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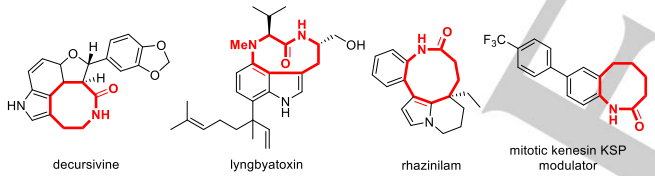
Direct Photocatalytic Synthesis of Medium-Sized Lactams through C–C Bond Cleavage

Na Wang[+], Qiang-Shuai Gu[+], Zhong-Liang Li, Zhuang Li, Yu-Long Guo, Zhen Guo, and Xin-Yuan Liu*

Abstract: We have developed a novel two-step ring-expansion strategy for expeditious synthesis of all ring sizes of synthetically challenging (hetero)aryl-fused medium-sized lactams from readily available 5–8-membered cyclic ketones. This step-economic approach is featured by a unique remote radical (hetero)aryl migration from C to N under visible-light conditions. Broad substrate scope, good functional group tolerance, high efficiency, and mild reaction conditions make this protocol very attractive. In addition, this method also provides expedient access to 13–15-membered macrolactams upon further one-step manipulation. Mechanistic study indicated that the reaction involved amidyl radical and was promoted by acid.

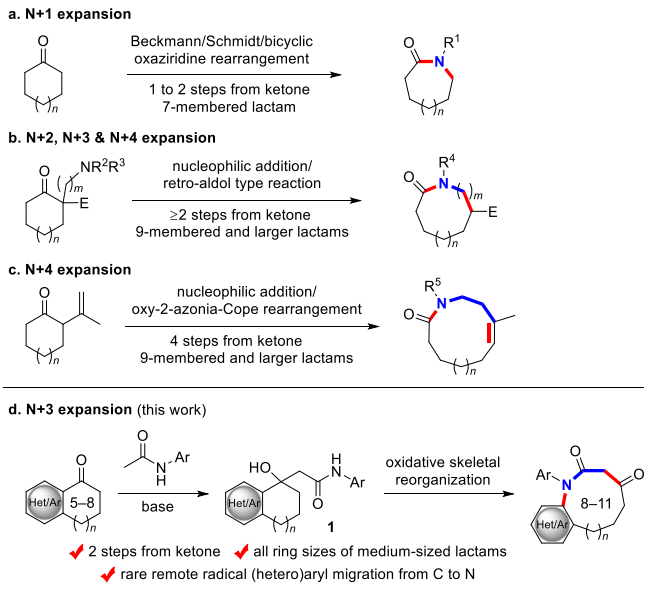
Medium-sized lactams (8–11-membered rings)[1] are found in a wide range of natural products and molecules of biological significance, such as decursivine, lyngbyatoxin, rhazinilam, and other biologically active compounds[2] (Scheme 1). Nevertheless, efficient access to such skeletons remains a challenging topic due to unfavourable transannular interactions and entropic/enthalpic reasons.[3] The ring expansion strategy dispenses with the high-dilution technique commonly required for a direct head-to-tail cyclization strategy[4] and is also more flexible for accessing a full range of ring sizes compared with a cycloaddition strategy.[5] Thus, the development of such ring expansion methods has been thriving for decades.[6]



Scheme 1. Biologically active medium-sized lactams.

Among others, ketone has served as an excellent platform for developing several types of practical ring-expansion methodologies toward medium-sized lactams.[7] The first type encompasses the classic Beckmann rearrangement, Schmidt rearrangement and bicyclic oxaziridine rearrangement as well as their variants, in which one nitrogen atom is inserted aside the ketone carbonyl group (N+1 expansion, Scheme 2a).[8] These reactions feature short synthetic steps (1 to 2 steps) while suffering from the difficulty in preparing the ketone starting material, which itself has a medium-sized ring. As a result, such reactions typically find applications in preparation of 7-membered or smaller lactams. The second type includes a number of protocols relying on a common mechanism: intramolecular nucleophilic addition of *N*-nucleophile to ketone followed by a retro-aldol type reaction (N+2, N+3, and N+4 expansion, Scheme 2b).[6a, 6b, 6i] The third type is based on tandem nucleophilic addition and oxy-2-azonia-Cope rearrangement (N+4 expansion, Scheme 2c).[9] Both of these two types of expansion methodologies are capable of inserting multiple atoms and thus are amenable to practical preparation of a broad scope of lactams (typically 9-membered and larger). Nonetheless, compared with the first type, these two normally require multi-step preparation of expansion substrates from cyclic ketones. Besides, all these three types of methodologies fail to provide a practically efficient route toward 8-membered lactams, which have raised recent synthetic interests.[6h] With our continuing efforts[10] in developing radical-initiated skeletal reorganization for the construction of carbo- and heterocyclic systems,[11] we herein report a general and efficient two-step N+3 ring-expansion strategy for convenient access to all ring members of medium-sized, i.e., 8–11-membered, lactams from readily available cyclic (hetero)aryl ketones under mild visible-light conditions[12] (Scheme 2d) via a rare remote radical (hetero)aryl migration from C to N.[13] On this basis, we have also developed a N+4 ring-expansion strategy leading to 13–15-membered macrolactams upon further one-step manipulation.

