

Construction of Polycyclic γ -Lactams and Related Heterocycles via Electron Catalysis

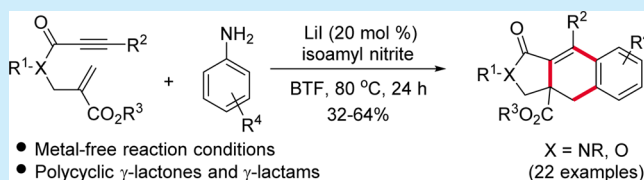
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S Supporting Information

ABSTRACT: Cascade radical cyclization of 1,6-enynes for the construction of biologically important polycyclic γ -lactams and related heterocycles is reported. In these radical cascade processes, three new C–C bonds are formed and transition metals are not required to run these sequences. The mild reaction conditions, broad substrate scope, and the importance of the heterocyclic products render the approach valuable.



Nitrogen-containing fused heterocycles are widely found in natural products, biologically active structures, medically relevant compounds, and other fine chemicals.¹ Among them, the polycyclic γ -lactams have received considerable attention due to their important biological activities (Figure 1). For instance, salinosporamide A was isolated from a marine

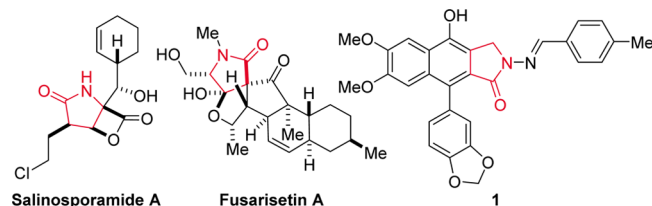


Figure 1. Examples of biologically important molecules containing a polycyclic γ -lactam unit.

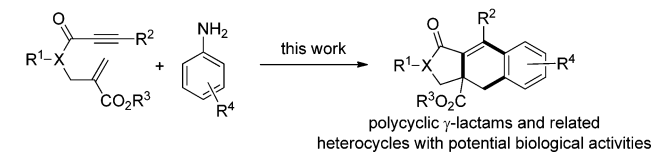
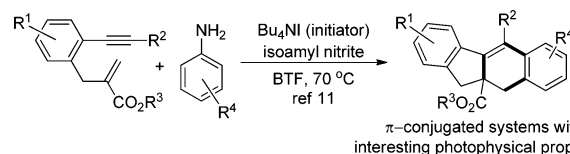
actinomycete by Fenical and co-workers, which has been proven to be a potent proteasome inhibitor.² Fusarisetin A, isolated from the soil fungus *Fusarium* sp. FN080326, was shown to inhibit acinar morphogenesis (77 μ M), cell migration (7.7 μ M), and cell invasion (26 μ M) in these cell lines without any significant cytotoxicity.³ More importantly, polycyclic γ -lactam derivative **1** exhibited efficient inhibitory effects on proliferation of cancer cells.⁴ This biological activity has made the synthesis of polycyclic γ -lactams quite attractive, and several straightforward and robust methods for the construction of polycyclic γ -lactams have been elegantly established.⁵

Cascade radical cyclization of 1,*n*-enynes is a powerful approach for the construction of carbon and heterocyclic ring structures.^{6,7} However, to the best of our knowledge, radical cascade cyclization of 1,*n*-enynes toward the construction of polycyclic γ -lactams is a largely unexplored research area. More significantly, most of the reported methods for the construction of polycyclic γ -lactams from 1,*n*-enynes are based on transition-metal catalysis.⁸ Consequently, developing novel and efficient transformations of 1,*n*-enynes to synthesize some important

heterocyclic compounds under transition-metal-free reaction conditions is still highly desirable.

Within the frame of our program devoted to the development of radical cascade reactions using electron catalysis,⁹ we recently disclosed that aryl radicals, generated from commercially available anilines,¹⁰ can regioselectively undergo radical cascade cyclization with arene-conjugated 1,6-enynes, providing polycyclic π -conjugated materials that show interesting photo-physical properties (Scheme 1).¹¹ Motivated by these findings,

Scheme 1. 1,6-Enynes as Aryl Radical Acceptors for the Construction of Valuable Compounds



we became interested in further exploring the reactivity of aryl radicals with other types of 1,6-enynes and assumed that the method might be extended to access biologically relevant heterocyclic ring frameworks, such as polycyclic γ -lactams. Herein we describe the preliminary results of this study.

