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Photoinduced copper-catalyzed alkoxyl radical-triggered ring-expansion/aminocarbonylation cascade

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ABSTRACT

A photoinduced copper-catalyzed alkoxyl triggered C–C bond cleavage/aminocarbonylation cascade is presented. Through adjusting the structure of alkoxyl radical precursors, functionalized lactones and keto-amides were synthesized with good yields and excellent functional group tolerance under redox-neutral conditions. Notably, this protocol enables the integration of lactone fragments with many amine drugs and drug fragments.

The carbonylation reaction using CO as atom economy carbonyl source represents a robust and valuable chemical transformation in industry and academia, which is regarded as one of the most efficient tools for the synthesis of various kinds of carbonyl compounds such as carboxylic acids, esters, amides, and ketones. Thus, substantial efforts from chemists have been devoted to the development of highly efficient protocols for carbonylation reactions and significant progress has been made over past decades [1–6], especially the palladium-catalyzed carbonylations [7–9]. In the early stages, traditional palladium-catalyzed carbonylation reactions of C(sp^3)-X bonds was more challenging than the C(sp^2)-X bonds, due to the inherent slow oxidative addition to the metal and competitive β-H elimination of alkyl metal species (Scheme 1a) [10,11]. To overcome these obstacles, organic chemists have developed the Pd/*hv*-assisted catalysis strategy [12–15]. For instance, Ryu disclosed a robust ultraviolet (UV) light-induced Pd-catalyzed atom transfer radical carbonylation reactions of alkyl iodides [16,17]. Arndtsen demonstrated an elegant visible-light induced Pd-catalyzed radical carbonylation reaction of alkyl iodides [18]. Different with the traditional Pd catalysis, the Pd/*hv*-assisted catalysis strategy have altered the reaction pathway from two-electron redox events to single electron transfer, enabling carbonylation of alkyl iodides successfully under mild conditions. Benefiting from the flourishing development of free radical chemistry, the visible-light driven carbonylation reactions have been developed far beyond the alkyl halides and Pd catalysis [19–21]. For instance, a variety of photocatalytic carbonylation of alkyl radical precursors such as carboxylic acids, Katritzky salts, organosilicates and others have been reported by different research communities [22–29]. Among them, the group of Xiao and Chen presented the impressing photoinduced Cu or Ir-catalyzed aminocarbonylation of cycloketone oxime esters *via* a C–C cleavage process, providing a series of cyanoalkylated amides [28,29]. Despite this significant progress, it still deserves to explore step- and atom-economy carbonylation reactions, allowing rapid construction of complex carbonyl derivatives from simple feedstocks [30–32].

Since the pioneering works of Schreiber, Suginome and Suárez *et al.* in 1980s, the alkoxyl radical-mediated ring expansion strategy has emerged as an attractive approach to accessing medium-sized and macrolactones [33–35]. However, only few examples and applications of this strategy have been explored so far, probably due to the difficulty and challenging in the generation of alkoxyl radicals and the further functionalization of carbon-centered radicals (radical int **I**) generated through radical triggered ring-expension [33–38]. Recently, our group have successfully disclosed the redox-neutral ring expansion/cross-couplings of hemiketal hydroperox-

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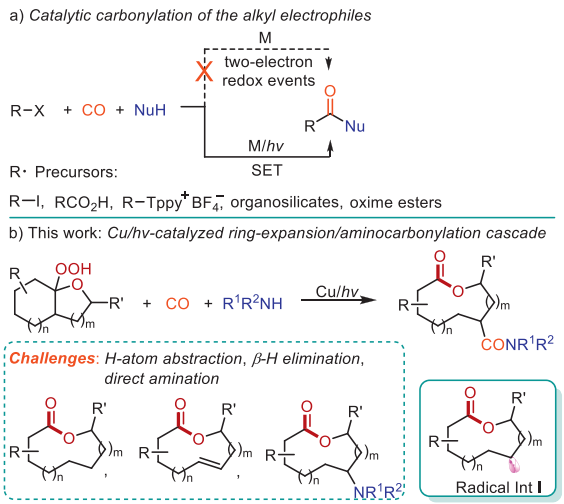
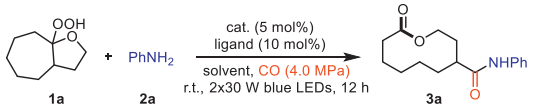


