Chinese Chemical Letters 36 (2025) 110207

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Rapidly diastereoselective assembly of ten-membered *N*-heterocycles between two 1,3-dipoles and their diversity to access fused *N*-heterocycles

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ARTICLE INFO

Article history:
Received 16 April 2024
Revised 26 June 2024
Accepted 2 July 2024
Available online 2 July 2024

Keywords:
1,3-Dipole
Ten-membered *N*-heterocycles
Aza-Claisen rearrangement
[3+3] Cycloaddition
Nitrone
Anti-inflammatory

ABSTRACT

The development of general and practical strategies toward the construction of medium-sized rings is still challenging in organic synthesis, especially for the multiple stereocenters control of substituted groups on the ring owing to the long distance between groups. Thus, stereoselective synthesis of multi-substituted ten-membered rings is attractive. Herein, a rapid assembly of various highly substituted ten-membered nitrogen heterocycles between two 1,3-dipoles through a tandem [3 + 3] cycloaddition/aza-Claisen rearrangement of *N*-vinyl-α,β-unsaturated nitrones and aza-oxyallyl or oxyallyl cations are disclosed. Products containing two or multiple stereocenters could be obtained in up to 96% yield with high regioselectivity and diastereoselectivity. Selective N-O bond cleavages of ten-membered nitrogen heterocycles lead to various novel 5,6,6-perifused benzofurans, bicyclo[4.4.0] or bicyclo[5.3.0] skeletons containing three or multiple continuous stereocenters in good yields and high diastereoselectivity. Biological tests show that the obtained ten-membered *N*-heterocycles and bicyclo[4.4.0] skeletons inhibited nitric oxide generation in LPS-stimulated RAW264.7 cells and might serve as good anti-inflammatory agents.

Medium-sized ring compounds (8 to 12 atoms) are important structural units which are particularly prevalent in biologically active molecules and natural products [1-3]. The construction of medium-sized ring compounds is still difficult because of their unfavourable transannular interactions and entropic effects. Ten-membered rings, are also one of the most important medium-sized units occurring in many bioactive compounds and natural products, such as *muramine*, *protopine*, *dysazecine*, *salvia miltiorrhiza*, and *picralphylline* (Scheme 1A) [4-7]. Intramolecular cyclization strategies have been successfully used for the synthesis of ten-membered ring compounds, such as cyclizations [8-11], ring-closing metathesis [12-14], ring expansion [15,16], aza-Claisen rearrangement (ACR) [17-19], and related transformations [20-23], however, these methods usually required multi-step synthesis of complex starting materials and lack of scaffold diversity. Moreover, the efficiency was always low owing to the long distance between the two reaction sites at the terminus and the increasing size of the rings. Thus, the development of novel strategy to access ten-membered ring skeletons is greatly in demand.

Cycloaddition reactions, as one of the most powerful and versatile strategies in the synthesis of cyclic molecules, have been made great progress toward the construction of five to seven-membered ring skeletons with biological activities [24-31]. Some examples were reported to prepare medium-sized ring molecules by direct cycloadditions, however, only limited examples toward the synthesis of ten-membered ring compounds by cycloadditions were reported up to now because it involves higher-order cycloadditions (Scheme 1B) [32-36]. For examples, Shibata's [5 + 5] cycloaddition of 3,3-difluorooxindoles with vinyl ethylene carbonates

