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Visible light photoredox and Polonovski-Potier cyclizations for the synthesis of (\pm) -5-epi-cermizine C and (\pm) -epimyrtine

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ABSTRACT

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Quinolizidine alkaloids epi-cermizine C and epimyrtine were synthesized from a common intermediate in 5-6 steps from commercially available materials. The key step involved an allylsilane cyclization with an iminium ion formed by oxidation of a tertiary amine. Oxidative annulation was promoted either catalytically by visible light photoredox catalysis or by stoichiometric Polonovski-Potier conditions. There was a modest difference in diastereoselectivity between the two methods, with photoredox providing the key quinolizidine intermediate in 4.7:1 dr versus 2:1 dr for the Polonovski route.

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Visible light photoredox catalysis has become a powerful platform for accomplishing single-electron transfer (SET) reactions. While SET has long been recognized as a fundamental photochemical pathway, a renewed appreciation for the versatility of Ru and Ir-based photosensitizers was central to the rapid development of new methods in this area.¹ $Ru(bpy)_3Cl_2$ and related Ir complexes,² absorb visible light radiation to give a long-lived excited state that can serve as oxidant or reductant according to the context of the reaction system. This has inspired a diverse array of novel methods that take advantage of the divergent reductive and oxidative pathways for these catalysts.²⁻³ For example, focusing only on the oxidation of amines, photoredox catalysis leads to several distinct reactive species. Initial single-electron transfer gives an amine radical cation that has been intercepted for intramolecular olefin hydroamination.⁴ A more common subsequent pathway involves deprotonation of the amine radical cation to an α -amino radical,⁵ which can be exploited for a number a processes, including: (1) radical addition to electron-deficient π -systems,⁶ (2) couplings with electron-deficient heterocycles,⁷ and (3) metal catalyzed crosscouplings.8 In cases where the amine radical cation is adjacent to a strained ring, fragmentation results in rearrangement to iminium ion radical that participates in cycloaddition reactions. Another key pathway involves a second oxidation, which converts the α -amino radical to an iminium ion, a versatile synthetic intermediate in its own right.¹⁰

Our group previously investigated the oxidative cyclization of simple amino alcohols to N,O-acetals to more completely understand the scope of amines that can be oxidized to iminium ions by visible light photocatalysis.11 Those cyclizations generally gave high conversion by GC and NMR analysis, but only moderate to low isolated yields, likely due to challenges related to the purification of N,O-acetal products. These findings were applied to a concise synthesis of (\pm) -tetrabenazine, whereby the final annulation was accomplished by a photoredox Mannich cvclization.¹² The substrate in that work, an N-alkyl tetrahydroisoquinoline, was an excellent oxidation substrate due to its weak benzylic C-H bond and an aromatic ring that could stabilize the N-alkyliminium ion through conjugation. Herein we report the use of photoredox catalysis for the oxidative cyclization of a more challenging substrate-an N-alkyl piperidine that is devoid of stabilizing features and compare these results with a two-step stoichiometric Polonovksi-Potier cyclization. Despite the body of research in photoredox catalysis, relevant oxidative cyclizations of piperidine substrates have not previously been published.

Quinolizidine alkaloids epi-cermizine C (1) and epimyrtine (2) were selected as synthetic targets due to their modest structural complexity (Figure 1). Epi-cermizine C (1) was first synthesized by Snider's group in 2007.¹³ (–)-Epimyrtine (2) and its diastereomer (+)-myrtine (3) are natural products that were isolated from *Vaccinium myrtillus* (Ericaceae).¹⁴ Epi-cermizine C (1),¹⁵ and particularly 2 and 3, represent popular targets for showcasing novel methods and synthetic strategies.^{14,15c,16}

Quinolizidine 4 was identified as a common retrosynthetic precursor wherein the exomethylene group presented an opportunity for either hydrogenation to 1 or oxidative cleavage to 2 (Scheme 1A). This key intermediate would be prepared through an allylsilane cyclization involving iminium ion 5, an intermediate formed through oxidation of a key compound, *N*-alkyl piperidine 6. Since this would be a challenging substrate for photoredox catalysis, a mechanistically complex process, we decided to compare those results with the two-step Polonovski-Potier conditions, which is understood to proceed though an



Figure 1. Quinolizidine alkaloids.

iminium ion.¹⁷ Relevant cyclizations of allylsilanes with Nacyliminium ions are known,¹⁸ with Remuson's synthesis of (+)myrtine (3) providing a key benchmark (Scheme 1B).^{16a,b} In that work, the N-acyliminium ion was formed by partial imide reduction to 9, followed by TFA-promoted solvolysis. The Nacyl group favors the formation of 12 in 7:3 dr favoring a stereochemical outcome consistent with myrtine (3) due to the presence of an unfavorable $A^{1,3}$ interaction in transition state 11. Our strategy is distinguished from this approach in several ways. Most obviously, oxidative iminium ion generation complements the imide reduction route from a redox perspective. In our case, allylsilane cyclization is anticipated to occur with a complementary stereochemical outcome due to the absence of an N-acyl group in transition state 5. Most importantly, the oxidative generation of 5 from N-alkyl piperidine 6 minimizes the number of redox state adjustments, thereby enabling more concise syntheses of alkaloids 1 and 2.