Scheme 1. Metal/*hv*-assisted catalyzed carbonylation of alkyl electrophiles with CO.

ides with diverse nucleophiles through Cu or Fe-catalyzed radical relay, enabling incorporation of diverse functional groups such as CN, N_3, X and others into the lactones, especially macrolactones [39]. Encouraged by this success, we wonder whether the radical int **I** could engage in the carbonylation reaction with CO under Cu/*hv* catalytic system. The challenges for this cascade include the competitive H-atom abstraction, the possible β-H elimination, and the direct amination of radical int **I** (Scheme 1b). Herein, we present the first photoinduced Cu-catalyzed alkoxyl radical-mediated ring-expansion/aminocarbonylation cascade, offering a straightforward access to lactones bearing an acylamino group. Remarkably, this protocol enables the integration of lactone, especially macrolactone fragments with many amine drugs and drug fragments in good yields.

To verify this hypothesis, we conducted the aminocarbonylation reaction of hemiketal hydroperoxide **1a** with aniline **2a** and CO gas under the Cu/*hv*-assisted catalysis (Table 1). To our delight, the ring expansion/aminocarbonylation reaction proceeded successfully in the presence of CuCl (5 mol%) as the catalyst and 2,2′:6′,2″-Terpy (10 mol%, $\mathbf{L_1}$) as the ligand in CF_3Ph with 4.0 MPa of CO under visible light irradiation, affording the desired lactone **3a** in 58% yield (entry 1). Solvent screening indicated that MeOH gave better yield than CF_3Ph and 1,4-dioxane, delivering the product **3a** in 88% yield (entries 2 and 3). It is worthy to mention that the oxycarbonylation product (ester) was not detected in this copper-catalytic system, even MeOH is also a good nucleophile. Other copper catalysts such as CuI, $Cu(OAc)_2$ and $CuSO_4$ were also examined, and $CuSO_4$ exhibited the best catalytic efficiency (entries 4–6). While the iron and cobalt catalysts were totally ineffective for this transformation (not shown). Apart from 2,2′:6′,2″-Terpy, other bidentate N ligands such as 2,2′-Bipy and 1,10-Phen were also effective, but resulted in relatively lower yields of **3a** (entries 7 and 8). The pressure of CO had a significant impact on the reaction efficiency. Satisfactorily, the reaction still worked well under 0.5 MPa of CO (entry 9), but no reaction occurred when the pressure of CO was reduced to 0.1 MPa (not shown). Finally, control experiments revealed that the reaction could also took place without ligand or visible light irradiation, but gave very poor yield of **3a** (entries 10 and 11). While no reaction took place in the absence of copper catalyst (entry 12).

Table 1
Optimization of reaction conditions.[a]



