Tailoring Unstrained Pyrrolidines via Reductive C–N Bond Cleavage with Lewis Acid and Photoredox Catalysis

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ABSTRACT: Skeletal remodeling of unstrained azacycles such as pyrrolidine remains a formidable challenge in synthetic chemistry. To achieve such remodeling, continuous development of the cleavage of inert C–N bonds is essential. In this study, we introduce an effective strategy for the reductive cleavage of C–N bond in *N*-benzoyl pyrrolidine, leveraging a combination of Lewis acid and photoredox catalysis. This method involves single-electron transfer to the amide, followed by site-selective cleavage at C2–N bond. Cyclic voltammetry and NMR studies demonstrated that the Lewis acid is crucial for promoting the single-electron transfer from the photoredox catalyst to the amide carbonyl group. This protocol is widely applicable to various pyrrolidine-containing molecules and enables inert C–N bond cleavage including C–C bond formation via intermolecular radical addition. Furthermore, the current protocol successfully converts pyrrolidines to aziridines, γ-lactones, and tetrahydrofurans, demonstrating the potential to expand synthetic strategies in skeletal remodeling.

■ INTRODUCTION

Cyclic amines, particularly pyrrolidines, stand as pivotal structures within both natural products and synthetic building blocks, serving as cornerstones in the synthesis of myriad *N*-containing molecules, profound biological and medicinal relevance (Figure 1A).[1] Historically, the chemical transformation of these motifs has enriched the synthetic toolkit, offering a cascade of valuable derivatives ranging for therapeutics to biological agents. Recently, peripheral functionalization through late-stage C–H functionalization has become a modern and popular method, offering versatile and efficient ways to embellish these amines.[2–7] In contrast to such peripheral functionalization, "skeletal remodeling", which involves deconstruction and re-editing the core ring structure, has recently garnered significant attention as a new approach in organic synthesis.[8–13] Skeletal remodeling can be divided into two phases: the cleavage of inert bonds and further transformations. This allows for the conversion of pyrrolidine frameworks into different-sized cyclic amines through insertion or contraction reactions, or into carbocycles through replacement reactions. Therefore, this method of modifying ring systems can have a substantial impact by enabling access to diverse structurally edited amines and unexplored chemical spaces.[14]

However, the establishment of versatile skeletal remodeling of pyrrolidines still faces significant challenges, particularly in the first phase involving C–N bond cleavage.[15] For example, ring-opening reactions via homolytic cleavage using radicals are well known for smaller rings such as aziridines and azetidines, driven by ring strain.[16–24,25,26] These methods, however, are not applicable to pyrrolidines, making the process more challenging (Figure 1B).[27] Although still limited to date, ingenious examples to tailor the unstrained pyrrolidine systems have been developed, which can be categorized into three mechanistically distinct approaches.

One approach is nucleophilic substitution of quaternary ammonium salts, von Braun type reactions (Figure 1C).[28,29] This protocol was recently improved by using chloroformates,[30] or difluorocarbene[3132] as more competent reagents. This transformation even facilitates the total synthesis of complex alkaloids[33,34]. Additionally, BAr_3-catalyzed ring opening has recently emerged as another approach exploiting ammonium intermediates.[3536] Another traditional example is the α-oxidation of cyclic amine followed by hemiaminal(ether) formation, where the resulting aldehyde further undergoes functionalization via oxidation and decarboxylative processes.[8,11,37–44] These oxidative approaches have recently been highlighted by a series of elegant works from the Sarpong group.[8,11–13,45]

