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A cheap metal catalyzed ring expansion/cross-coupling cascade: a new route to functionalized medium-sized and macrolactones†

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An efficient alkoxyl radical-triggered ring expansion/cross-coupling cascade was developed under cheap metal catalysis. Through the metal-catalyzed radical relay strategy, a wide range of medium-sized lactones (9–11 membered) and macrolactones (12, 13, 15, 18, and 19-membered) were constructed in moderate to good yields, along with diverse functional groups including CN, N_3, SCN, and X groups installed concurrently. Density functional theory (DFT) calculations revealed that reductive elimination of the cycloalkyl-Cu(III) species is a more favorable reaction pathway for the cross-coupling step. Based on the results of experiments and DFT, a Cu(I)/Cu(II)/Cu(III) catalytic cycle is proposed for this tandem reaction.

1 Introduction

Medium-sized lactones and macrolactones are structural cores of many bioactive pharmaceuticals, agrochemicals, and natural products (Fig. 1).[1] As a consequence, their synthesis has attracted sustained interest from chemists, and diverse strategies have been developed over the past few decades.[2] In this field, one of the most classical strategies is based on the end-to-end ring closing reactions, including transition metal-catalysed couplings, NHC-catalysed cyclizations, electrophilic halogenations, *etc.* wherein the C–O bond formation or C–C bond formation have been designed as the final step to realize cyclization (Scheme 1(i)).[2f,3]

Although significant progress has been made by means of transition metal catalysis, it is still challenging to achieve macrolactonization due to the obstacles of entropy and the competing intermolecular coupling side reactions.[4] In contrast to the cyclization strategy, the ring expansion strategy represents another promising and high-efficiency alternative to avoid the above-mentioned problems. Over the past few years, both ionic-type and the radical triggered ring expansion reactions have received much attention from the chemical community.[5] Among them, alkoxyl radical-triggered fragmentation of fused bicyclic systems has emerged as an efficient strategy for the construction of medium-
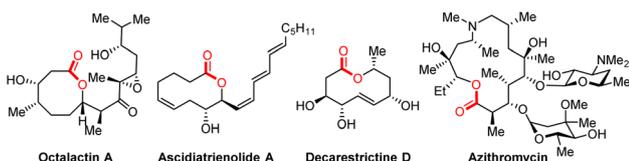

Fig. 1 Examples of drugs and natural products containing a macro-lactone framework.

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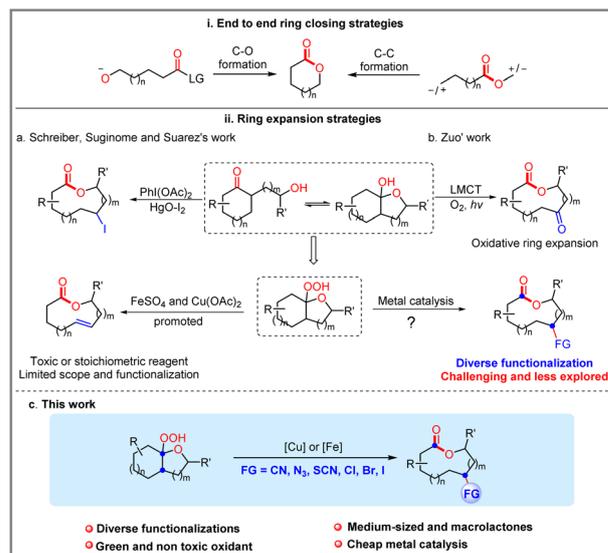
Scheme 1 Diverse strategies for macrolactones.