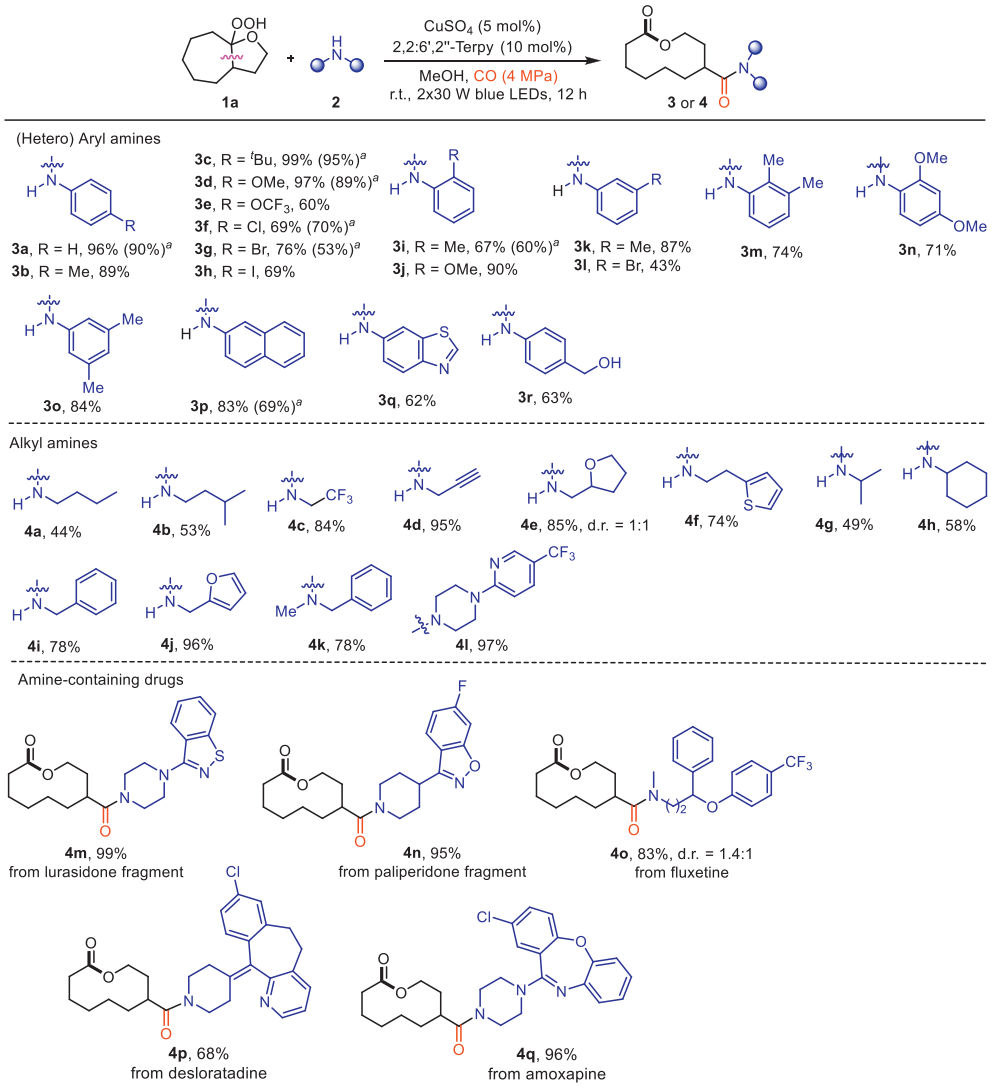
Entry	Catalyst	Ligand	Solvent	Yield (%)
1	CuCl	2,2′:6′,2″-Terpy	CF_3Ph	58
2	CuCl	2,2′:6′,2″-Terpy	1,4-Dioxane	69
3	CuCl	2,2′:6′,2″-Terpy	MeOH	88
4	CuI	2,2′:6′,2″-Terpy	MeOH	60
5	$Cu(OAc)_2$	2,2′:6′,2″-Terpy	MeOH	75
6	$CuSO_4$	2,2′:6′,2″-Terpy	MeOH	98 (96)[b]
7	$CuSO_4$	2,2′-Bipy	MeOH	75[b]
8	$CuSO_4$	1,10-Phen	MeOH	64[b]
9	$CuSO_4$	2,2′:6′,2″-Terpy	MeOH	90[b,c]
10	$CuSO_4$	2,2′:6′,2″-Terpy	MeOH	26[b,d]
11	$CuSO_4$	–	MeOH	30[b]
12	–	2,2′:6′,2″-Terpy	MeOH	NR

[a] Reaction conditions: **1a** (0.4 mmol, 2.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.), catalyst (5 mol%), ligand (10 mol%), CO (4.0 MPa) and solvent (2 mL) under the irradiation of 2 × 30 W blue LEDs at room temperature for 12 h; isolated yields.
[b] 1.5 equiv. of **1a** was used.
[c] 0.5 MPa of CO was used.
[d] Without light irradiation.

