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Amide and Amine Nucleophiles in Polar Radical Crossover Cycloadditions: Synthesis of γ-Lactams and Pyrrolidines

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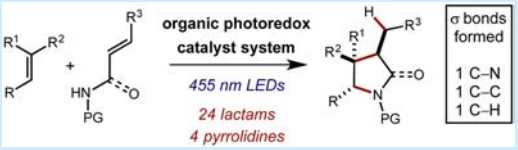
Supporting Information

ABSTRACT: In this work we present a direct catalytic synthesis of γ-lactams and pyrrolidines from alkenes and activated unsaturated amides or protected unsaturated amines, respectively. Using a mesityl acridinium single electron photooxidant and a thiophenol cocatalyst under irradiation, we are able to directly forge these important classes of heterocycles with complete regiocontrol.



Heterocyclic γ-lactam and pyrrolidine motifs represent a significant portion of chemical space present in natural products, physiologically active synthetic entities, and catalysts.[1−7] Due to the ubiquity and importance of these structures, particularly as pharmacophores, methods that enable the generation of these heterocycles utilizing novel disconnections have been a significant area of study. Many groups have developed unique approaches to these structures that compliment traditional γ-lactam/pyrrolidine forming strategies. Intramolecular strategies such as Rh-catalyzed C−H insertion,[8] Pd-catalyzed alkene functionalization,[9,10] and halolactamization[11−16] have been developed for γ-lactam synthesis. In addition, intermolecular strategies such as allylsilane annulation,[17] nitro-Mannich/lactamization cascades,[18−20] *N*-heterocyclic carbene-catalyzed imine/enal annulations,[21] and tandem Michael addition/elimination sequences have been explored.[22,23] Regarding pyrrolidine synthesis, intramolecular strategies such as alkene hydroamination[24−34] and halocyclization[35] have been extensively studied and intermolecular approaches such as a Michael addition/reductive cyclization[36] and polar/radical redox processes have been reported.[37,38]

Our laboratory has developed a program focused on novel redox-neutral transformations employing a dual catalyst system comprised of an organic single electron photooxidant and a redox-active H-atom donor to access the unique reactivity of olefin cation radicals. We have demonstrated methods for anti-Markovnikov olefin hydrofunctionalization[39,32,40−42] as well as O-containing heterocycle synthesis by polar radical crossover cycloadditions (PRCC, Figure 1).[43,44] Herein, we disclose our efforts toward the direct synthesis of γ-lactam and pyrrolidine heterocycles from alkenes and activated unsaturated *N*-nucleophiles using an acridinium organic photoredox catalyst (**1**) and redox active H atom donor cocatalyst.

We began our investigation into γ-lactam synthesis using β-methylstyrene (**2a**) as the alkene partner and *N*-activated cinnamamide nucleophiles (Figure 2A). A major hurdle for this method was steering reactivity toward *N*-addition (lactam formation, **4**) over O-addition (imidate formation, **5**), also a challenge for halolactamization strategies.[14,35] Sulfonyl-protected amides produced generally clean reactions, while more

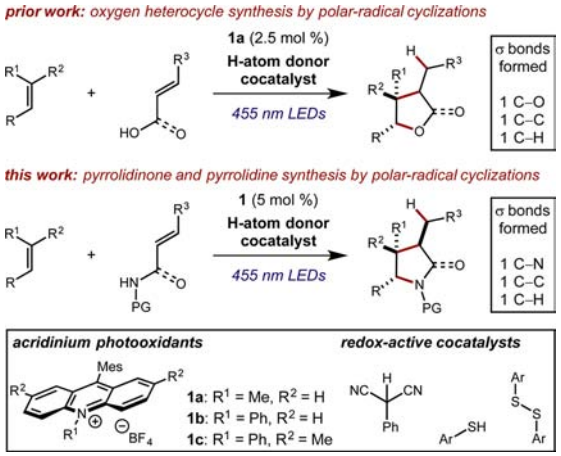


Figure 1. Prior photoredox polar radical cyclization work and proposed *N*-heterocycle synthesis.

labile protecting groups (Boc, trifluoroacetyl), or nucleophiles lacking protecting groups, lead to decomposition or no reaction. A catalyst system comprised of the mesityl acridinium photooxidant (**1a**) and 4-methoxythiophenol as a H-atom donor was employed to probe the effect of sulfonyl electronics (Ms, Ts, Ns, Tf) on conversion and product distribution. In all cases, only trace uncyclized products were observed. More electron-deficient protecting groups resulted in higher conversion and greater selectivity for γ-lactam formation, with *N*-Tf substrate **3d** producing the lactam **4a** in a 58% yield and an N/O ratio of 5.8:1.