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https://doi.org/10.1016/j.cclet.2024.110207
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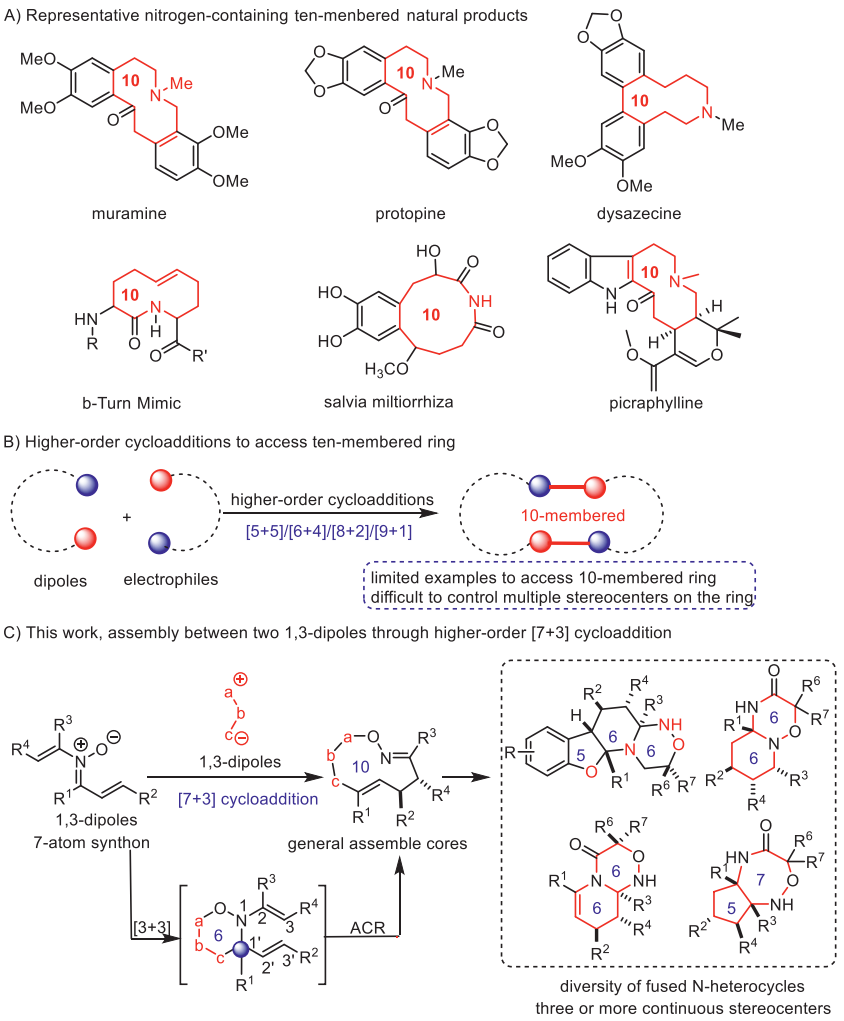
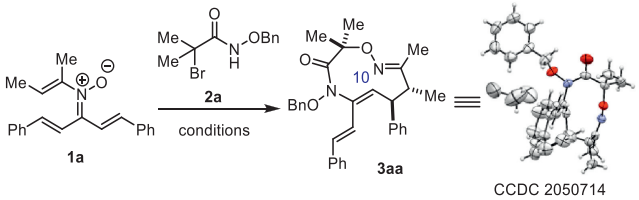


Scheme 1. Cycloaddition strategies toward the preparation of ten-membered *N*-heterocycles.