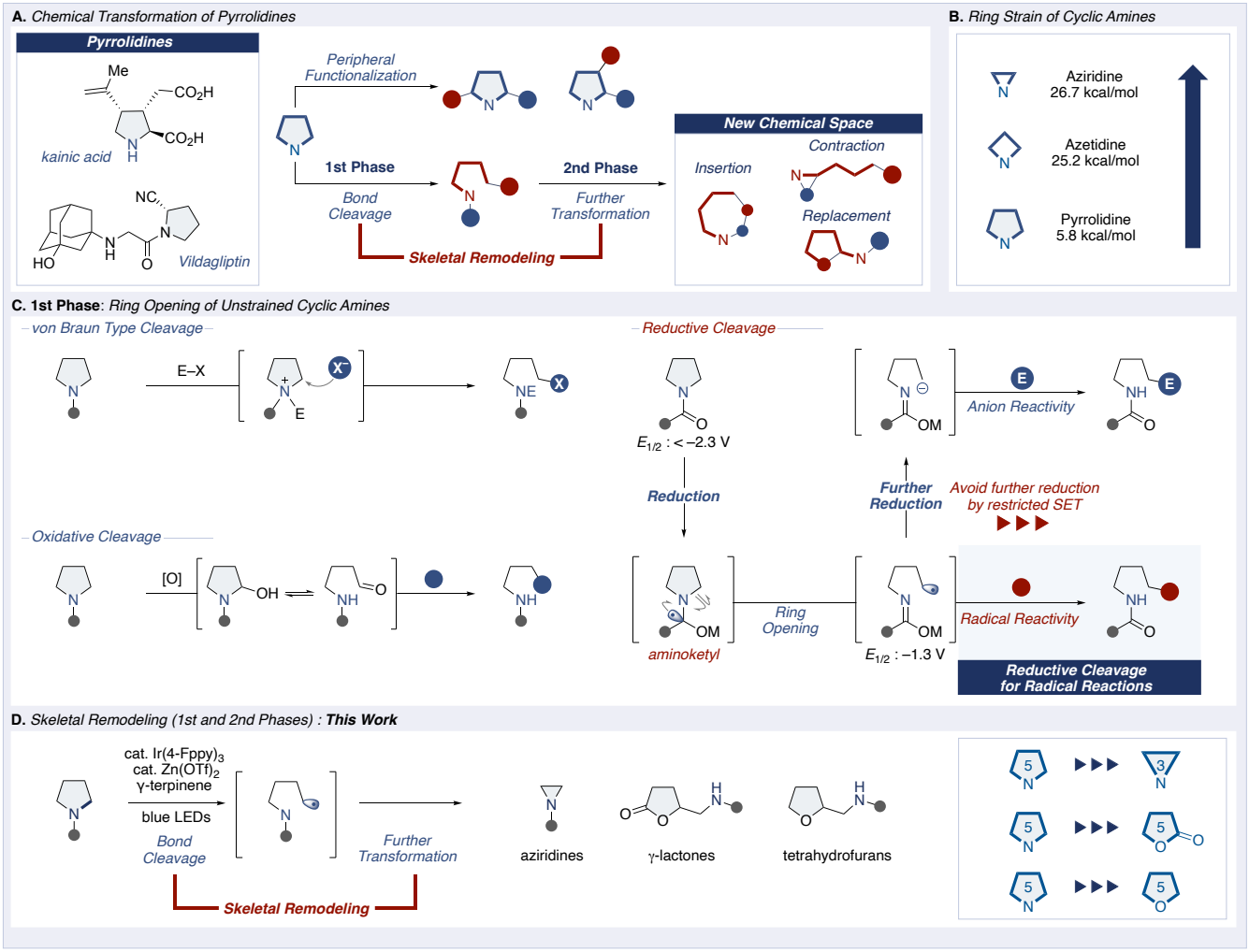


Figure 1. (A) Chemical transformation of pyrrolidines. (B) Ring strain of cyclic amines. (C) 1st phase: Ring opening of unstrained cyclic amines. (D) Skeletal remodeling of pyrrolidines (1st and 2nd phases).

Contrasting to the above two strategies based on the electron-rich nature of amines, reductive C–N bond cleavage has been less employed. Early examples represented hydrogenolysis of cyclic amines using molecular hydrogen with transition metals.[46] Thereafter, single-electron reduction of carbonyl handle affording aminoketyl radical, has gained as a new alternative of reductive C–N bond cleavage. Pioneered by Szostak and Procter, the ring opening of *N*-acyl pyrrolidines using TmI_2 ($E°(Tm^{III/II})$ = – 2.2 V vs. SCE) more reducing than SmI_2 was achieved.[47] More recently, Yu and coworkers reported a protocol for the reductive ring opening of *N*-Boc pyrrolidines with aryl or ester group at C2-position employing consecutive photo-induced electron transfer (ConPET).[48] These highly reductive approaches have faced the challenge that the choice of functionalization after reductive ring opening remains limited to transformations involving carbanion intermediates. This limitation is likely due to the resulting radical being more susceptible to further reduction than the parent compound. The requirement for strong reduction conditions and stoichiometric reductant could further reduce the accompanying carbon radical into a carbanion. We assumed that successfully avoiding multiple reduction could engage the reductive opening of cyclic amines in radical-mediated functionalization.

To this end, we envisioned that restricted single-electron transfer (SET), which is difficult with stoichiometric reductant or conPET strategy, would provide access to radical-mediated transformations. To avoid the problematic further reduction of the susceptible carbon radical (–0.3 ~ –1.3 V vs. SCE),[49] we focused on redox-neutral and catalytic approach enabled by photoredox catalysis. Generally, the reduction of amide requires highly reducing power far beyond the range of standard photocatalysts. However, aromatic amide possesses a relatively less negative reduction potential, making them a feasible option ($E_{1/2}$ = –2.3 V vs. SCE).[50] Thus, we envisioned that employing highly reducing photoredox catalyst for the reduction of aromatic amides would be a successful combination to achieve radical-based C–N bond cleavage of pyrrolidines.