To confirm the product assignments and stereochemistry, the lactam and imidate adducts were isolated and subjected to epimerization/deprotection experiments (Figure 2B). We presumed that the 3,4-*trans*/4,5-*trans* diastereomer would be the most stable;[44] therefore, DBU-catalyzed epimerization of a 3,4-*cis*/4,5-*trans* adduct would result in diastereomer inversion while a 3,4-*trans*/4,5-*trans* adduct would be enriched. Subjecting

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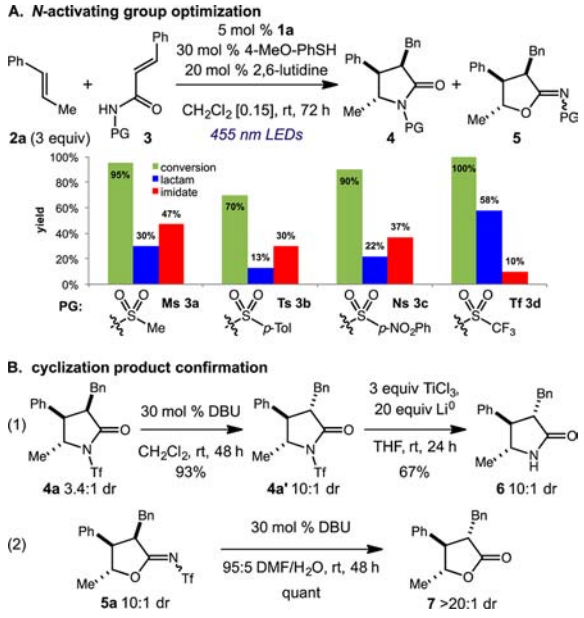
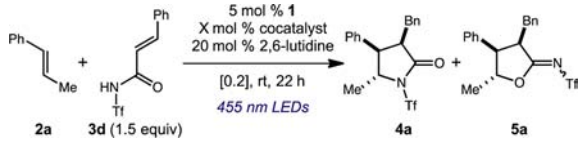


Figure 2. Activating group optimization, product identification.

the major product **4a** to DBU-catalyzed epimerization resulted in diastereomeric inversion producing **4a′** in 10:1 dr. Subjecting epimerized adduct **4a′** to $TiCl_3/Li^0$ deprotection revealed γ-lactam **6**, confirming the major product of the cyclization as the desired 3,4-*cis*/4,5-*trans* lactam. Likewise, subjecting the minor cyclization product, the presumed 3,4-*cis*/4,5-*trans* imidate **5a**, to DBU-catalyzed epimerization/hydrolysis in DMF/H_2O produced 3,4-*trans*/4,5-*trans* lactone **7**.

Continuing the optimization with β-methylstyrene and **3d**, we observed an increase in the yield of **4a** by using *N*-Ph catalyst **1b** in place of *N*-Me catalyst **1a** (Table 1, entries 1−2). A screen of various thiophenols as H-atom donor cocatalysts revealed that