[37], Zhao group developed [6+4] cycloaddition of vinyl oxetanes with azadienes [38], Deng and co-workers developed Pd-catalyzed [6+4] cycloaddition of π-allyl all carbon 1,6-dipoles with azadienes [39], Lu and Lan group reported [8+2] cycloaddition of vinyl carbamates with photogenerated ketenes [40], and Ma group developed [9+1] of 1,5-bisallenes with organic halides [41]. These higher-order cycloadditions toward the preparation of various ten-membered heterocycles have been shown the cycloaddition between 1,3-dipoles and various electrophiles (oxindoles, azadienes, ketenes, or allenes), however, the kind of [7+3] higher-order cycloaddition to access ten-membered ring has not yet been reported. Nitrones are important 1,3-dipoles and have been extensively used as building blocks in organic synthesis [42-45], which have been successfully used to prepare eight- or nine-membered ring compounds [46-49]. On the other hand, aza-oxyallyl or oxyallyl cations are also important intermediates to access five to seven-membered rings by [3+2], [3+3], and [4+3] cycloadditions [50-54]. Based on the [3+3] cycloaddition of *N*-aryl or alkyl nitrones with aza-oxyallyl or oxyallyl cations to form six-membered ring [55,56]. We surmised that regioselective [3+3] cycloaddition of *N*-vinyl-α,β-unsaturated nitrones with another 1,3-dipoles would give six-membered skeletons containing a quaternary carbon center and a 1,5-dinene moiety. To release the tension of quaternary carbon center [57,58], a sequence of aza-Claisen rearrangement (ACR) might offer a general and useful approach to access various ten-membered *N*-heterocycles containing two or multiple stereocenters, which perhaps could serve as important intermediates to access various fused *N*-heterocycles by N-O bond cleavage, such as 5,6,6-perifused benzofurans, bicyclo[4.4.0] or bicyclo[5.3.0] skeletons containing three or multiple continuous stereocenters (Scheme 1C). The *N*-vinyl-α,β-unsaturated nitrones were easily obtained by Chan-Lam reaction of oximes with alkenyl boronic acids under mild reaction conditions [59], and they would serve as 7-atom synthon in the higher-order [7+3] cycloaddition. As far as we known, the multiple stereocenters control in medium-sized ring is still a challenge because the substituted groups might be far away from each other to be controlled. While the stereo-defined ACR reaction would facilitate to control the stereocenters in ten-membered rings with high diastereoselectivity. This new method establishes the assembly of two types of 1,3-dipoles as a toolbox for the accessing ten-membered *N*-heterocycles containing two or more stereocenters.

Herein, we report an assembly of two 1,3-dipoles for the preparation of ten-membered ring compounds as well as their perifused *N*-heterocycles. The protocol includes the following points. (1) The ten-membered ring is constructed by copper-catalyzed [3+3] cycloaddition/aza-Claisen rearrangement under mild reaction conditions, which is interesting due to its value in addressing the formation of a ten-membered ring *via* [3+3] cycloaddition from *N*-vinyl-α,β-unsaturated nitrones with other 1,3-dipoles. (2) The structurally unique multi-substituted ten-membered rings might be used as a platform model for discovering some synthet-

Table 1
Optimization of the reaction conditions.[a]



CCDC 2050714

Entry	Cat.	Base	Solvent	t (h)	**3aa** (%)[b]
1	-	K_2CO_3	TFE	24	12
2	-	K_2CO_3	Toluene	24	16
3	-	K_2CO_3	MeCN	24	20
4	-	K_2CO_3	THF	24	6
5	-	K_2CO_3	DMSO	24	<5
6	$Fe(OTf)_3$	K_2CO_3	MeCN	18	55
7	$Yb(OTf)_3$	K_2CO_3	MeCN	12	51
8	$Sc(OTf)_3$	K_2CO_3	MeCN	10	63
9	$Cu(OAc)_2$	K_2CO_3	MeCN	18	64
10	CuI	K_2CO_3	MeCN	18	57
11	CuOTf	K_2CO_3	MeCN	5	75
12	CuOTf	Na_2CO_3	MeCN	18	71
13	CuOTf	KOH	MeCN	24	50
14	CuOTf	NEt_3	MeCN	24	6
15	CuOTf	*i*-Pr_2NEt	MeCN	24	43

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), Cat. (20 mol%, unless noted), base (2.0 equiv.), solvent (2 mL), at room temperature.
[b] isolated yield.

ically useful nitrogen perifused cycles. (3) This study might offer useful information for the designing ten-membered rings or *N*-perifused ring analogs with potent good bioactivity.