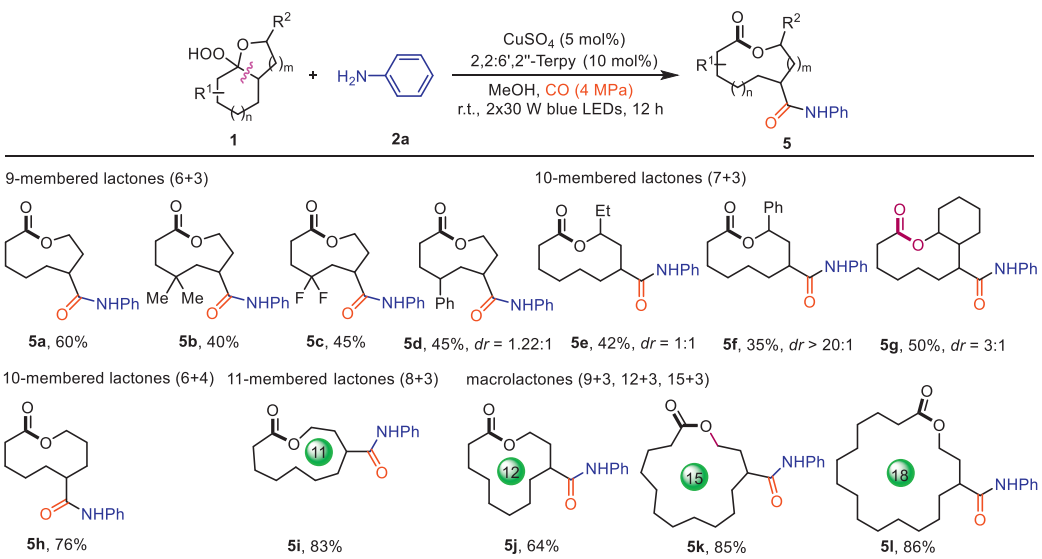
With optimized conditions in hand, the aminocarbonylation of hemiketal hydroperoxide **1a** with structurally diverse amines **2** was first evaluated. As shown in Scheme 2, a variety of aryl amines were engaged efficiently in this transformation, delivering the desired products **3a**-**3r** in moderate to good yields. Aryl amines bearing electron-donating groups (Me, ^{t}Bu and OMe) or weak electron-withdrawing groups (OCF_3, Cl, Br and I) on *para*-, *meta*- and *ortho*-positions of aromatic ring all were amenable, affording the desired products **3a**-**3l** in good to excellent yields. Valuable functional groups such as Br (**3g** and **3l**) and I (**3h**) were survived under the present conditions, which offer opportunities for further functionalization. Disubstituted aryl amines also worked well to deliver the desired products **3m**-**3o**. Heteroaryl amines such as benzo[*d*]thiazol-6-amine furnished the product **3q** in 62% yield. Notably, the 4-amino benzyl alcohol reacted chemoselectively to afford the amide **3r** in 63% yield. Satisfactorily, the scope of amines was not limited to aryl amines. Primary and secondary alkyl amines were also competent nucleophiles, furnishing the corresponding products **4a**-**4l** in moderate to good yields. Functional groups such as CF_3 (**4c**), carbon-carbon triple bond (**4d**) and ether (**4e**) were well-tolerated. Benzylamine and N-Me benzylamine furnished the products **4i** and **4k** in good yields. Remarkably, drug fragments and drugs containing amine moiety also participated in this reaction efficiently, affording the expected products **4m**-**4q** in excellent yields, which highlight great application potential of this protocol for the modification of complex amine-containing molecules. However, when diaryl amine was subjected to the reaction system, no reaction was observed (not shown).

Next, the aminocarbonylation of various hemiketal hydroperoxides were examined by using phenylamine **2a** as the model nucleophile (Scheme 3). The ring expansion/amincarbonylation cascade proceeded smoothly to afford the desired CONHPh-containing lactones in moderate to good yields, which are difficult to obtain by other methods. A range of 9-, 10- and 11-membered lactones were easily synthesized by adjusting the ring size and substituents of substrates (**5a**-**5i**). Remarkably, this protocol is also applicable for the synthesis of CONHPh-functionalized 12-, 15- and 18-membered macrolactones (**5j**-**5l**).