Table 1. Lactam Reaction Optimization



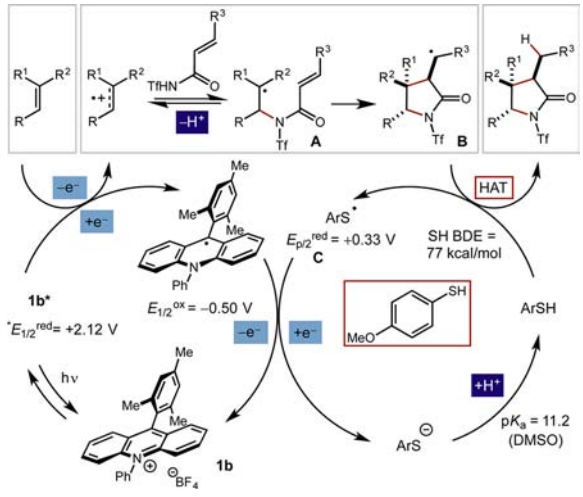
entry	catalyst	H-atom donor	solvent	yield **4a** (**5a**)[b]
1	**1a**	30 mol % 4-(MeO)PhSH	CH_2Cl_2	60% (10%)
2	**1b**	30 mol % 4-(MeO)PhSH	CH_2Cl_2	73% (12%)
3	**1b**	30 mol % 2-(MeO_2C)PhSH	CH_2Cl_2	19% (5%)
4	**1b**	30 mol % PhSH	CH_2Cl_2	56% (6%)
5	**1b**	30 mol % 4-(MeO)PhSH	CH_2Cl_2	63% (11%)
6	**1b**	30 mol % 2.4-$(MeO)_2$PhSH	CH_2Cl_2	59% (9%)
7	**1b**	20 mol % 4-(MeO)PhSH	CH_2Cl_2	63% (9%)
8	**1b**	20 mol % 4-(MeO)PhSH	acetone	34% (40%)
9	**1b**	20 mol % 4-(MeO)PhSH	MeCN	30% (55%)
10	***1b***	***20 mol % 4-(MeO)PhSH***	***$CHCl_3$***	***68% (13%)***
11[c]	**1b**	20 mol % 4-(MeO)PhSH	$CHCl_3$	28% (4%)
12[d]	**1b**	20 mol % 4-(MeO)PhSH	$CHCl_3$	0% (0%)
13	**1b**	none	$CHCl_3$	7% (0%)
14	none	20 mol % 4-(MeO)PhSH	$CHCl_3$	0% (0%)

[a]Reactions run in N_2-sparged solvents at 0.2 mmol scale under 2 × 455 nm LED lamps for 22 h. [b]Yield relative to $(Me_3Si)_2O$ NMR internal standard of crude reaction mixture. [c]2,6-Lutidine omitted. [d]Light excluded.

electron-deficient aryl thiols such as methyl thiosalicylate (entry 3) or thiophenol (entry 4) resulted in diminished yields relative to 4-methoxythiophenol (entry 5).[45] More electron-rich H-atom donors such as 2,4-dimethoxythiophenol (entry 6) did not increase reaction efficiency. We were however pleased to see that H-atom donor loading could be lowered from 30 to 20 mol % with no deleterious effect (entry 7). More polar solvents such as acetone (entry 8) or acetonitrile (entry 9) resulted in diminished or reversed lactam/imidate selectivity. A modest increase in yield and, more importantly, crude reaction purity was observed with $CHCl_3$ relative to CH_2Cl_2 (entry 10). Control experiments demonstrated the importance of each reaction component: without base, light, H-atom donor, or **1b**, little or none of **4a** was formed (entries 11−14).

We propose a mechanism analogous to the lactone-forming PRCC (Scheme 1).[44] Excitation of acridinium catalyst **1b**

Scheme 1. Proposed Mechanism



generates excited state species **1b*** which oxidizes the alkene, generating a cation radical and the reduced acridine radical. Nucleophilic attack by the unsaturated amide nucleophile and deprotonation produce C-centered radical **A**, which readily undergoes 5-*exo*-trig cyclization to form exocyclic radical **B**. The lactam product is formed by H-atom transfer from 4-(MeO)-C_6H_4SH (BDE = 77 kcal/mol),[46] and electron transfer between the acridine radical and thiyl radical **C** reoxidizes the acridinium catalyst.[47,48] Protonation of the thiolate (pK_a = 11.2 in DMSO)[46] regenerates the H-atom donor. An alternative mechanism is also plausible, whereby the *N*-sulfonyl amide nucleophile ($E_{p/2}^{ox}$ = +1.88 V vs SCE) is deprotonated and oxidized to the amidyl radical, in analogy to recent work by Moeller.[49] This might allow alkenes outside the range of the acridinium photooxidant to be used; yet, 1,1-disubstituted/terminal aliphatic alkenes of higher oxidation potential than **1b*** were not competent reaction partners.