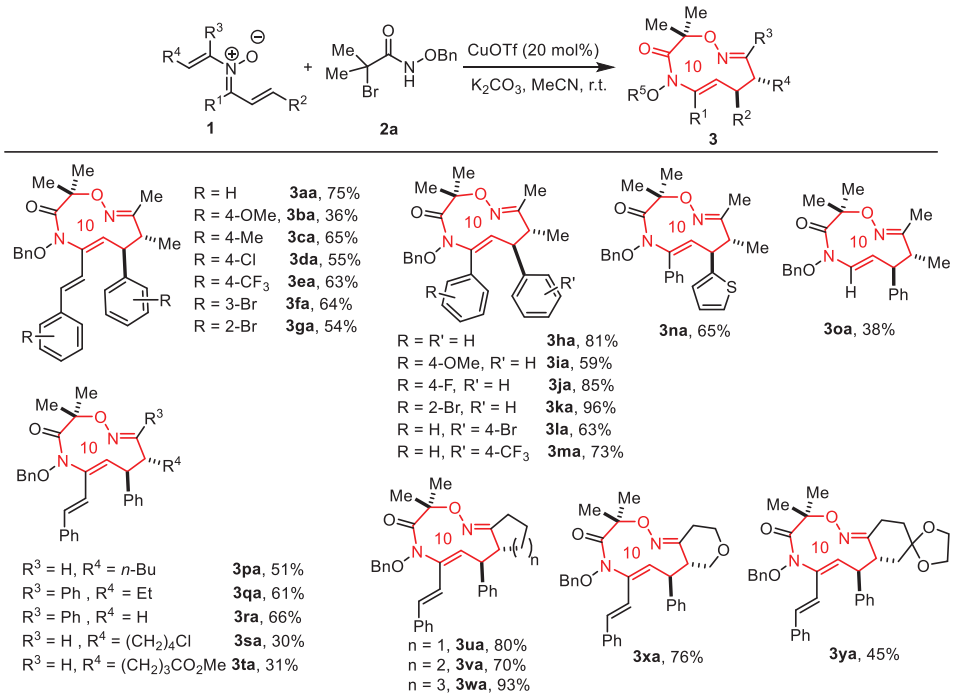
Our investigations started with *N*-vinyl-α,β-unsaturated nitrone **1a** and aza-oxyallyl cation as a 1,3-dipole generated from α-bromoamide **2a** as the model substrates. As shown in Table 1, 1**a** reacted with **2a** affording the desired ten-membered ring product **3aa** in 12% yield as single isomer in the presence of K_2CO_3 in 2,2,2-trifluoroethanol (TFE) (Table 1, entry 1). The structure of **3aa** was determined by its X-ray diffraction analysis. The structure showed that C=N and C=C bonds in the ten membered ring are both *E*-configuration, and Ph and Me groups on the ring had a *trans*-relationship. Solvents screening revealed that MeCN gave **3aa** in better yield than other solvents, such as toluene, THF, and DMSO (Table 1, entries 2-5). The test of Lewis acid catalysts showed that the addition of Lewis acid definitely promoted the reaction and CuOTf gave **3aa** in the best result with 75% yield (Table 1, entries 6-11). The effect of bases indicated that the reaction ran smoothly either inorganic or organic base, especially for NEt_3 gave lower yield of **3aa** (Table 1, entries 12-15, more details for optimization conditions, see Table S1 in Supporting information). Therefore, the optimal conditions for preparing **3aa** was 20 mol% of CuOTf and K_2CO_3 as base in MeCN at room temperature.