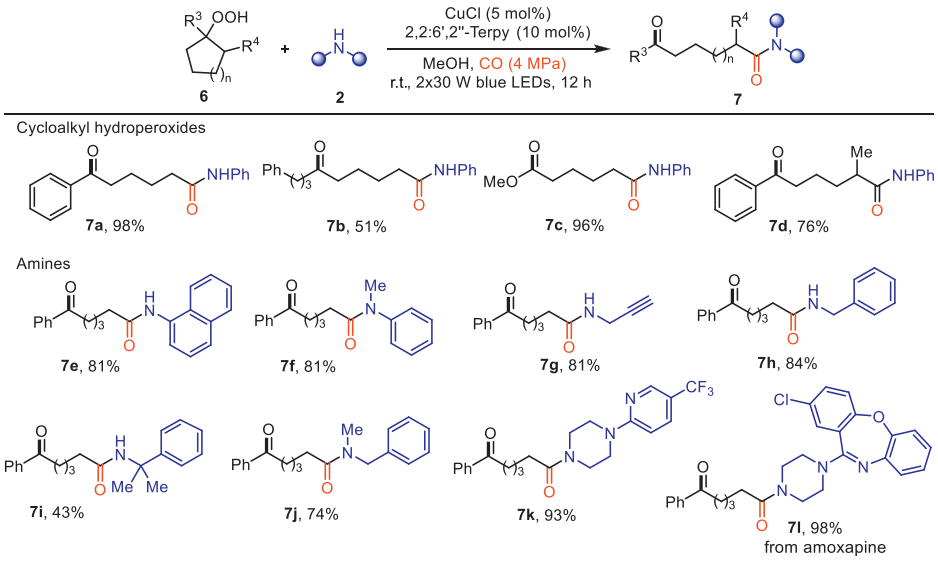
Apart from the ring-expansion to lactones, the aminocarbonylation of monocyclic hydroperoxides **6** were also evaluated [40–48]. As expected, the reactions worked efficiently to afford a range of keto-functionalized amides (Scheme 4). Not only 1-aryl but also 1-alkyl substituted cyclopentyl hydroperoxides were efficient substrates (**7a** and **7b**). When 1–methoxy-substituted substrate was subjected into the reaction, the anticipated ester-containing amide **7c** was obtained in 96% yield. 1,2-Disubstituted substrate suffered the C–C cleavage regioselectively to afford the **7d** as sole product



Scheme 2. Scope of amines. Reaction conditions: **1a** (0.3 mmol, 1.5 equiv.), **2** (0.2 mmol, 1.0 equiv.), $CuSO_4$ (5 mol%), 2,2′:6′,2″-Terpy (10 mol%), CO (4 MPa) and MeOH (2 mL) under the irradiation of 2 × 30 W blue LEDs at room temperature for 12 h; isolated yields. [a] 0.5 MPa of CO was used.



Scheme 3. Scope of hemiketal hydroperoxides. Reaction conditions: **1** (0.3 mmol, 1.5 equiv.), **2a** (0.2 mmol, 1.0 equiv.), $CuSO_4$ (5 mol%), 2,2′:6′,2″-Terpy (10 mol%), CO (4 MPa) and MeOH (2 mL) under the irradiation of 2 × 30 W blue LEDs at room temperature for 12 h; isolated yields.

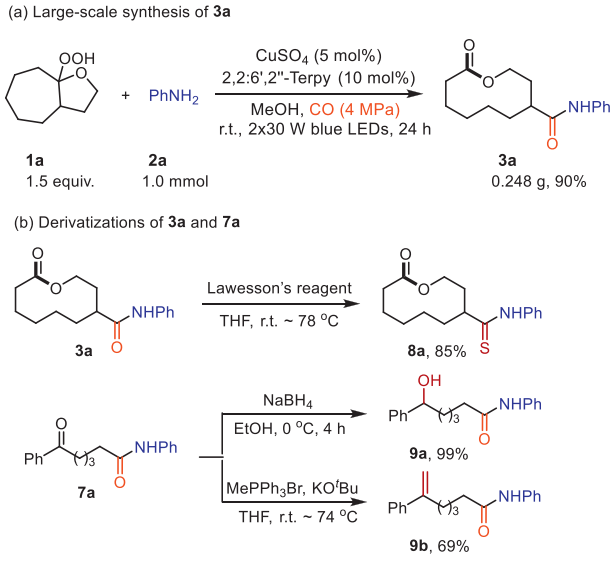


Scheme 4. Scope of cycloalkyl hydroperoxides and amines. Reaction conditions: **6** (0.4 mmol, 2.0 equiv.), **2** (0.2 mmol, 1.0 equiv.), CuCl (5 mol%), 2,2′:6′,2″-Terpy (10 mol%), CO (4 MPa) and MeOH (2 mL) under the irradiation of 2 × 30 W blue LEDs at room temperature for 12 h; isolated yields.