Our investigations commenced using the nitrogen-tethered 1,6-enyne **2a** and aniline **3a** as model substrates (Table 1). To our delight, 36% yield of the polycyclic γ -lactam **4aa** was obtained by using isoamyl nitrite for in situ diazonium salt

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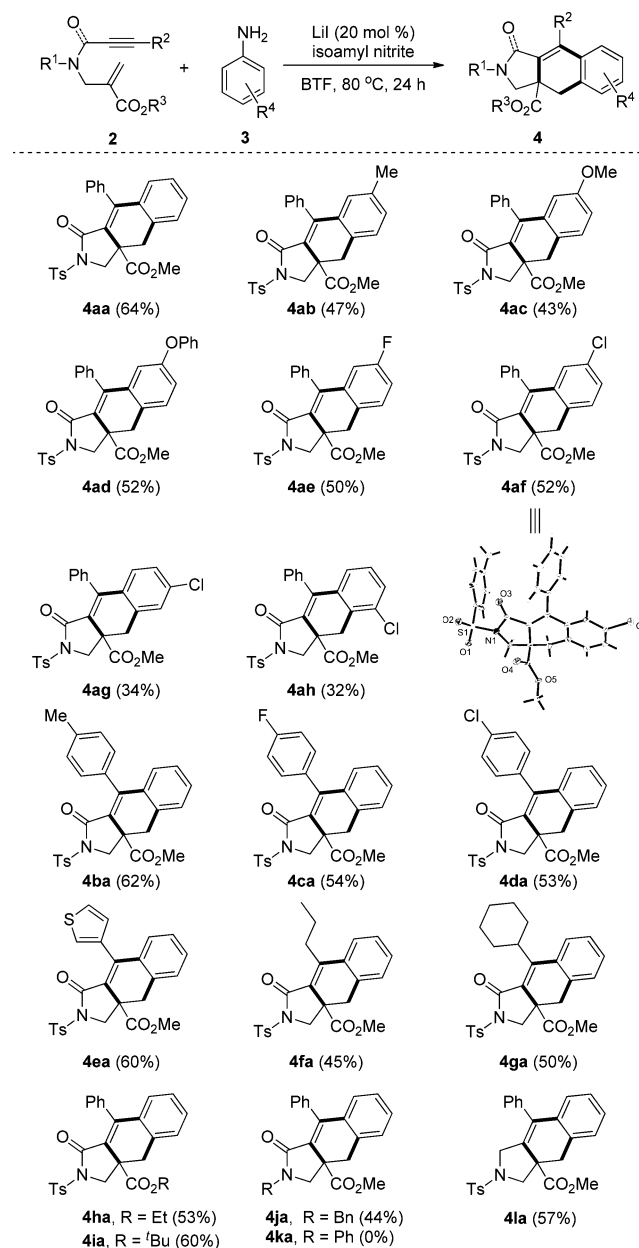
Table 1. Reaction Optimization between 2a and 3a^a

entry	initiator	solvent	yield ^b (%)
1	<i>n</i> -Bu ₄ NI	BTF	36
2	<i>n</i> -Bu ₄ NI	CH ₃ CN	31
3	<i>n</i> -Bu ₄ NI	EtOAc	25
4	<i>n</i> -Bu ₄ NI	CH ₂ Cl ₂	21
5	<i>n</i> -Bu ₄ NI	toluene	19
6	<i>n</i> -Bu ₄ NI	1,4-dioxane	trace
7	NaI	BTF	32
8	KI	BTF	45
9	LiI	BTF	51
10	CuI	BTF	trace
11	FeI ₂	BTF	17
12	NiCl ₂	BTF	45
13		BTF	39
14 ^c	LiI	BTF	52
15 ^{c,d}	LiI	BTF	64

^aReaction conditions: 2a (0.2 mmol), 3a (0.4 mmol), initiator (0.04 mmol), and isoamyl nitrite (0.5 mmol) in solvent (2 mL) were stirred at 70 °C for 24 h under argon atmosphere. ^bIsolated yield. ^cStirred at 80 °C. ^dAfter the mixture was stirred for 10 h, additional 0.4 mmol of 3a and 0.5 mmol of isoamyl nitrite were added.