sized lactones and macrolactones (Scheme 1(ii)). In the 1980s, Schreiber, Suginome and E. Suárez et al. respectively disclosed several impressive examples for oxidative fragmentation of hemiketals, which offered the olefinic- and iodo-substituted medium-sized lactones (Scheme 1(iia)).[6] Later on, Posner and Maio et al. successfully applied this strategy to the synthesis of natural (−)-phoracantholide-J and (+)-cis-lauthisan.[7] However, these methods still suffer from requirement of toxic reagents (HgO) or stoichiometric amounts of organic oxidants (PhI(OAc)$_2$). In addition, only few examples were investigated. In recent years, a rapid development of alkoxyl radical triggered C–C bond cleavage has occurred, but focusing on the ring-opening reactions.[8] For the ring expansion aspect, the group of Zuo disclosed an elegant photocatalytic aerobic oxidative ring expansion of α-hydroxyalkylketones to the keto-macrolactones through the LMCT process (Scheme 1(iib)),[9] whereas it is limited to introducing a carbonyl group into the macrolactone framework. Despite this impressive success in the radical ring expansion strategy, diverse functionalization based on the nascent carbon radical of ring expansion is still challenging and less explored. Therefore, exploration of new catalytic systems and chemical transformations is still highly desirable and rewarding to carry forward the ring expansion strategy for the diverse functionalized macrolactone synthesis.

In recent years, radical mediated C–C bond cleavage has emerged as a powerful platform for the C–C and C–X bond formation, taking advantage of the broad radical precursors, diverse mild catalytic system, as well as excellent selectivity and functional group tolerance.[10] In these reactions, the generated carbon-centered radical intermediates could undergo diverse chemical transformations, including radical–radical coupling, radical addition and so on. As we know, the transition metal catalyzed radical relay strategy offered an attractive avenue for radical transformations.[11] Recently, the groups of Liu, Stahl and others disclosed some elegant examples of C(sp^3)–H functionalization reactions through the copper catalyzed radical relay strategy.[12] Inspired by these studies and our previous studies,[13] we intend to challenge the diverse synthesis of functionalized macrolactones through a ring expansion/cross-coupling cascade based on the transition metal catalyzed radical relay strategy (Scheme 1(iic)). Therein, the reactive transition metal species (with different valence states) not only serve as a SET reagent but also capture the nascent carbon-centered radical to form new chemical bonds.[11]

Herein, we disclose a range of efficient copper or iron-catalyzed ring expansion/cross-coupling cascade of hemiketal hydroperoxides with different nucleophiles (TMSCN, TMSN$_3$, NH$_4$SCN, and HX), which affords a variety of functionalized medium-sized lactones and macrolactones in good to excellent yields under mild conditions.

2 Results and discussion

Initially, the hemiketal hydroperoxide **1a** and TMSCN were elected as model substrates to find the optimal conditions under copper catalysis (Table 1). Luckily, the ring expansion/cyanation of **1a** proceeded efficiently by using CuI (5 mol%) as the catalyst and 1,10-phen (5 mol%) as the ligand in THF at ambient temperature, affording the desired cyano-substituted medium-sized lactone **2a**

Table 1 Optimization of the ring expansion/cyanation of **1a** with TMSCN[a]


CCDC: 2193944

Entry	Catalyst (mol%)	Solvent	Ligand	Yield (%)
1	CuI	THF	1,10-Phen	88
2	CuI	DMF	1,10-Phen	78
3	CuI	MeOH	1,10-Phen	98(95)[b]
4	CuI	Toluene	1,10-Phen	14
5	CuOTf	MeOH	1,10-Phen	40
6	Cu(OAc)$_2$	MeOH	1,10-Phen	12
7	Fe(OTf)$_2$	MeOH	1,10-Phen	N.R.
8	CuI	MeOH	2,2′-bpy	70
9	CuI	MeOH	—	40
10	—	MeOH	1,10-Phen	N.R.
11	CuI	MeOH	1,10-Phen	95[b,c]

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), TMSCN (0.3 mmol, 1.5 equiv.), catalyst (0.01 mmol, 5 mol%), ligand (0.01 mmol, 5 mol%), solvent (2.0 mL), at 25 °C for 12 h under N$_2$. Yields were determined by GC-FID analysis using dodecane as the internal standard. [b] Isolated yields. [c] Reaction for 10 min.

in 88% yield.[14] Solvent screening revealed that MeOH was the optimal solvent, yielding **2a** in 98% yield (entries 1–4). Other copper catalysts such as CuOTf and Cu(OAc)$_2$ were less effective than CuI, while an iron catalyst such as Fe(OTf)$_2$ was totally ineffective (entries 5–7). The screening of ligands indicated that 1,10-phen gave better yield than 2,2′-bpy (entry 3 vs. entry 8). The control experiments revealed that the ligand is beneficial to obtain a higher yield and copper catalyst was essential for the success of this transformation (entries 9 and 10). Surprisingly, it was found that the reaction could be completed in 10 min, giving a 95% isolated yield of **2a** (entry 11).

