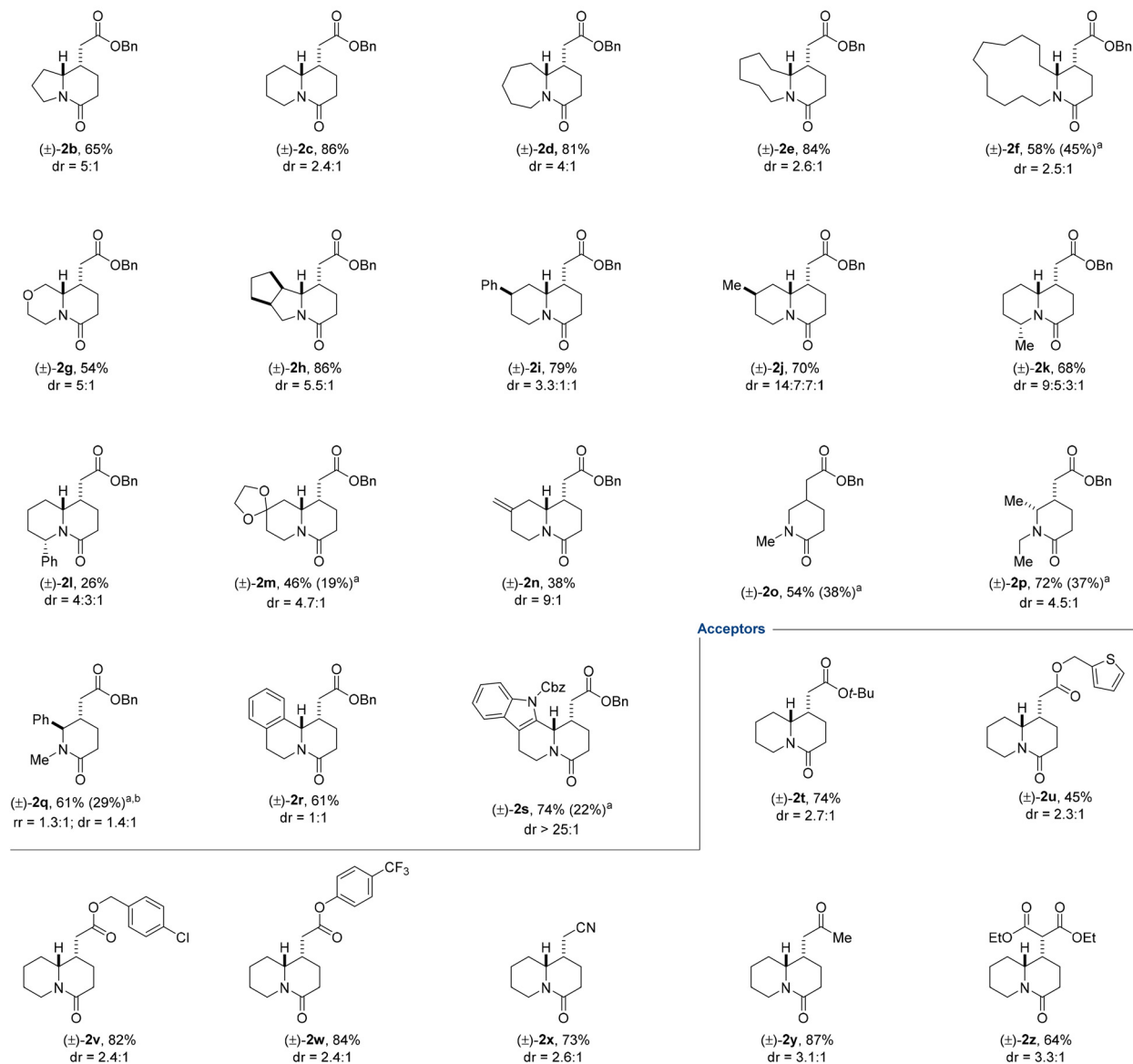
Entry	Acridine (mol%)	Acid (mol%)	Conc. (M)	Yield (%)	dr
1	<b>3a</b> (10)	TfOH (8)	0.1	54	2.9 : 1
2	<b>3a</b> (10)	BF <sub>3</sub> ·OEt <sub>2</sub> (8)	0.1	43	2.5 : 1
3	<b>3a</b> (10)	Sc(OTf) <sub>3</sub> (8)	0.1	67	2.1 : 1
4	<b>3a</b> (10)	Sc(OTf) <sub>3</sub> (15)	0.1	74	2.2 : 1
5	<b>3a</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.1	80	2.3 : 1
6	<b>3b</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.1	<10	ND
7	<b>3c</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.1	79	2.3 : 1
8	<b>3d</b> (10)	—	0.1	33	2.2 : 1
9	<b>3d</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.1	64	2.5 : 1
10	<b>3a</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.2	84	2.2 : 1
11	<b>3a</b> (5)	Sc(OTf) <sub>3</sub> (20)	0.2	84	2.3 : 1
12	<b>3a</b> (2.5)	Sc(OTf) <sub>3</sub> (20)	0.2	79	2.2 : 1
13	<b>3a</b> (10)	—	0.2	19	2.1 : 1
14	—	Sc(OTf) <sub>3</sub> (20)	0.2	NR	—
15 <sup>a</sup>	<b>3a</b> (10)	Sc(OTf) <sub>3</sub> (20)	0.2	NR	—