generation¹⁰ in combination with *n*-Bu₄NI as a radical initiator in benzotrifluoride (BTF) at 70 °C for 24 h (Table 1, entry 1). Other reaction parameters including solvent, initiator, and reaction time were then systematically varied. As summarized in Table 1, the reaction media had a significant effect on the reaction efficiency. BTF could be replaced by CH₃CN albeit with a slightly decrease in yield (31%) (Table 1, entry 2). Other solvents such as EtOAc, CH₂Cl₂, and toluene turned out to be less suitable for this cascade (Table 1, entries 3–5), and only a trace amount of 4aa was observed in 1,4-dioxane (Table 1, entry 6). To further improve the reaction efficiency, the influence of radical initiator was examined (Table 1, entries 7–9). With NaI yield decreased to 32%, while with KI and LiI yield was improved to 45% and 51%, respectively. Notably, worse results were achieved upon using transition-metal salts as radical initiators (Table 1, entries 10–12). In the absence of any initiator, 4aa was isolated in 39% yield (Table 1, entry 13). Likely, isoamyl nitrite acted as the initiator in this case. A further enhancement in the product yield was obtained upon increasing the reaction temperature from 70 to 80 °C (52%) (Table 1, entry 14), and the highest yield was achieved by increasing the amount of 3a and isoamyl nitrite (64%) (Table 1, entry 15).

With optimal reaction conditions in hand (Table 1, entry 15), we next investigated the scope and limitations of this radical cascade process by using various substituted anilines in combination with the nitrogen-tethered 1,6-enyne 2a as the reaction partner. As shown in Scheme 2, both electron-donating (Me, OMe, OPh) and electron-withdrawing groups (F, Cl) can be successfully introduced at the *para*-position of the aniline component, revealing that *para*-electronic modification of the aniline does not substantially alter reaction efficiency. The corresponding polycyclic γ -lactams 4ab–af were isolated in moderate to good yields. The structure of 4af was unambiguously confirmed by X-ray diffraction analysis (see Table 1 and Figure S1 in the Supporting Information).¹²

Scheme 2. Substrate Scope^{a,b}

^aReaction conditions: 2 (0.2 mmol), 3 (0.4 + 0.4 mmol), LiI (0.04 mmol), and isoamyl nitrite (0.5 + 0.5 mmol) in BTF (2 mL) were stirred at 80 °C for 24 h under argon atmosphere. ^bIsolated yield.

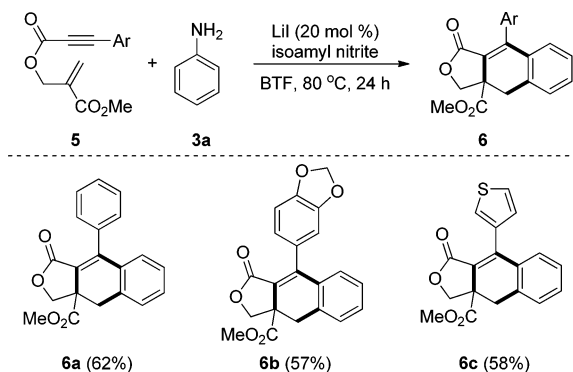
However, lower yields were obtained for anilines bearing radical substituents at the *meta* and *ortho* positions (4ag and 4ah), likely for steric reasons.

Next, the scope of the reaction was examined with respect to the 1,6-enyne component 2. Electron-donating and electron-withdrawing substituents are tolerated at the *para*-position of the R²-aryl group, and the corresponding products 4ba–da were obtained in 53–62% yield. Note that a thienyl group can be installed as the alkyne substituent to afford the polycyclic γ -lactam 4ea in 60% yield. The R²-aryl substituent can be replaced by an alkyl substituent as documented for the propyl and cyclohexyl congener. The corresponding heterocycles 4fa and 4ga were isolated in 45% and 50% yield, respectively.

Good yields were also obtained when the activating methyl ester moiety was replaced by a bulkier ethyl and *tert*-butyl ester functionality (**4ha** and **4ia**). We also tested whether the *N*-tosyl group in the 1,6-enyne can be substituted by other *N*-protecting groups. While all of our attempts to carry out the reaction with an *N*-phenyl-protected substrate failed, the *N*-benzyl-protected 1,6-enyne afforded the targeted product **4ja** in 44% yield. Importantly, the reaction of nitrogen-tethered 1,6-enyne **2l** with aniline **3a** under the optimized reaction conditions afforded polycyclic pyrrole product **4la** in 57% yield,¹³ showing that the carbonyl group next to the *N* atom is not required for this cascade.