With the optimal conditions in hand, the generality and limitations of hemiketal peroxides **1** for this ring expansion/cyanation reaction were evaluated (Scheme 2). Substrates derived from a variety of strained and unstrained cycloalkanones with oxiranes were all amenable to afford the cyano-substituted medium-sized lactones (9 to 11-membered) and macrolactones (12 to 19-membered) in moderate to good yields (**2a–2i, 2j–2p, 2s, 2r** and **2t–2x**). The ring strain did not show obvious impact on the reaction efficiency (**2a, 2h** and **2s–2x**). Synthetically useful functional groups which existed in the carbocycle framework such as alkenyl (**2f**), alkynyl (**2g**), ester (**2l**), and halogen (**2n**) groups survived well in this transformation. Substrates synthesized from 2-substituted oxiranes also reacted smoothly to produce the desired lactones **2b–2g** in good yields. In addition, substrates derived from six, seven and eight-membered cyclic ketones with oxetanes furnished the four-atom ring enlarged lactones **2h, 2i, 2q** and **2r** in moderate to good yields. Remarkably, natural epicoprostanol could also be modified to afford the ring expansion/cyanation product **2y** in good yield, highlighting the potential applications of our protocol
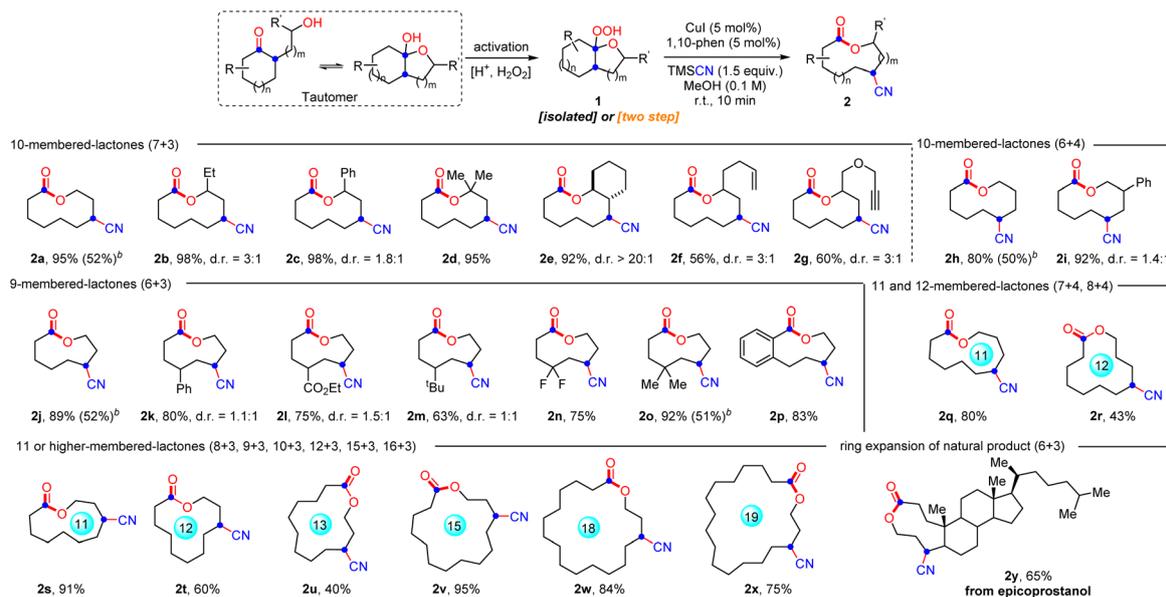
Scheme 2 Scope of the ring expansion/cyanation.[a] Reaction conditions A: **1** (0.2 mmol, 1.0 equiv.), TMSCN (0.3 mmol, 1.5 equiv.), CuI (0.01 mmol, 5 mol%) and 1,10-phen (0.01 mmol, 5 mol%) in MeOH (2.0 mL) at 25 °C for 10 min under N$_2$. Isolated yields.[b] Total yield through a two-step telescoped procedure is given in parentheses.