A key objective was the development of a rapid synthesis of N-alkylpiperidine **6** from inexpensive starting materials (Scheme 2). Preparation of **6** commenced with the Michael addition of piperidine to methyl crotonate. This solventless reaction used only a slight excess of piperidine (1.25 equiv) and gave **15** in 81% yield after bulb-to-bulb distillation. Conversion of ester **15** to bis-(silylmethyl) carbinol **16** relied on the addition of the reagent prepared from CeCl₃ and TMSCH₂MgCl.¹⁹ Elimination



^a Conversion by GC-MS (±)-epi-cermizine C (1) (±)-epimyrtine (2) **Scheme 3.** Oxidative allylsilane cyclization and conversion to quinolizidine alakloids.

of the β -hydroxysilane required careful addition of HCl to a 0-4 °C solution of **16** to avoid proteodesilylation of product allylsilane **6**. Thus, key N-alkyl piperidine **6** was prepared via a three step sequence in 63% overall yield from commercially available reagents.

With 6 in hand, attention was directed to achieving its oxidative cyclization to quinolizidine (\pm) -4 (Scheme 3). Photoredox cyclization of N-alkylpiperidine 6 with catalytic Ru(bpy)₃Cl₂ (1 mol %) and blue LED (460 nm) gave a 4.7:1 mixture of quinolizidines (±)-4a and (±)-4b, which were isolated in 50% yield as their free bases after bulb-to-bulb distillation. The stereochemical outcome was confirmed by conversion of (\pm) -4a to known compounds 1 and 2 (see below).²⁰ Optimal photoredox cyclization results were obtained when the reaction was conducted under an atmosphere of oxygen (balloon); an air atmosphere gave unsatisfactorily slow conversions. Control reactions verified that both Ru(bpy)₃Cl₂ and light were necessary for the reaction (Scheme 3 inset). Monitoring reaction progress by GC-MS indicated that the ratio of quinolizidine diastereomers gradually and reproducibly increased with time-from 2:1 dr at 24 h (82% conversion), to 4.7:1 dr at 43 h (100% conversion). This epimerization favored formation of the thermodynamic product, quinolizidine (\pm) -4a, wherein the methyl group is equatorial.

For comparison, treatment of 6 with *m*-CPBA gave 17, followed by exposure to trifluoroacetic acid (TFAA), which produced a mixture of quinolizidines (±)-4a and (±)-4b in 74% yield. The second step of this process required K₂CO₃ to mitigate proteodesilylation of 17. This Polonovski-Potier route provided an overall yield of 57% for quinolizidines (±)-4a and (±)-4b that was comparable with photoredox conditions, but it gave only a 2:1 dr of the products, a ratio that did not vary with time. This suggests a kinetic ratio of 2:1 dr for quinolizidines formed by allylsilane cyclization with an iminium ion intermediate, an irreversible process under Polonovski conditions. One plausible explanation for epimerization under photoredox conditions could involve re-oxidation of the quinolizidine to an amino radical cation that then undergoes rapid ring-opening/ring-closure to favor the thermodynamic product. However, we have not yet investigated the mechanism for the equilibration that occurs under these conditions.

Only one additional step was required to convert (\pm) -4 to each of the final products. Simple hydrogenation gave (\pm) -epicermizine C (1), whereas oxidative cleavage of the double bond gave (\pm) -epi-myrtine (2).²⁰ In both cases, the desired products were separated from the minor diastereomers by careful chromatography. It should be noted that the final products were the only compounds purified by chromatography in this work, as all intermediates were purified by bulb-to-bulb distillation, or used crude in the following reactions.

In summary our group has developed concise syntheses of (\pm) -epi-cermizine C (1) and (\pm) -epimyrtine (2), which diverge from a common intermediate that is accessible in 4-5 steps from inexpensive reagents. Yields for the two-step Polonovski-Potier and photocatalytic cyclizations were comparable, yet the photocatalytic route was shorter by one step and proceeded with improved diastereoselectivity. The observed epimerization of quinolizidines under photoredox conditions may prove useful in future syntheses.

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Supplementary Material

Supplementary data associated with this article can be found, in online version, at [Insert link here].

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- Comparison of ¹H and ¹³C NMR data for 1 and 2 with literature data confirmed their relative stereochemistry, and supported the assignment of (±)-4a. Tabulated NMR data with these comparisons, and copies of NMR spectra, are provided in the supporting information.

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Graphical Abstract

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Highlights

- Epi-Cermizine C and epimyrtine prepared in 5-6 steps from commercial reagents.
- Two oxidative cyclization conditions used to prepare quinolizidine alkaloids.
- Photoredox and Polonovski cyclizations gave different diastereoselectivities. • Acception