To further illustrate the synthetic utility of this methodology, we also applied this radical cascade to the construction of other biologically important polycyclic ring systems. To our delight, we found that our approach can be extended to the synthesis of polycyclic γ -butyrolactones. The starting esters **5a–c** containing a 1,6-enyne moiety are readily prepared (see the SI), and the cascade was studied using aniline as the aryl radical precursor. Pleasingly, we found that under the conditions optimized for the lactam synthesis the cascade worked well and the targeted γ -butyrolactones **6a–c** were obtained in 57–62% yield (Scheme 3). It is worth noting that **6b** contains the core structure of collinusin, a natural lignan lactone which exhibits antiviral activity.¹⁴

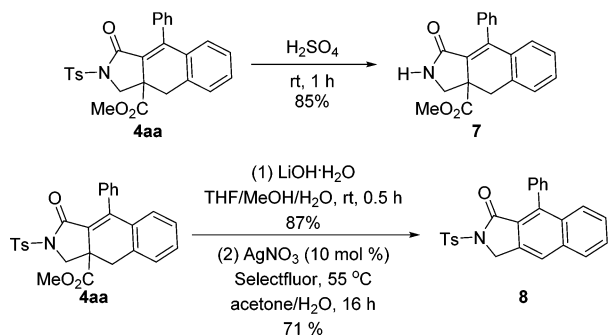
Scheme 3. Construction of Polycyclic γ -Butyrolactone Derivatives^{a,b}



^aReaction conditions: **5** (0.2 mmol), **3a** (0.4 + 0.4 mmol), LiI (0.04 mmol), and isoamyl nitrite (0.5 + 0.5 mmol) with BTF (2 mL) was stirred at 80 °C for 24 h under argon atmosphere. ^bIsolated yield.

The synthetic value of this method was further demonstrated by investigating follow-up chemistry using **4aa** as a substrate (Scheme 4). Treatment of **4aa** under acidic conditions for 1 h at

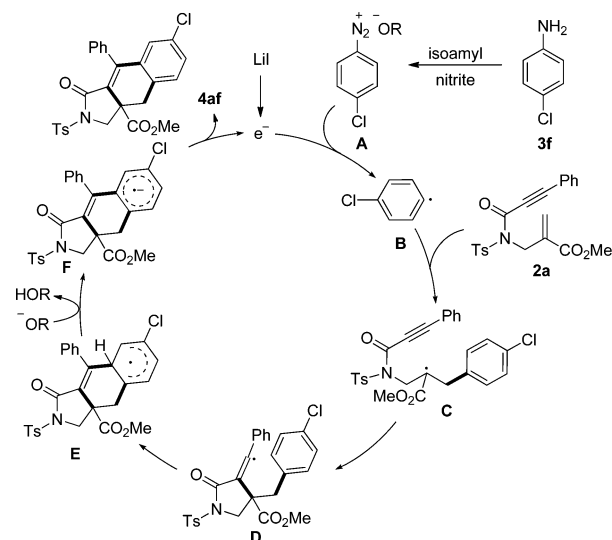
Scheme 4. Follow-up Chemistry



room temperature gave the corresponding detosylated polycyclic γ -lactam **7** in 85% yield.^{15a} Hydrolysis of the ester group was achieved by treating **4aa** with $\text{LiOH}\cdot\text{H}_2\text{O}$ in a mixture of MeOH, THF, and water at room temperature for 0.5 h to give the corresponding acid in 87% yield.^{15b} Silver-catalyzed oxidative decarboxylation of this acid provided aromatization product **8** in 71% isolated yield.^{15c}

A plausible reaction mechanism is proposed in Scheme 5 to explain the formation of polycyclic γ -lactam **4af**. First, 4-

Scheme 5. Plausible Reaction Mechanism



chloroaniline **3b** reacts with isoamyl nitrite to the corresponding diazonium salt **A**. Then, reaction of **A** with LiI generates aryl radical **B** in the initiation step. Chemoselective radical addition of **B** to the activated alkene of 1,6-enyne **2a** provides tertiary alkyl radical **C**,¹⁶ which subsequently undergoes a 5-*exo* cyclization to deliver vinyl radical **D**. Next, radical **D** cyclizes onto the arene to give cyclohexadienyl radical **E**, which in turn gets deprotonated¹⁷ by the alcoholate derived from isoamyl nitrite to provide arene radical anion **F**. Radical anion **F** is eventually oxidized to generate the final polycyclic γ -lactam product **4af**, formally liberating an electron to complete the catalytic cycle.

In conclusion, cascade radical cyclizations of 1,6-enynes with aryl radicals for the construction of polycyclic γ -lactams were developed. Commercially available arylamines were used as radical precursors and LiI as a radical chain initiator. The cascade comprises three C–C bond-forming steps and showed broad substrate scope providing polycyclic γ -lactams in moderate to good yields. More significantly, the method could be efficiently extended to the synthesis of polycyclic pyrrole and γ -butyrolactone derivatives. These cascades proceed by electron catalysis, and transition metals are not required to run these processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03267.

Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra (PDF)

X-ray data for compound **4af** (CIF)

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Notes

The authors declare no competing financial interest.

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