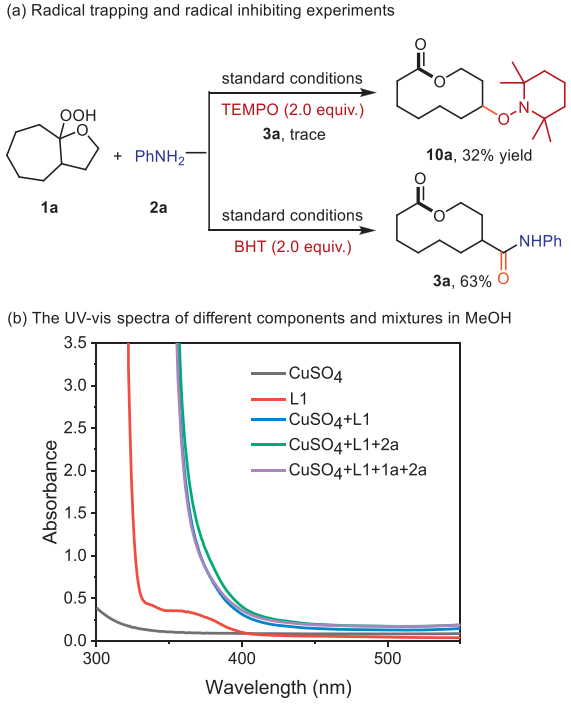
in 76% yield. In terms of amines, aryl, alkyl and benzyl amines, as well as drugs were all compatible with this transformation, producing the corresponding amides **7e**-**7l** in satisfied yields.

To demonstrate the application potential of this protocol. Large-scale synthesis and derivatizations of **3a** were performed. Conducting the model reaction of **1a** and **2a** on a 1.0 mmol scale did not damage the yield of **3a** after prolonging the reaction time to 24 h. Treatment of **3a** with Lawesson's reagent delivered the thioamide **8a** in 85% yield. The carbonyl group in amide **7a** could be reduced selectively to give the hydroxyl–contained amide **9a** in almost quantitative yield. In addition, the Wittig reaction of **7a** also proceeded efficiently to afford the unsaturated amide **9b** in 69% yield (Scheme 5).