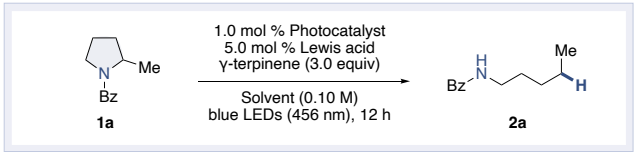
In this study, we report the successful generation of carbon radicals using a combination of zinc triflate and a photoredox catalyst. This approach not only facilitated carbon–carbon bond formation with alkenes and alkynes but also enabled the skeletal remodeling of pyrrolidines into aziridines, γ-lactones, and tetrahydrofurans (Figure D).

■ RESULTS AND DISCUSSION

We commenced our investigation by screening reaction conditions in the ring-opening reaction of *N*-benzoyl-2-

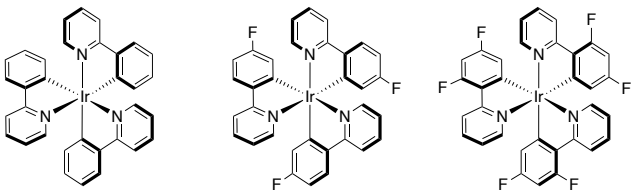
methylpyrrolidine **1a** (Table 1). Irradiation with blue LEDs (λ_{max} = 456 nm) in the presence of Ir(ppy)$_3$ ($E_{1/2}^{red}(Ir^{III}*/Ir^{IV})$= –1.73 V vs. SCE)[51] and γ-terpinene yielded no product (Table1, Entry 1). We attributed this result to the difficulty of single-electron amide reduction and tested several Lewis acids to activate the amide carbonyl group. The desired acyclic product **2a** was obtained, albeit in a considerably low yield accompanied by unreacted **1a** (Table 1, Entries 2–4). The yield of **2a** was markedly improved when Zn(OTf)$_2$ was used (Table 1, Entry 5). Relevant additives, Zn(OAc)$_2$ and TfOH, were less effective compared to Zn(OTf)$_2$ (Table 1, Entries 6 and 7). To our delight, we found that the combination of Zn(OTf)$_2$ and Ir(4-Fppy)$_3$ ($E_{1/2}^{red}(Ir^{III}*/Ir^{IV})$ = –1.91 V vs. SCE) dramatically improved the conversion, providing **2a** in 92% yield

Table 1. Optimization of the Reaction Conditions.[a]



Entry	Photocatalyst	Lewis acid	Solvent	**2a** /%
1	Ir(ppy)$_3$	none	CH_2Cl_2	0
2	Ir(ppy)$_3$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	5
3	Ir(ppy)$_3$	TMSOTf	CH_2Cl_2	6
4	Ir(ppy)$_3$	Sc(OTf)$_3$	CH_2Cl_2	1
5	Ir(ppy)$_3$	Zn(OTf)$_2$	CH_2Cl_2	30
6	Ir(ppy)$_3$	Zn(OAc)$_2$	CH_2Cl_2	trace
7	Ir(ppy)$_3$	TfOH	CH_2Cl_2	13
8	Ir(4-Fppy)$_3$	Zn(OTf)$_2$	CH_2Cl_2	92
9	Ir(dFppy)$_3$	Zn(OTf)$_2$	CH_2Cl_2	0
10	Ir(4-Fppy)$_3$	Zn(OTf)$_2$	THF	2
11	Ir(4-Fppy)$_3$	Zn(OTf)$_2$	DMF	0
12[b]	Ir(4-Fppy)$_3$	Zn(OTf)$_2$	CH_2Cl_2	84
13[c]	Ir(4-Fppy)$_3$	Zn(OTf)$_2$	CH_2Cl_2	0
14	Ir(4-Fppy)$_3$	none	CH_2Cl_2	0