With the optimized conditions in hand, the scope of *N*-vinyl-α,β-unsaturated nitrones **1** reacting with **2a** was explored. As shown in Scheme 2, various dibenzylideneacetone-derived *N*-vinyl nitrones with electron-donating and electron-withdrawing groups at the *para*, *meta*, and *ortho*-positions of aryl rings proceeded smoothly to afford the corresponding ten-membered lactam products **3aa-3ga** bearing two stereocenters in good yields only with *trans*-diastereomers. The chalcone-derived *N*-vinyl nitrones were also evaluated. The corresponding products **3ha-3na** were obtained in good to excellent yields with *trans*-diastereomers only when either aryl ring was present with electron-donating or electron-withdrawing groups at *para*, or *ortho*-positions. The reaction also tolerated 2-thienyl group furnishing product **3na** in 65% yield. While cinnamaldehyde-derived nitrone **1o** delivered the desired product **3oa** in 38% yield owing to the easy decomposition of nitrone **1o**. In addition to α,β-unsaturated ketone moieties, the vinyl moieties on the *N*-atom of nitrones were also tested. The *N*-vinyl moieties could be present with linear and cyclic vinyl substituents, affording the corresponding ten-membered lactams in moderate to good yields (**3pa-3ya**). The monosubstituted or disubstituted linear vinyl groups could be present with alkyl and aryl groups bearing sensitive functional groups (**3pa-3ta**). The reaction also tolerated five to seven-membered carbon rings and pyran ring on the *N*-atom (**3ua-3ya**). Pleasingly, the R^4 chains of nitrones with a chloro (**1s**), an ester (**1t**), and an acetal group (**1y**) on the six-membered ring also delivered **3sa**, **3ta**, and **3ya** in 30%, 31%, and 45% yields. These sensitive functional groups could be easily converted to useful groups and it provides a synthetic handle for further manipulation.

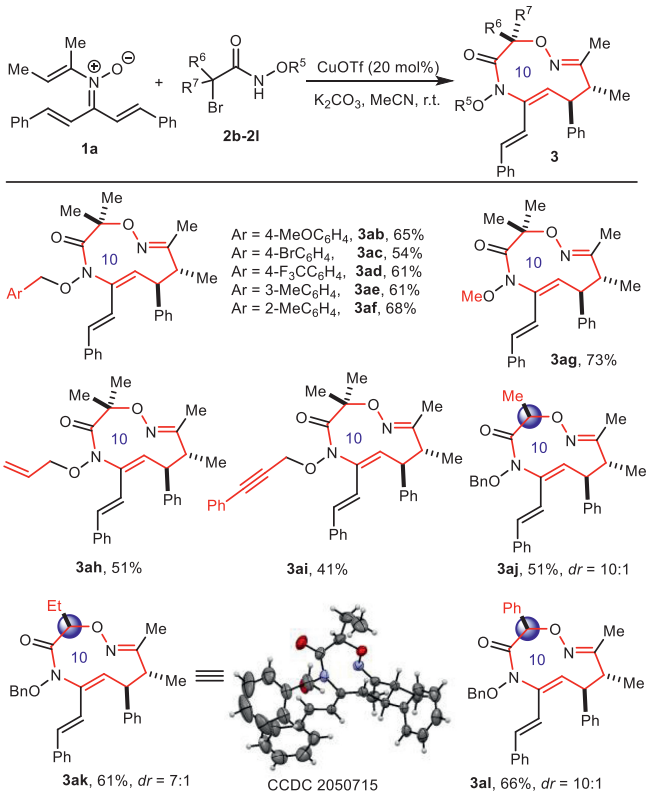
Next, the substrate scope of α-bromohydroxymates **2** was evaluated (Scheme 3). It was found that a wide range of α-bromohydroxymates **2** reacting with *N*-vinyl nitrone **1a** were smoothly converted to ten-membered lactams **3ab-3al** in good yields. The R^5 group could be present with different benzyloxy and alkyloxy groups. Pleasingly, the R^5 group was compatible with vinyl and alkynyl groups (**3ah-3ak**). When the R^6 group was methyl, ethyl or phenyl substituents and the R^7 group was hydrogen, *N*-benzyloxy α-bromoamides (**2j**, **2k**, and **2l**) produced **3aj**, **3ak**, and **3al** in 51%, 61%, and 66% yields, respectively, and their diastereomeric ratios were ranging from 7:1 to 10:1. These structures containing three stereocenters were determined by X-ray diffraction of compound **3ak**, showing that the phenyl group and ethyl group was *cis*-position. This method provides a good approach to access ten-membered lactams bearing two or three substituents faraway from each other with high diastereoselectivity in the ten-membered rings. However, *N*-benzyl/*N*-phenyl α-bromoamides did not deliver the desired ten-membered ring products under the optimal conditions and only nitrone was recovered. The plausible reason is that the *N*-benzyl/*N*-phenyl substituent is not sufficient enough to stabilize the *in situ*-generated aza-oxyallyl cation [60,61].