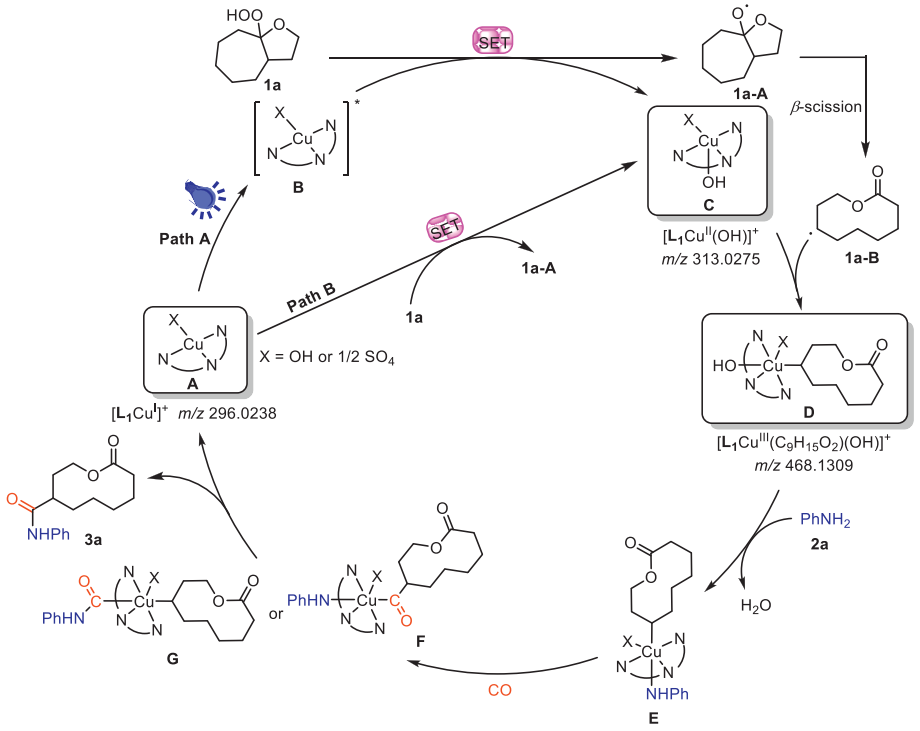
According to the literature and our previous studies, we speculate that this C–C bond cleavage/aminocarbonylation cascade proceeded *via* a radical pathway. To confirm this inference, some control experiments were conducted. When 2.0 equiv. of TEMPO was added into the reaction of **1a** and **2a**, the formation of **3a** was inhibited and the TEMPO-adduct **10a** was isolated in 32% yield. The addition of BHT (2.0 equiv.) decreased the yield of **3a** from 96% to 63% (Scheme 6a). These results provided support for the radical mechanism. To elucidate the impact of visible light irradiation on the reaction, the UV–vis spectra for each component of the reaction and different mixtures were measured (Scheme 6b). It was found that the single $CuSO_4$ and ligand $\mathbf{L_1}$ did not absorb light in the visible region. While the complex of $CuSO_4/\mathbf{L_1}$ showed an obvious bathochromic shift, which enabled the possible excitation with visible light. Further addition of the substrates (**2a** or **1a** + **2a**) to the complex mixture did not affect the absorption behavior of copper-ligand complex. These results suggested that the $Cu/\mathbf{L_1}$ complex was photoactive species in this domino catalytic cycle, which is consistent with fact that both Cu species and light irradiation were critical for the high efficiency of this reaction.



Scheme 5. Large-scale synthesis and derivatizations of products.



Scheme 6. Mechanism studies.



Scheme 7. Proposed reaction mechanism.

Based on the primary experiments and literature [28,49,50], a possible catalytic cycle was proposed (Scheme 7). Initially, the $Cu^{I}\mathbf{L_1}$ complex is formed and is excited to an excited state $[Cu^{I}\mathbf{L_1}]^*$ upon the visible light irradiation (path A), which under-goes the single-electron transfer (SET) event with **1a** to afford the oxygen center radical **1a-A** and the Cu^{II} species **C**. Then, the intermediate **1a-A** engages in β-scission to give the carbon center radical **1a-B**. After that, the radical **1a-B** reacts with the species **C** to deliver the Cu^{III} species **D**, which subsequently involves in a ligand exchange with amine **2a** to provide the Cu^{III} species **E**. Further sequential coordination and insertion of CO forms the acylcopper intermediate **F** or **G**. Finally, reductive elimination of **F** or **G** furnishes the final product **3a** and regenerates the active $Cu^{I}\mathbf{L_1}$ catalyst. Luckily, some important metallic copper species including cationic $[\mathbf{L_1}Cu^{I}]^+$, $[\mathbf{L_1}Cu^{II}(OH)]^+$ and $[\mathbf{L_1}Cu^{III}(C_9H_{15}O_2)(OH)]^+$ could be successfully detected by HRMS. In view of the formation of **3a** without the visible-light irradiation, we speculate that the ground state $[Cu^{I}\mathbf{L_1}]$ could also undergo the single-electron transfer (SET) event with **1a** to afford the intermediate **1a-A** (path B).

In conclusion, we have developed a photoinduced, earth-abundant copper catalyzed alkoxyl triggered C−C bond cleavage/aminocarbonylation cascade with CO under redox-neutral conditions. Through adjusting the structure of alkoxyl radical precursors, a series of valuable lactone or carbonyl group-functionalized amides were synthesized with good yields and excellent functional group tolerance under mild conditions. Remarkably, this protocol allowed the combination of lactone fragments with many amine drugs and drug fragments. Mechanism study revealed that the $Cu/\mathbf{L_1}$ complex was the photoactive species, and a $Cu^{I}/Cu^{II}/Cu^{III}$-based catalytic cycle was involved for this transformation. This work is a significant and promising example in both the carbonylation and the radical ring-expansion fields.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109263.

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