Photocatalysts

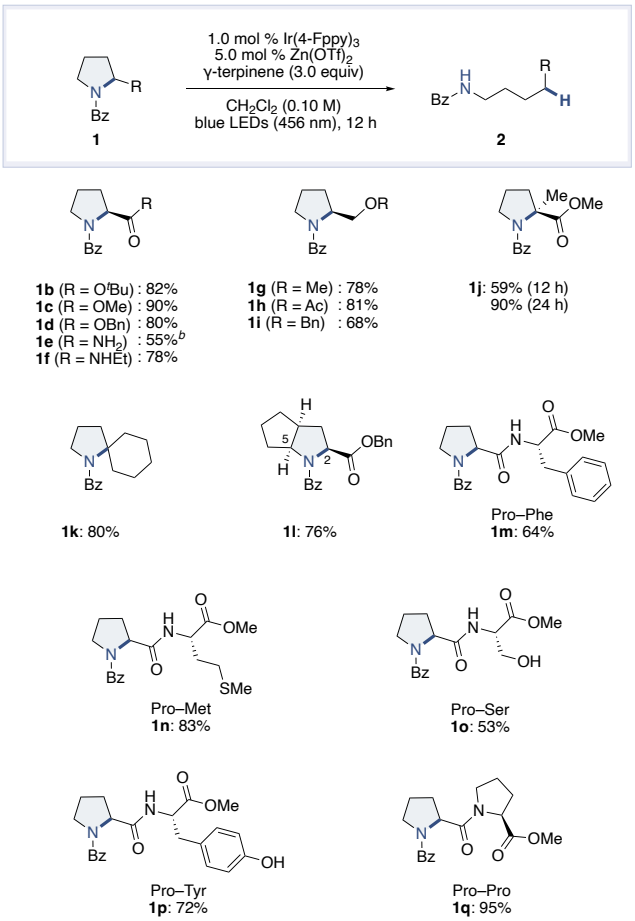


[a] Conditions: **1a** (0.10 mmol), 1.0 mol % Photocatalyst, 5.0 mol % Lewis acid, γ-terpinene (3.0 equiv) in solvent (0.10 M), blue LEDs (456 nm), 12 h, and under a N_2 atmosphere. Yields were determined by ^{1}H NMR analysis. [b] 1,4-Cyclohexadiene was used instead of γ-terpinene. [c] Without irradiation. [d] ($E_{1/2}$ ($Ir^{IV}/Ir^{III}*$) and $E_{1/2}$ (Ir^{IV}/Ir^{III}) V vs. SCE).[51]

(Table 1, Entry 8). Switching to Ir(dFppy)$_3$ ($E_{1/2}^{red}(Ir^{III}*/Ir^{IV})$= = –1.28 V vs. SCE) failed to produce the desired product (Table 1, Entry 9). THF and DMF were not suitable, presumably because the interaction between Zn(OTf)$_2$ and these solvents hampered the desired transformation (Table 1, Entries 10 and 11).[52] Replacing γ-terpinene with 1,4-cyclohexadiene (1,4-CHD) slightly reduced the yield (84%) of **2a** (Table 1, Entry 12). This result may attributed to the faster HAT rate of γ-terpinene than 1,4-CHD.[53] Control experiments revealed the requirement for both visible light and Lewis acid (Table 1, Entries 13 and 14).

With the optimal conditions in hand, we evaluated the substrate scope of the reductive ring opening of pyrrolidines (Scheme 1). Esters (**1b**–**1d**) and amides (**1e** and **1f**) at the C2-position on pyrrolidine were tolerated under these conditions, and the ring-opened products **2** were obtained in excellent yields, except for **2e**, which was insoluble to CH_2Cl_2 and obtained in a moderate yield by using a CH_2Cl_2/DMF mixed solvent. Prolinol derivatives (**1g**–**1i**) could be readily converted. Pyrrolidine **1j** possessing quaternary carbon at the C2-position was less reactive compared to **1c**, but prolonged reaction time to 24 h led to an increase in the yield of **2j** (90%).

Scheme 1. Scope of the Ring Opening of Pyrrolidines.[a]



[a] Conditions: **1** (0.20 mmol), 1.0 mol % Ir(4-Fppy)$_3$, 5.0 mol % Zn(OTf)$_2$, γ-terpinene (3.0 equiv) in CH_2Cl_2 (0.10 M) under a N_2 atmosphere and blue LEDs (456 nm) irradiation for 12 h. Isolated yields. [b] CH_2Cl_2/DMF (0.10 M, 9:1).

Sterically demanding spirocyclic pyrrolidine **1k** reacted smoothly to furnish **2k** without extended reaction time. Taken together with the result of **1g-i**, the reduction of the pendant C2 ester is not essential, unlike other reductive approaches in the C–N bond cleavage of proline derivatives.[54–56] In the reaction of a fused bicycle **1l**, regioselective C–N bond cleavage occurred at the ester-substituted C2-carbon and afforded the

sole product in a good yield. This regioselectivity could be attributed to the stability of the resulting radical intermediate.[57] Proline containing dipeptides (**1m**–**1q**) participated in this protocol and the corresponding products were obtained in moderate to excellent yields (53–95%). Oxidizable methionine, and nucleophilic serine and tyrosine residues were all accommodated, demonstrating the high level of chemoselectivity of this catalytic system. Notably, one pyrrolidine of **1q** remained intact under the reaction conditions, probably due to different susceptibilities for the reduction between aromatic and aliphatic amides.