Reactions were performed with 0.2 mmol of **1a**. All yields correspond to isolated yields of chromatographically pure products. <sup>a</sup> Reaction was run in the dark. ND = not determined; NR = no reaction.

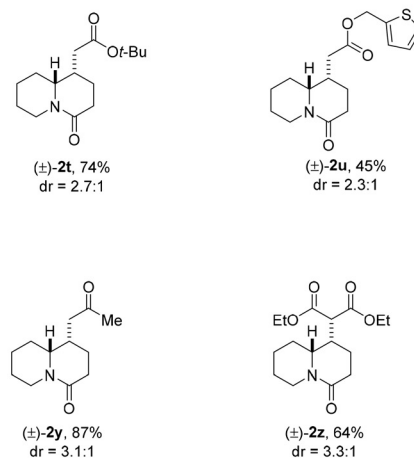




## Amines



## Acceptors



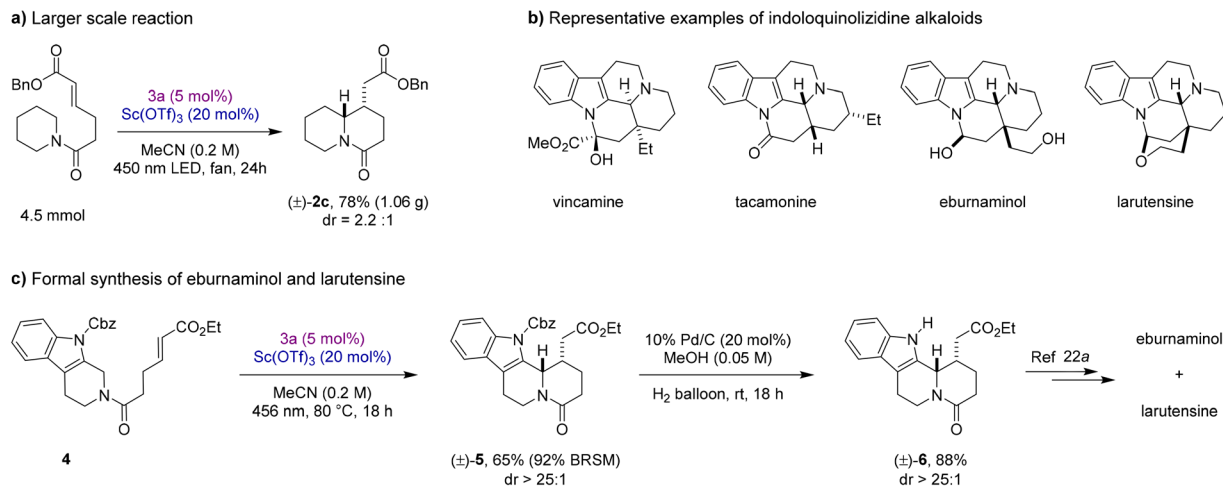
**Scheme 2** Reaction scope. Reactions were performed with 0.2 mmol of **1**. All yields correspond to chromatographically isolated products. <sup>a</sup> Reaction was heated at 80 °C along with light irradiation. Yields in parenthesis correspond to room temperature reaction. <sup>b</sup> Depicted structure and dr correspond to major isomer, see the SI for details.