We started our investigation by finding that treatment of **1A** (Table 1, R^1 = H, R^2 = *m*-CF_3, n = 1), readily prepared from



Scheme 2. Ring-expansion strategies for synthesis of medium-sized lactams from ketone.

[a] N. Wang, Z. Li, Y.-L. Guo, Prof. Dr. X.-Y. Liu*
Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen 518055, China
E-mail: liuxy3@sustc.edu.cn
Website: http://liuxy.chem.sustc.edu.cn/
N. Wang, Prof. Dr. Z. Guo
College of Materials Science & Engineering, Key Laboratory of Interface Science and Engineering in Advanced Materials, Ministry of Education, Taiyuan University of Technology, Shanxi, 030024, China
Dr. Q.-S. Gu, Dr. Z.-L. Li
Academy for Advanced Interdisciplinary Studies, Southern University of Science and Technology, Shenzhen, 518055, China.
[+] These authors contribute equally to this work.
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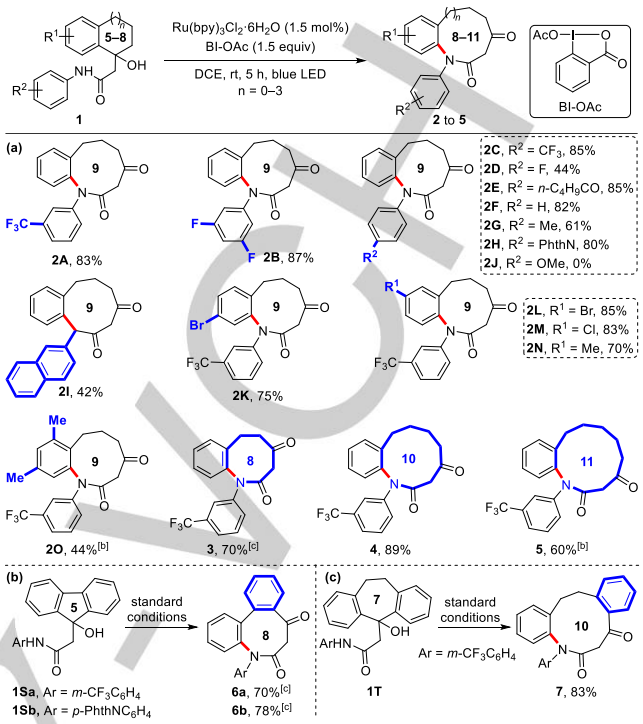
commercially available 1-tetralone in one step (see SI for details), with photocatalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1.5 mol%) and acetoxybenziodoxole (BI-OAc, 1.5 equiv) under blue LED irradiation in 1,2-dichloroethane (DCE) at room temperature afforded 9-membered lactam **2A** in 83% isolated yield (Table S1, entry 1 and Table 1a). Upon further reaction condition optimization (see Table S1 for details), we found that the cyclic benziodoxole structure was essential for the reaction, because hydroxylbenziodoxole (BI-OH) (Table S1, entry 2) was only slightly less effective than BI-OAc while acyclic PhIO as well as molecular oxygen failed to afford the desired product (Table S1, entries 3 and 4). In addition, control experiments demonstrated that photocatalyst, BI-OAc, and light are all indispensable for the current reaction (Table S1, entries 10–12).