With the ideal reaction parameters identified, we set out to investigate the scope of the transformation with respect to the unsaturated amide (Scheme 2). Model system product **4a** was produced in 64% isolated yield and 5.2:1 N/O ratio favoring the lactam. Cinnamamide nucleophiles with varying aromatic substitution afforded the expected lactams (**4b**, **4c**) in similar yields to **4a.** We were pleased to find that β-aryl substitution is not required for radical cyclization as β,β-dialkyl unsaturated amides formed the anticipated cycloadducts (**4d** and **4e**) in

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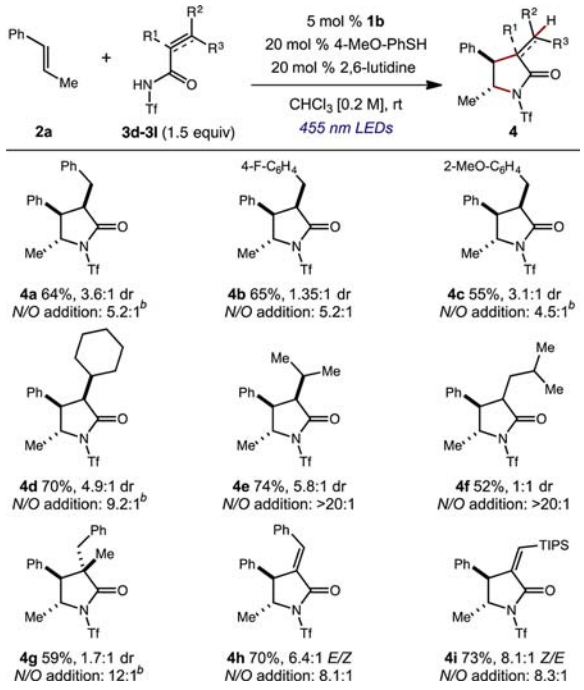
Scheme 2. Lactam Formation: Amide Scope[a]

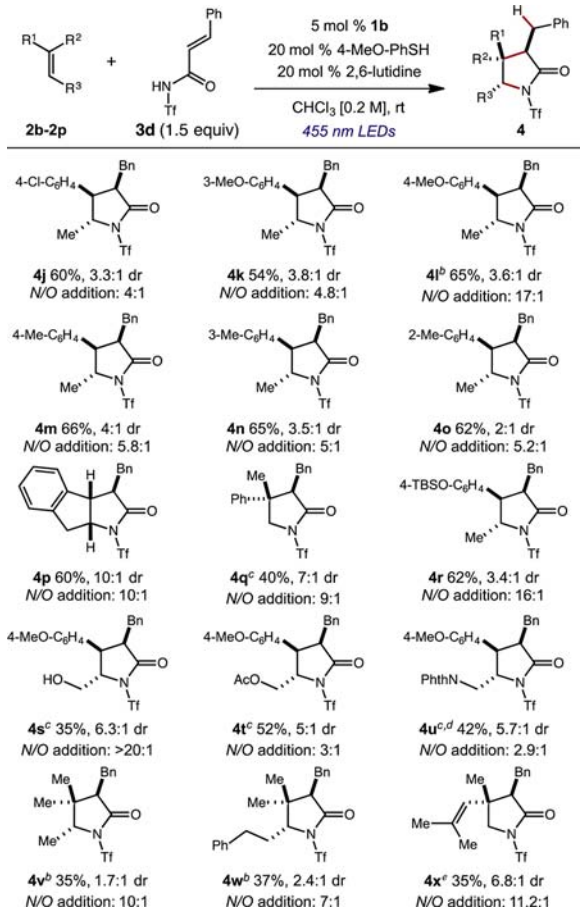


[a]Reactions were run in N_2-sparged solvents on a 0.5 mmol scale under 2 × 455 nm LED lamps for 24 h. Yields represent average of two isolated yields at 0.5 mmol scale. N/O ratio determined by ^{1}H NMR relative to $(Me_3Si)_2O$ internal standard. [b]Imidate characterization provided in the Supporting Information for comparison.

higher yields (70% and 74%), dr (4.9:1 and 5.8:1), and N/O ratios (9.2:1 and >20:1). Monosubstituted β-alkyl unsaturated amides were also successful in this context, as *N*-Tf β-isopropylacrylamide **3i** afforded lactam **4f** in 52% yield and nearly complete regioselectivity (N/O > 20:1), albeit with no diastereocontrol. Formation of an α-quaternary center was possible using *N*-Tf α-methylcinnamamide **3j** as the nucleophile to give **4g** in 59% yield and modest diastereoselectivity. We also were successful in employing *N*-Tf propiolamide nucleophiles to furnish lactams bearing substituted exocyclic olefins in high yields (**4h** and **4i**). Interestingly, alkene formation is *Z*-selective for the Si-*i*Pr$_3$-substituted propiolamide, presumably due to rapid equilibration of the fleeting vinyl radical species which partitions the bulky silyl group away from the adjacent phenyl substituent.