in the late-stage functionalization of complex molecules. Finally, to simplify the synthetic procedure, a telescoped protocol was tested. Satisfactorily, the two-step reactions of α-hydroxyalkylketones also proceeded smoothly to deliver the target lactones in moderate yields (**2a**, **2h**, **2j** and **2o**, for details, see the ESI†). Finally, it is worth mentioning that changing the 1,10-phen to other ligands, such as d*t*bpy and Biox ligands failed to improve the d.r. value of **2b**, but resulted in a decreased yield of **2b**. In addition, with the reaction of **1p** as an example, the use of chiral ligands instead of 1,10-phen did not improve the reaction enantioselectivity (for details, see the ESI,† S-10).

Subsequently, the ring expansion/cross-coupling cascade with other useful nucleophiles was also examined. Satisfactorily, TMSN$_3$, NH$_4$SCN and HX all were efficient nucleophiles, affording the corresponding N$_3$-substituted, SCN-substituted and halogenated medium-sized lactones and macrolactones in moderate to good yields under slightly modified reaction conditions (Scheme 3). For TMSN$_3$, the iron catalyst showed much better catalytic efficiency than the copper catalyst, while the copper catalyst is more efficient for the nucleophiles NH$_4$SCN and HX. Notably, the ligand was unnecessary for these transformations. Undoubtedly, the success of incorporating these functional groups provides opportunities for further functionalization of the lactones. As expected, it was found that the functional groups installed into the lactone products can be easily converted to diverse functional groups in good yields, which demonstrated the great significance of this ring expansion/cross-coupling cascade (Scheme 4(a)). For example, the CN-containing lactone **2a** could be hydrolyzed selectively to give the amide **6** in 60% yield. The N$_3$-containing lactone **3a** underwent the copper(ı)-catalyzed [3 + 2] cycloaddition reaction with phenylacetylene smoothly to afford 1,2,3-triazole **7** in 70% yield. In the presence of trifluoroacetic anhydride, a copper(ı)-
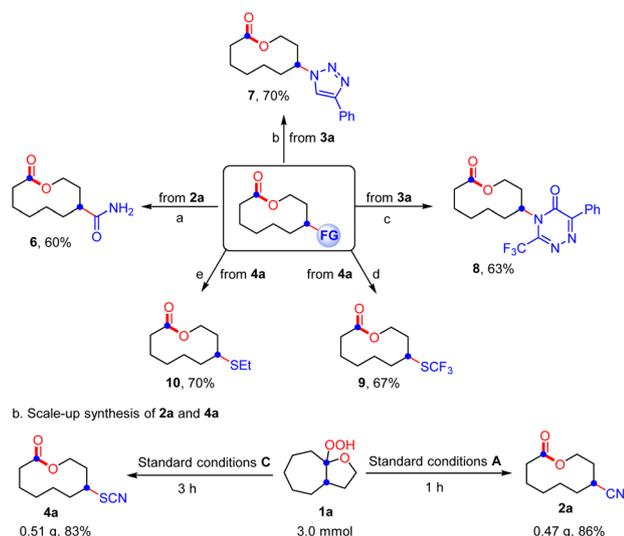
catalyzed interrupted click reaction also worked to deliver the 3-trifluoromethyl-substituted 1,2,4-triazinone **8** in 63% yield. The SCN-containing lactone **4a** could also be converted into the CF$_3$S- or EtS-substituted lactones **9** and **10** in good yields. In addition, the scale-up synthesis of **2a** and **4a** was also conducted, respectively. When the reactions were carried out on a 3.0 mmol scale, both gave good yields (Scheme 4(b)). However, other nucleophiles such as alcohol, phenol and thioalcohol failed to provide the desired products (not shown).