To provide insight into the mechanistic details of this reductive C–N bond cleavage, we performed a radical clock experiment (Figure 2A). Treatment of pyrrolidine **1r** with a cyclopropyl moiety afforded olefin **2r** in a good yield, suggesting the intermediacy of cyclopropylcarbinyl radical in the ring opening of pyrrolidine. We next examined the effect of *N*-acyl groups in this reaction (Figure 2B). 2-Methyl substituted pyrrolidines bearing three different *N*-acyl substituents, **1a**, **1s**, and **1t** were subjected to the established conditions. **1a** was converted into the corresponding product **2a** in 88% isolated yield. In contrast, no reaction was observed when acetyl pyrrolidine **1s** and trifluoro acetyl pyrrolidine **1t** were used as the starting materials. We presumed that, in the cases of **1s** and **1t**, single-electron transfer from the excited photocatalyst to amide carbonyl did not occur. To gain insights into the interaction between $Zn(OTf)_2$ and pyrrolidines **1a**, **1s**, and **1t**, we examined the sensitivity of ^{13}C NMR to the addition of $Zn(OTf)_2$ (Figure 2C). The result indicated that amide carbonyl carbon of **1a** and **1s** undergo a downfield chemical shift with increasing the amount of $Zn(OTf)_2$. In contrast, no change was observed in the experiment for **1t**. These results are consistent with the successful reduction of benzoyl pyrrolidine **1a** facilitated by the coordination of $Zn(OTf)_2$ to the amide carbonyl. On the other hand, no reaction progress was observed with **1s** despite the successful coordination of $Zn(OTf)_2$. To better understand the different reactivity between **1a** and **1s**, we measured cyclic voltammetry (CV) (Figure 2D). The reduction peak of **1a** was observed at –2.68 V, while no apparent peak was detected with **1s**. Considering that the acetyl group is more difficult to reduce compared to the benzoyl group with similar tertiary amide, the reduction peak of **1s** seems to be far from the measurable range under the present conditions. Taken together, coordination $Zn(OTf)_2$ to amide carbonyl of **1a** would facilitate single-electron transfer and enable the present reductive C–N bond cleavage.

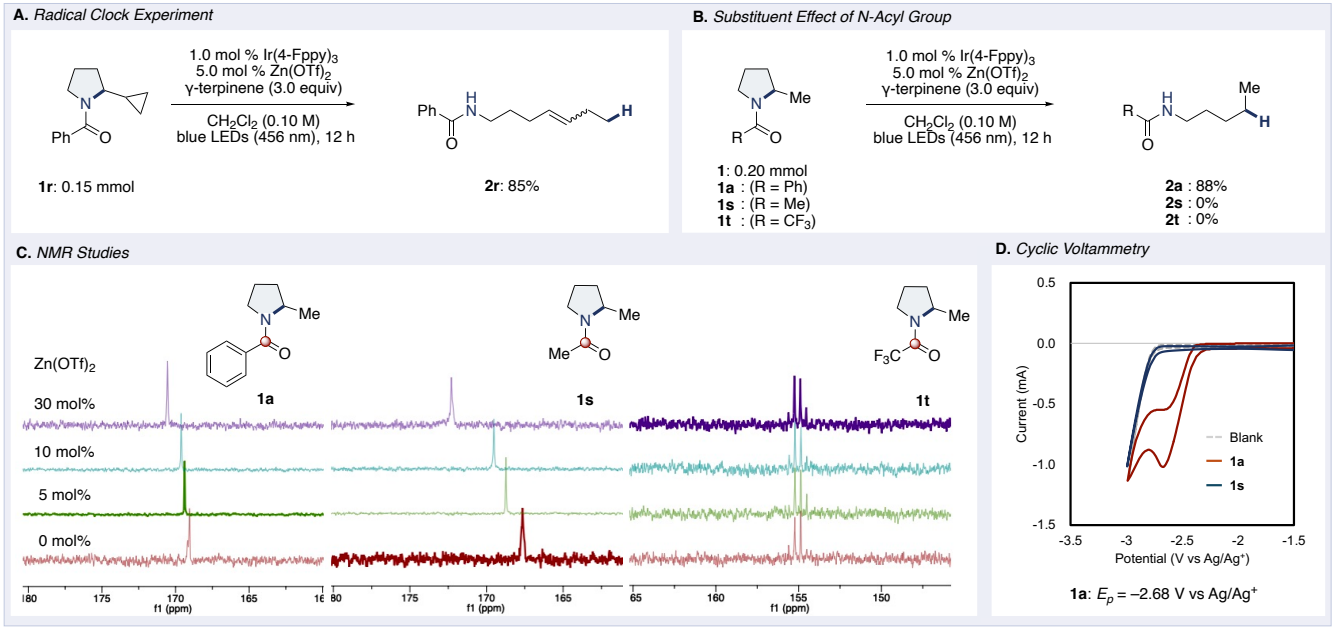


Figure 2. Mechanistic investigations. (A) Radical clock experiment. (B) Substituent effect of *N*-acyl group. (C) NMR studies. (D) Cyclic voltammetry experiments. See the Supporting Information for the details of the experiments.