Using nucleophile **3d**, we examined the oxidizable alkene scope of the transformation (Scheme 3). Both electron-deficient (**4j**, **4k**) and -rich (**4l**−**4o**) lactams could be readily accessed from the corresponding β-methylstyrene derivatives in useful chemical yields and with modest relative stereocontrol. Lactams **4m**−**4o** demonstrate that steric effects on the styrene derivatives do not have a great impact on reaction efficiency. Furthermore, we found that initial olefin geometry was inconsequential with regards to product relative stereochemistry.[50] Indene also participated in the title reaction, producing fused tricyclic species **4p** in 60% yield and 10:1 dr. The lactam derived from α-methylstyrene was isolated in lower yields but still produced the desired lactam **4q** with a β-quaternary stereocenter in a 7:1 dr. The reaction displayed a reasonable tolerance to functional groups, as a TBS ether (**4r**), free alcohol (**4s**), ester (**4t**), and phthalamide (**4u**) in the starting styrenes were all retained under these reaction conditions. Though markedly less reactive, trisubstituted alkenes did provide modest amounts of the

Scheme 3. Lactam Formation: Alkene Scope[a]

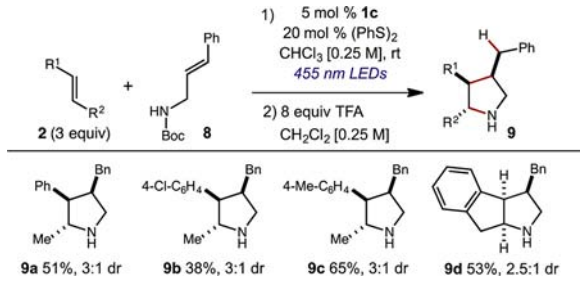


[a]Reactions were run in N_2-sparged solvents on a 0.5 mmol scale under 2 × 455 nm LED lamps for 24 h. Yields represent average of two isolated yields at 0.5 mmol scale. N/O ratio determined by ^{1}H NMR relative to $(Me_3Si)_2O$ internal standard. [b]3 equiv of anethole to 1 equiv of **3d**. [c]2 equiv of alkene to 1 equiv of **3d**. [d]Isolation at 0.25 mmol scale. [e]1 equiv of diene to 1 equiv of **3d**.

expected lactams **4v** and **4w** (35% and 37% yields, respectively). Lastly, while noticeably less efficient, diene substrate 2,4-dimethyl-1,3-pentadiene produced lactam **4x** in 35% yield (6.8:1 dr) as the exclusive regioisomer, retaining a trisubstituted alkene in the final adduct.

Finally, we sought to employ this method to directly access pyrrolidine heterocycles (Scheme 4). Using cinnamyl amine as a

Scheme 4. Pyrrolidine Formation: Scope[a]



[a]Reactions were run in N_2-sparged solvents on a 0.5 mmol scale under 2 × 455 nm LED lamps for 24 h. Yields shown represent average of two isolated yields after Boc removal/deprotection.

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model nucleophile, we examined protecting groups and quickly found that the Boc protecting group offered the best balance between reactivity and product purity/separation compared to *N*-Ts and *N*-Tf alternatives. Phenyldisulfide, which partitions to thiophenol during the course of the reaction,[51] was the optimum H-atom donor for the system and yields were highest when excess alkene was employed. A brief examination of the reaction scope demonstrated the promise for this transformation, as several pyrrolidines were directly isolated (**9a**−**9d**) following TFA deprotection of the initial crude mixture of Boc-protected adducts. Efforts are underway to expand the scope of this transformation and explore applications in natural product synthesis.

In summary, we have developed mild, efficient synthetic methods to access γ-lactam and pyrrolidine heterocycles through a photoredox-mediated approach from simple oxidizable alkenes and unsaturated nucleophiles. The reactions displayed good functional group compatibility, and deprotection of the initial adducts to the parent heterocycles was demonstrated. We believe that these transformations will be of broad use to practitioners of medicinal chemistry and natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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