Subsequently we investigated the generality of this reaction under the optimal conditions (Table 1). We first examined the effect of substituents on the aryl ring of the aniline moiety. A variety of substrates bearing electron-withdrawing groups, such as trifluoromethyl, fluoro, and carbonyl groups, on either the *para*- or *meta*-position of the aniline were suitable for the reaction to afford desired products **2A**–**2E** in 44–87% yields. More importantly, substrates bearing phenyl rings unsubstituted (**1F**) or substituted by slightly electron-releasing groups (**1G**–1**H**) or a naphthalene ring (**1I**) all worked well to afford **2F**–**2I** in 42–82% yield. Unfortunately, the reaction of substrate **1J** with a strong electron-donating group (-OMe) afforded no expected product, likely due to undesired oxidative decomposition. We next investigated the effect of substituents on the aryl ring of the tetrahydronaphthalene moiety. Both electron-withdrawing (**2K**–**2M**) and –releasing (**2N**) groups were well tolerated to provide expanded lactams in good yields. However, substrates **1O** exhibited a sluggish reaction rate, possibly caused by the disfavoured steric interaction between the *ortho*-Me group with the expanding ring.

Subsequently, we explored the scope for the expanding ring. As mentioned above, 8-membered lactams are exceptionally recalcitrant to practical preparation by known expansion methods based on ketone. To our delight, substrate **1P** featuring a yet-to-expand five-membered ring was applicable for the expansion process to provide 8-membered lactam **3** in 70% yield, albeit with an elongated reaction time. Meanwhile, substrate **1Q** possessing a 7-membered ring underwent the desired expansion smoothly to give 10-membered lactam **4**. More encouragingly, substrate **1R** bearing an 8-membered ring delivered 11-membered lactam **5** in 60% yield with an extended reaction time. Furthermore, the expansion of substrates **1Sa**, **1Sb**, and **1T** having additional fused aryl rings within the backbones of the expanding rings proceeded straightforwardly to afford 8-membered lactams **6a**/**6b** and 10-membered lactam **7** in good yields, respectively (Table 1b and 1c). All these excellent results are in great support for the potential wide application of the current protocol in constructing a rich diversity of medium-sized lactams.

Encouraged by these exciting results, we speculated that heteroaryl ketone might also be compatible with our current protocol, thus enabling facile assembly of heteroaryl-fused medium-sized lactams. Gratifyingly, both 2-pyridyl- or 4-pyridyl-

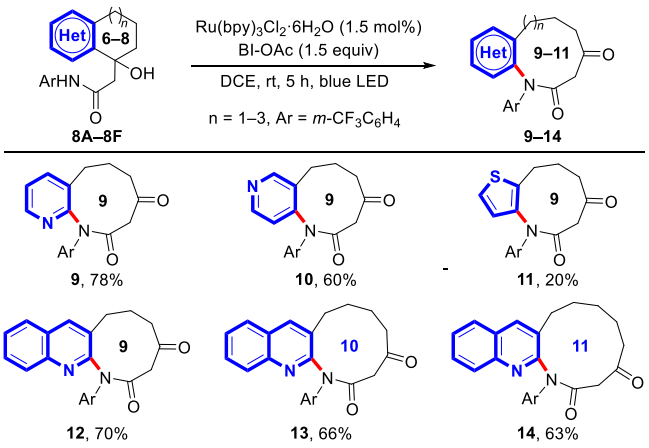
Table 1: Scope of medium-sized lactams fused with aryl rings.[a]



[a] Reaction conditions: **1** (0.20 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.003 mmol), BI-OAc (0.30 mmol) in DCE (2 mL) at room temperature under irradiation of blue LED. Yields of isolated products are given. [b] Reaction time is 24 h. [c] Reaction time is 12 h. Phth = phthaloyl.

containing substrates **8A** and **8B** were effectively transformed to the corresponding pyridyl-fused medium-sized lactams **9** and **10**, respectively, in satisfactory yields under the optimized conditions (Table 2). Similarly, an array of 2-quinolyl-fused substrates **8C**–**8F** reacted smoothly to afford a small library of 9- to 11-membered medium-sized lactams **12**–**14** in 63–70% yields. The structure of **12** was confirmed by X-ray crystallographic analysis (see Figure S1 in SI).[14] In addition, a labile electron-rich thiophenyl ring in substrate **8C** survived our oxidative reaction conditions to deliver

Table 2: Scope of medium-sized lactams fused with heteroaryl rings.[a]



[a] Reaction conditions: **8** (0.20 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.003 mmol), BI-OAc (0.30 mmol) in DCE (2 mL) at room temperature under irradiation of blue LED. Yields of isolated products are given.