A plausible mechanism for the ring opening reaction is outlined in Figure 3. First, an excited state photoredox catalyst $^*\mathbf{Ir^{III}}$ is generated under the irradiation of blue LEDs ($\mathbf{Ir^{III}} \rightarrow {}^*\mathbf{Ir^{III}}$). Single-electron transfer (SET) from $^*\mathbf{Ir^{III}}$ to **1'**, a complex of **1** and $Zn(OTf)_2$, occurs, followed by the ring opening of pyrrolidine to furnish a radical intermediate ($^*\mathbf{Ir^{III}} \rightarrow \mathbf{Ir^{IV}}$). We believe that β-scission of the generated aminoketyl radical necessitates the ring strain of pyrrolidine based on the observation of a significantly lower reactivity of piperidine under this ring opening conditions (see the Supporting Information). The alkyl radical generated from the ring opening would then undergo hydrogen-atom transfer (HAT) from γ-terpinene, leading to zinc imidate along with a γ-terpinene-derived radical, which would subsequently be oxidized to a cation by $\mathbf{Ir^{IV}}$ ($\mathbf{Ir^{IV}} \rightarrow \mathbf{Ir^{III}}$). Finally, proton transfer from the γ-terpinene-derived cation to the zinc imidate would provide the desired ring-opened product **2** along with regeneration of $Zn(OTf)_2$.

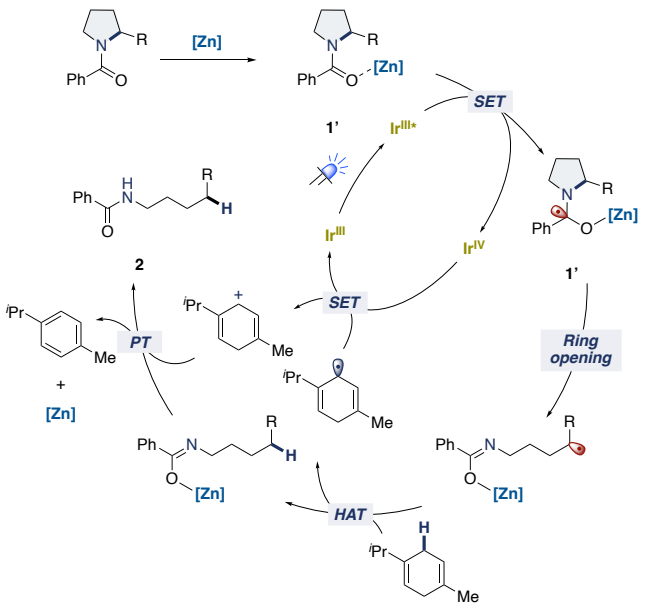
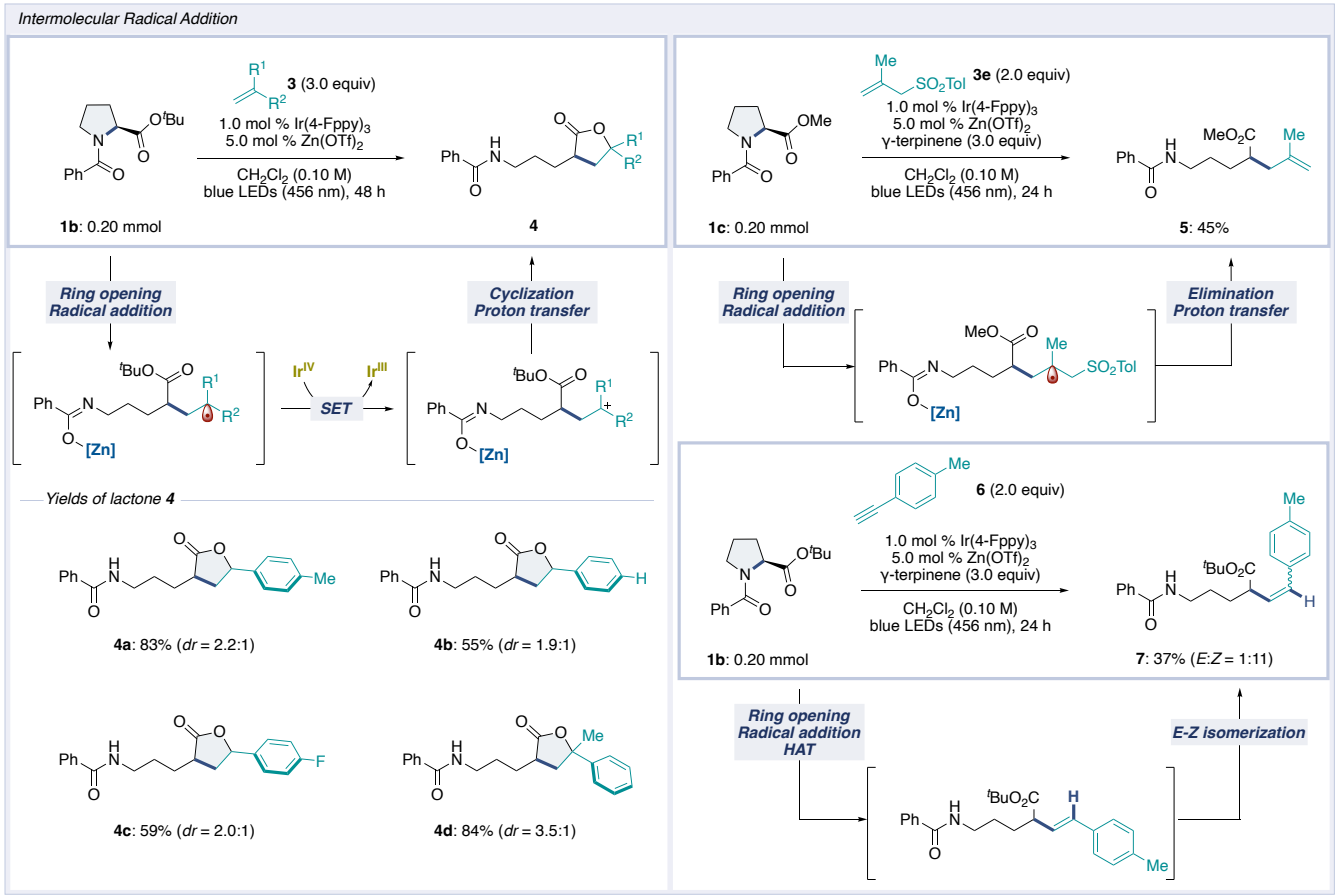