reactivity substrates, as we had observed previously albeit in a different context.<sup>16p</sup> A notable example is tetrahydro- $\beta$ -carboline **2s**, which exhibited a 52% increase in yield upon heating. In contrast, **2n** did not benefit from elevated temperature, likely because its exocyclic alkene underwent competing oligomerization or other side reactions that became more prominent at higher temperatures. Other low-reactivity substrates reevaluated under heating conditions resulted in

improved yields (**2f**, **2m**, **2o**, **2p**, **2q**, **2s**). Having identified the beneficial role of the elevated temperature under irradiation, we next assessed the scalability and broader synthetic potential to benchmark the transformation for preparative applications.

The method proved amenable to scale-up and enabled the production of **2c** in gram scale, showcasing the robustness of the protocol (Scheme 3a).





**Scheme 3** Scale-up and synthetic utility.

Indoloquinolizidine alkaloids constitute a large family of natural products with diverse biological activities including CNS, cardiovascular, and antiproliferative properties.<sup>21</sup> Representative members include vincamine, tacamonine, eburnaminol, larutensine, *etc.* all featuring fused ABCDE architectures derived from tetrahydro- $\beta$ -carboline precursors (Scheme 3b).<sup>22</sup> Eburnaminol and larutensine are isolated from the stems and bark of *Kopsia larutensis*, traditionally used as anti-inflammatory agents.<sup>23</sup> Despite long standing interest, stereoselective and scalable access to these fused ring systems remain challenging.<sup>22</sup> To demonstrate the synthetic utility of our transformation, the reaction was applied to the formal syntheses of the indoloquinolizidine alkaloids (±)-eburnaminol and (±)-larutensine (Scheme 3c). Key to the formal synthesis was ensuring diastereoselective intramolecular Giese addition of  $\alpha$ -amidyl radical derived from **4** onto the pendent acrylate functionality. Initial attempts using Boc-protected substrates resulted in competing Boc-deprotection under the reaction conditions (not shown). Switching to a Cbz protecting group furnished cyclized product **5** with the desired stereochemistry in 65% yield as a single detectable diastereomer. The remainder of the mass balance consisted of recovered starting material **4**, as illustrated by a 92% yield based on recovered starting material. Attempts to force the reaction to completion by extending the reaction time resulted in loss of diastereoselectivity, possibly due to product oxidation and epimerization *via* an  $\alpha$ -amidyl radical (not shown). Hydrogenolysis of **5** afforded key intermediate **6** in 88% yield, completing the formal syntheses of (±)-eburnaminol and (±)-larutensine *via* Smith's reported procedures.<sup>22a</sup>

## Conclusions

In summary, a modular Lewis acid acridine photoredox catalytic platform has been developed for challenging intra-

molecular Giese additions of  $\alpha$ -amidyl radicals, providing efficient access to privileged annulated nitrogen heterocycles. The method features mild conditions, broad substrate scope, scalability, and compatibility with structurally complex intermediates. Its value is highlighted through formal syntheses of the indoloquinolizidine alkaloids eburnaminol and larutensine, demonstrating the platform's utility for constructing fused indole-quinolizidine architectures.

## Author contributions

S. J., D. R. L. R. and D. S. conceptualized the study. S. J. and D. R. L. R. performed the bulk of the experiments with assistance by E. N. G. and I. G., under D. S. supervision. S. J. and D. S. wrote the manuscript with input from D. R. L. R.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

Supplementary information (SI): experimental procedures, characterization data, and NMR spectra. See DOI: <https://doi.org/10.1039/d6qo00525j>.

## Acknowledgements

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