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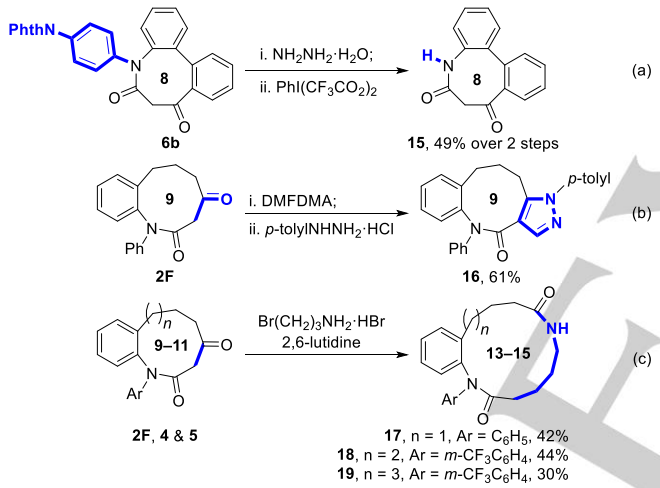
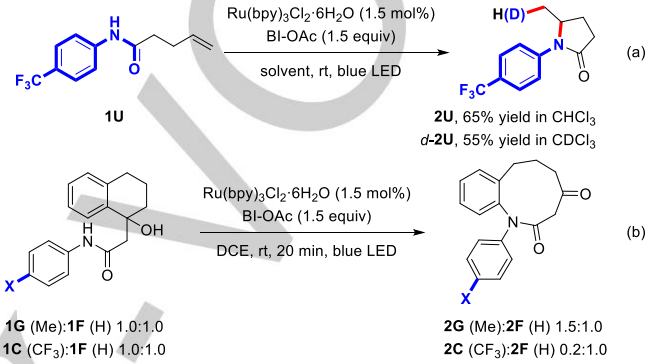
desired lactam **11**, albeit in low yield.

To demonstrate the application potential of this strategy, versatile transformations were performed. The aryl group of **6b** was successfully removed to release the free lactam **15** in 49% overall yield (Scheme 3a), thus validating the applicability of our protocol in synthesis of naturally occurring or biologically active medium-sized secondary lactams (Scheme 1).[2] Furthermore, upon treatment of **2F** with DMFDMA and subsequent cyclization of the obtained enamine intermediate with *p*-tolylhydrazine, the fused pyrazole **16** was generated in 61% yield (Scheme 3b). Most importantly, we developed a further one-step N+4 ring-expansion strategy for access to a range of macrolactams from the obtained β-keto lactams.[6] As such, the reaction of 9–11-membered β-keto lactams with 3-bromopropylamine afforded 13–15-membered lactams **17**–**19** in 30–44% yields (Scheme 3c). Besides, other common and useful manipulations, such as tandem ketone reduction and dehydration, nucleophilic addition to ketone with allyl Grignard reagent, and Suzuki coupling of aryl bromide with an aryl boronic acid, of our prepared medium-sized lactams were also readily effected (Scheme S1 in SI).



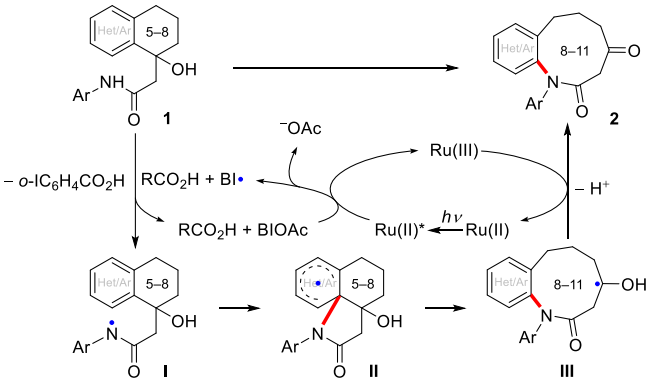
Scheme 3. Versatile transformations. DMFDMA = *N*,*N*-Dimethylformamide dimethyl acetal.