To shed light on the reaction mechanism, the radical inhibiting and trapping experiments were first performed (Scheme 5(a)). The addition of 2.0 equiv. of TEMPO to the reaction of **1a** and TMSCN almost completely inhibited the formation of **2a**, along with a TEMPO-adduct detected by HMRS. The yield of **2a** was also decreased to 53% when radical inhibitor BHT (2.0 equiv.) was added. Moreover, replacing TMSCN with 1,2-diphenylethylene as the radial acceptor could afford the alkenylated product **11** in 10% yield under standard conditions. All these results suggest a radical pathway for this ring expansion/cross-coupling cascade. Then, the effect of the ligand was investigated. Without a ligand, just 40% yield of **2a** was isolated. When a CuI/1,10-phen complex was used as the catalyst, the product **2a** was obtained in 77% yield. These results indicated that the ligand plays an important role in the copper-catalyzed process (Scheme 5(b)). Luckily, some important metallic copper species including cationic [LCu^{II}]$^+$, [LCu^{III}(OH)]H$^+$ and [LCu^{III}(CN)]H$^+$ could be successfully detected by HRMS (Fig. 2, for details, see the ESI†). Density functional theory (DFT) calculations were performed to learn more about the reaction mechanism, and the energy profile for the reaction is shown in Fig. 2. Initially, a single electron transfer (SET) reaction occurs between Cu(ı) species **SM** and hemiketal hydroperoxide **1a**, producing the alkoxyl radical **IM1** and Cu(ıı) hydroxide iodide species **IM3** (−9.9
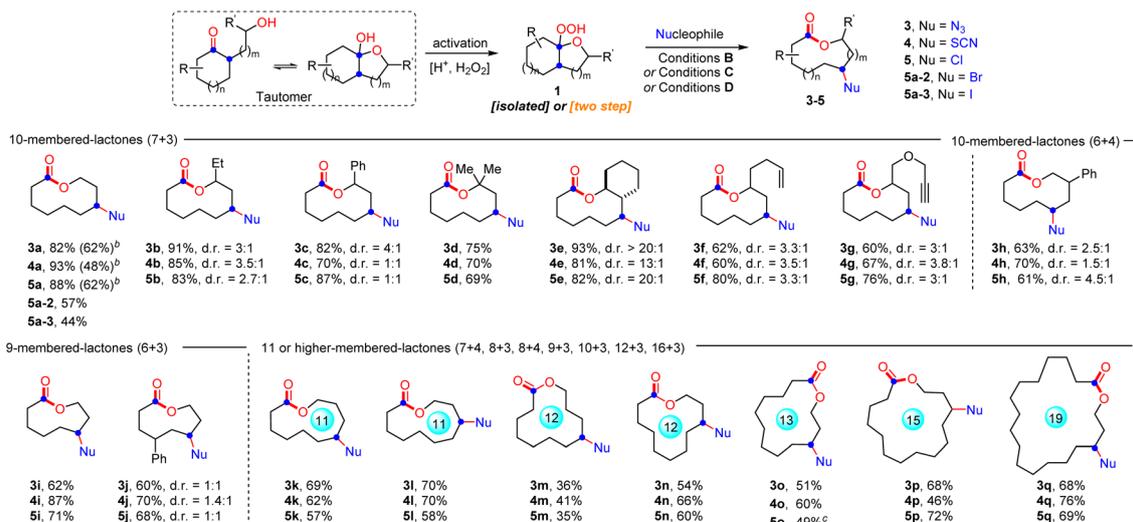
Scheme 3 Scope of other ring expansion/functionalizations.[a] Reaction conditions B for **3**: **1** (0.2 mmol, 1.0 equiv.), TMSN₃ (0.3 mmol, 1.5 equiv.) and Fe(OTf)₂ (0.01 mmol, 5 mol%) in EtOAc (2.0 mL) at 25 °C for 10 min under N₂. Isolated yields. Reaction conditions C for **4**: **1** (0.2 mmol, 1.0 equiv.), NH₄SCN (0.3 mmol, 1.5 equiv.) and CuCl (0.01 mmol, 5 mol%) in MeCN (2.0 mL) at 25 °C for 1 h under N₂. Isolated yields. Reaction conditions D for **5**: **1** (0.2 mmol, 1.0 equiv.), HCl (36%, aq.) or HBr (40%, aq.) or HI (55–58%, aq.) (0.4 mmol, 2.0 equiv.), and CuCl (0.01 mmol, 5 mol%), in NMP (2.0 mL) at 25 °C for 10 min under N₂. Isolated yields.[b] Total yield through a two-step telescoped procedure is given in parentheses.[c] 2.0 equiv. MgCl₂ as the chlorine source.