Figure 3. Plausible Mechanism.

To further explore the radical reactivity of this catalytic system, we investigated C–C bond formation through intermolecular radical addition (Scheme 2). The reaction of pyrrolidine **1b** with α-methylstyrene (**3a**) in the absence of γ-terpinene furnished lactone **4a** via a sequence of steps involving ring opening/radical addition to **3a**, oxidation of the generated benzyl radical, cation-mediated cyclization, and proton transfer.[58] This transformation highlighted the utilization of photoredox catalysis, which enables restricted single-electron transfer. In addition to **3a**, stylene (**3b**), 1-fluoro-4-vinylbenzene (**3c**), and prop-1-en-2-ylbenzene (**3d**) were tolerated in this lactone formation reaction. Additionally, treatment of pyrrolidine **1c** with allyl sulfone **3e** afforded alkene **5** via the extrusion of an aryl sulfonyl radical.[59] Furthermore, 1-ethynyl-4-methylbenzene(**6**) was also accommodated in the radical addition reaction, and the (*Z*)–isomer of styrene **7** was predominantly obtained from pyrrolidine **1b**. The regioselectivity may be a consequence of *E*–*Z* isomerization, which is supported by experiments of a similar π-system under the current reaction conditions (see the Supporting Information).[60] This sequence of exploration underscores the versatility and efficiency of our catalytic system in facilitating a variety of radical-mediated transformations, expanding the scope of potential synthetic applications.