Our initial mechanistic study revealed significant inhibition of the reaction of **1A** by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), indicating a possible radical process (See Scheme S2 in SI). In addition, the possible involvement of amidyl radical[15] was firstly supported by the formation of hydroamination products **2U** and *d*-**2U** from **1U**, featuring an anilide moiety the same with that in substrate **1C,** under the otherwise optimized conditions except that solvent was changed to $CHCl_3$/$CDCl_3$ (Scheme 4a). The reaction was reminiscent of reported radical hydroamination mediated by amidyl radical,[16] likely via a pathway involving *5-exo-trig* intramolecular cyclization followed by hydrogen/deuterium abstraction from $CHCl_3$/$CDCl_3$. The formation of amidyl radical was further supported by a slight electronic effect of substitution on the aniline ring favouring electron-releasing groups (Scheme 4b), as reported in literature.[16a] As for the generation of amidyl radical, the luminescence quenching experiments revealed that BI-OAc rather than substrate **1A** effectively quenched the excited Ru(II) (Figure S2 in SI). In addition, the cyclic voltammetry study on reduction potential indicated benziodoxolonyl radical (BI·) together with a carboxylic acid (ca. ≥ +2.0 V for 2-iodobenzoic acid vs Fc^+/Fc in DCE) rather than Ru(III) (+0.95 V vs Fc^+/Fc in DCE) likely oxidized the substrates (+1.41 V for **1A** and +1.58 V for **1C** vs Fc^+/Fc in DCE) to amidyl radical species. The indispensable role of carboxylic acid was substantiated by greatly accelerated reaction rates in presence of stoichiometric amounts of side products acetic acid and 2-iodobenzoic acid (Figures S3–4 in SI) and significantly diminished yield in presence of base (less than 15% yield after overnight stirring, see SI for details).



Scheme 4. Mechanistic study.

Based on the mechanistic study discussed above, a plausible mechanism is proposed in Scheme 5. The reaction was initiated by oxidation of the photoexcited $Ru(bpy)_3^{2+*}$ to $Ru(bpy)_3^{3+}$ by BI-OAc to generate BI·.[17] Substrate **1** was then oxidized by BI· together with carboxylic acid originating from either unproductive decomposition of BI-OAc or the reaction itself to provide amidyl radical **I**.[18] The amidyl radical **I** would subsequently attack the (hetero)aryl ring to form a new C–N bond in intermediate **II**, followed by selective C–C bond cleavage to furnish the neutral ketyl radical **III**. Single-electron oxidation of the neutral ketyl radical **III** by $Ru(bpy)_3^{3+}$ would deliver the medium-sized lactam and regenerate $Ru(bpy)_3^{2+}$.



Scheme 5. A plausible mechanistic pathway.

In summary, we have successfully developed a novel photocatalytic ring-expansion strategy for direct synthesis of a variety of synthetically challenging 8–11-membered (hetero)aryl-fused lactams from readily available cyclic ketones through a rare remote radical (hetero)aryl migration from C to N. The present

protocol exhibits broad substrate scope, good functional group tolerance, high yield, and mild reaction conditions, all of which warrant a great potential for wide application in preparation of medium-sized lactams. Further versatile transformations of the obtained medium-sized lactams, particularly the one-step ring expansion to macrolactams, have also been demonstrated to ensure a broad impact of this methodology in various related areas. Detailed mechanistic studies revealed a carboxylic acid-promoted pathway for generation of amidyl radical with I(III) reagents under visible light irradiation conditions.

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Keywords: amidyl radical • C–C bond cleavage • ketones • medium-sized lactams • ring expansion

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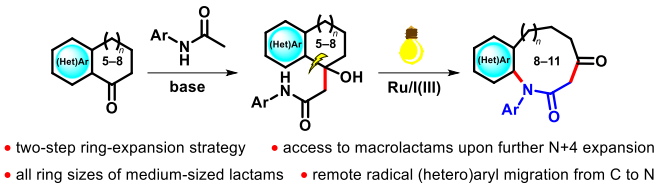

Growing ring under light: A two-step ring-expansion strategy for expedite synthesis of all ring sizes of synthetically challenging (hetero)aryl-fused medium-sized lactams from readily available 5–8-membered cyclic ketones has been developed. The key step involves an uncommon remote radical (hetero)aryl migration from C to N via C–C bond cleavage under mild visible light irradiation conditions.

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