(−33.2 kcal mol⁻¹), which was formed by a kinetically favorable transmetalation between **IM3** and TMSCN, giving d⁸ metal centered Cu(ɪɪɪ) cyanide species **IM5** (−37.6 kcal mol⁻¹). Reductive elimination of **IM5** has an energy barrier of only 1.0 kcal mol⁻¹. A triplet state for **IM5** is −33.8 kcal mol⁻¹, and triplet state for **TS** is −15.8 kcal mol⁻¹, indicating that the triplet state surface of **IM5** and **TS** is over the singlet state surface, as shown in Fig. S1† (for details, see the ESI†). This is in accordance with the Cu(ɪ)/Cu(ɪɪ)/Cu(ɪɪɪ) mechanism proposed in the previous copper-catalyzed radical reaction study.[12c,15] The C–C bond length of the transition state in the reductive elimination step is 2.22 Å, as shown in Fig. 3 (left), affording the final cyano-lactone product **2a** (−84.6 kcal mol⁻¹), and regenerating **SM** to finish the catalytic cycle. Another possible reaction pathway involved Cu(ɪ)/Cu(ɪɪ). Cu(ɪɪ) complex **IM4** accepting one electron from isocyanide, regenerating Cu(ɪ) *via* an

Scheme 4 Diverse derivatizations of lactone products and scale-up synthesis.[a] Reaction conditions: **2a** (0.2 mmol, 1.0 equiv.), Cu(OAc)₂ (0.004 mmol, 2 mol%), NEt₂OH (0.6 mmol, 2.0 equiv.), H₂O (0.1 M), 25 °C, 3 h under N₂.[b] **3a** (0.2 mmol, 1.0 equiv.), phenylacetylene (0.4 mmol, 2.0 equiv.), CuSO₄ (0.04 mmol, 20 mol%), sodium ascorbate (0.08 mmol, 40 mol%), t-BuOH/H₂O (1 : 1, 0.1 M), 25 °C, 24 h under N₂.[c] **3a** (0.2 mmol, 1.0 equiv.), phenylacetylene (0.4 mmol, 2.0 equiv.), CuI (0.01 mmol, 5 mol%), Et₃N (0.4 mmol, 2.0 equiv.), (CF₃CO)₂O (0.3 mmol, 1.5 equiv.), THF (0.1 M), 25 °C, 24 h under N₂.[d] **4a** (0.2 mmol, 1.0 equiv.), TMSCF₃ (0.4 mmol, 2.0 equiv.), Cs₂CO₃ (0.4 mmol, 2.0 equiv.), MeCN (0.1 M), 25 °C, 16 h.[e] **4a** (0.2 mmol, 1.0 equiv.), EtMgBr (0.6 mmol, 3.0 equiv.), THF (0.1 M), −40 °C, 4 h under N₂.