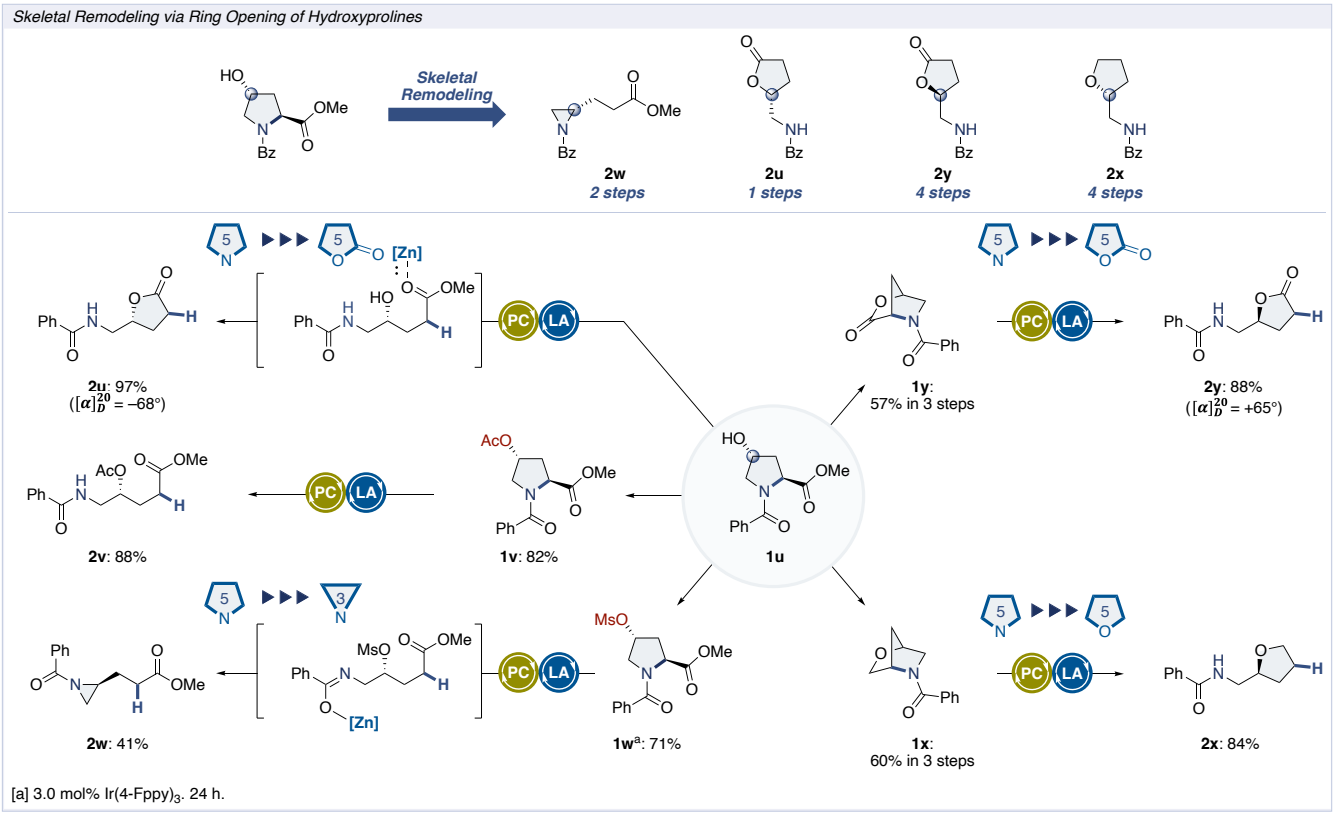
Scheme 2. Intermolecular Radical Addition



Next, to demonstrate the synthetic utility of this protocol, we subjected L-hydroxyproline derivatives to the optimal conditions to convert into the skeletal edited compounds (Scheme 3). The reaction of alcohol **1u** afforded lactone **2u** in 97% yield, presumably forged via Lewis acid-assisted lactonization. The *O*-acetyl variant **1v** was efficiently converted into the ring-opened product **2v**. When the acetyl group was replaced with a mesyl group (**1w**), aziridine **2w** was obtained via an intramolecular S_N2 fashion. Bridged bicyclic compounds **1x** and **1y** were reacted smoothly, and gave enantiomerically pure tetrahydrofuran **2x** and γ-lactone **2y** in good yields, respectively. Notably, **2y** is the enantiomer of **2u**, as confirmed by opti-

cal rotation measurements. This protocol successfully produces optically active compounds, leveraging the stereochemistry derived from L-hydroxyproline. This ability to manipulate the stereochemistry and achieve high yields underscores the robustness and versatility of our method in generating diverse and enantiomerically pure heterocycles.

Scheme 3. Skeletal Remodeling via Ring Opening of Hydroxy Pyrrolidine Derivatives.



■ CONCLUSIONS

In conclusion, we have developed a reductive C–N bond cleavage of *N*-benzyl pyrrolidines using photoredox catalysis with Lewis acid. This reaction enabled unique transformations via a radical mechanism, which were previously unattainable through traditional reductive pyrrolidine C–N bond cleavage, using widely available starting materials. In the context of amide bond activation, the present protocol represents a rare example of σC–N bond cleavage.[27,47,61–64] The critical role of Lewis acid was elucidated by NMR studies and cyclic voltammetry. Additionally, we successfully synthesized γ-lactones, aziridines, and tetrahydrofurans through skeletal remodeling reactions starting from hydroxyproline derivatives. Ongoing efforts in our laboratory are focused on exploring new transformations of nitrogen-containing compounds using photoredox catalysis, further expanding the synthetic utility of this approach.

ASSOCIATED CONTENT

Experimental procedures and spectroscopic data for compounds including ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes
The authors declare no competing financial interest.

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