kcal mol⁻¹). **IM1** undergoes β-scission selectively to afford the carbon-centered radical **IM2** with a 1.1 kcal mol⁻¹ energy barrier. Radical **IM2** then is trapped by copper complex **IM4**
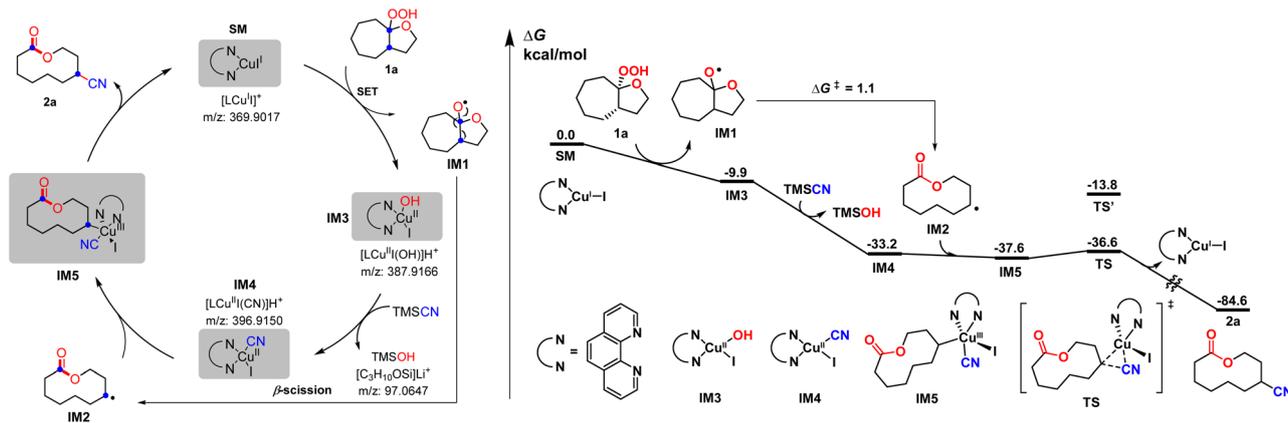
Scheme 5 Mechanism studies.

Fig. 2 Proposed mechanism and computed energy profile for the Cu-catalyzed ring expansion/cyanation reaction of **SM** to **2a**. Energies are in kcal mol^{-1}.
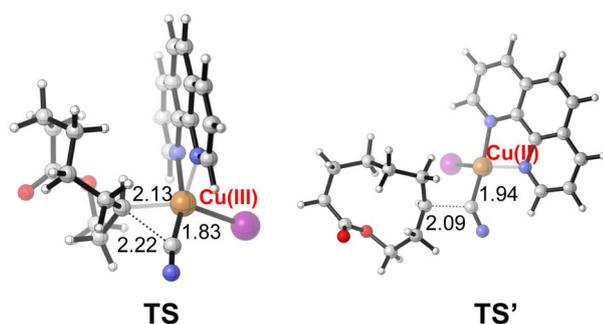

Fig. 3 The transition state structures for the formation of a cyano-lactone product involving the Cu(III) complex (left) or Cu(II) complex (right). Bond distance is labeled in Å.

outer-sphere pathway,[16] in which the **IM2** radical couples directly with the terminal carbon atom of **IM4**, with a 2.09 Å length of the C–C bond **TS′** as shown in Fig. 3 (right). The transition state energy of **TS′** is 22.8 kcal mol^{-1} higher than that of the Cu(III) complex reductive elimination transition state **TS**.

3 Conclusions

We have developed a highly efficient alkoxyl radical initiated ring expansion/cross-coupling cascade involving copper or iron catalysis. A wide range of medium-sized and macrolactones were constructed in moderate to good yields, accompanied by the introduction of diverse functional groups including CN, N$_3$, SCN, and X groups. In view of the mild conditions, wide substrate scope, good functional group tolerance and easy derivatizations of the products, this protocol should be of value to organic chemists. Furthermore, based on the results of experiments and DFT calculations, a Cu(I)/Cu(II)/Cu(III) catalytic cycle is proposed for this tandem reaction, wherein the reductive elimination of the cycloalkyl-Cu^{III} species is a more favorable reaction pathway for the cross-coupling step. This work would further expand the application potential of radical C–C bond cleavage in the functionalized medium-sized and macrocyclic compound synthesis.

Data availability

All experimental and characterization data including NMR spectra and DFT calculations are available in the ESI.† Crystallographic data for compound **2a** have been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 2193944.

Author contributions

S. Liu performed all the experiments and prepared the manuscript and ESI.† L. Zhang and H.-J. Miao performed the preparation of raw materials. P. Ma, S. Shen and K. N. Houk conducted the DFT calculations. L. Liu, X.-H. Duan and L.-N. Guo directed this project and revised the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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