Interestingly, as shown in Scheme 4, when α-bromo aryloxyamides **2** was used under the optimal conditions, the corresponding ten-membered lactams **3** could not be obtained. After further optimization conditions (Table S2 in Supporting information), we found that various α-bromo aryloxyamides **2** were reacted smoothly with different types of *N*-vinyl nitrones to afford the corresponding 5,6,6-perifused benzofuran heterocycles **4** containing five or six continuous stereocenters in acceptable yields as single diastereomers (**4am-4ap**). The structure of compound **4** was determined by X-ray diffraction analysis of compound **4am**. From the structure of **4am** we can see that **4** might be generated by a sequential [3,3]-sigmatropic rearrangement by the corresponding ten-membered lactams **3**. Particularly, the *N*-vinyl moieties of nitrone **1v** bearing cyclohexenyl and **1t** bearing a linear chain with an ester group affording **4vm** and **4tm** in 50% and 42% yields, respectively. α-Bromo aryloxyamides **2n** and **2o** presented with methyl and fluoro groups delivered compounds **4an** and **4ao** in 66% and 65% yields, respectively. Compound **4ap** containing six stereocenters was also obtained in 58% yield with one single isomer when the R^6 and R^7 groups of **2p** were methyl and hydrogen. This method provides a facile one-pot approach to access perifused benzofuran heterocycles containing continuous stereocenters that are still challenging to be prepared.

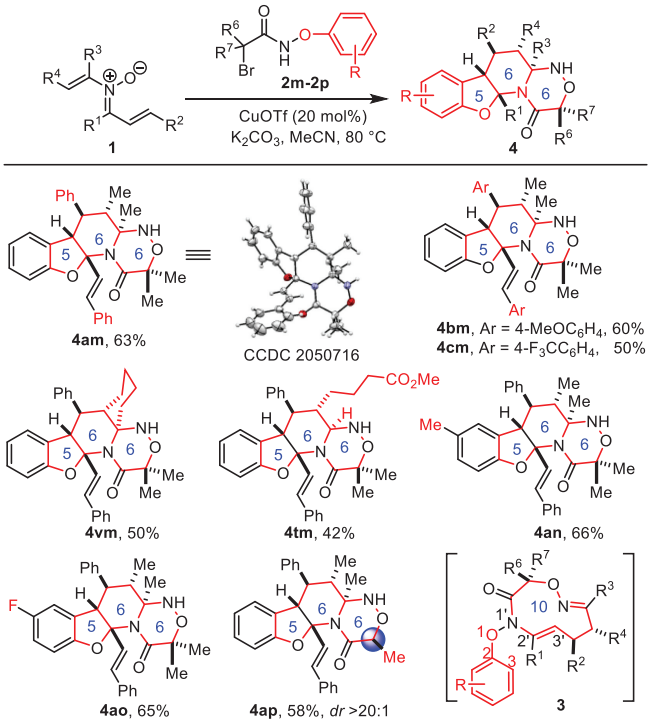
The oxyallyl cation as 1,3-dipole generated from α-tosyloxy ketones **5** were also tested for this cascade reaction. As shown in Scheme 5, it was found that *N*-vinyl nitrone **1a** reacted with α-tosyloxy ketone **5a** with 3.0 equiv. of NEt_3 in TFE at 40 °C to afford the desired ten-membered heterocycle **6aa** containing four stereocenters in 82% yield as single diastereomer (see Table S3 for optimizations in Supporting information). The relative configuration



Scheme 2. Substrate scope for *N*-vinyl nitrones **1**. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), CuOTf (20 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), r.t., 5-12 h, isolated yield.

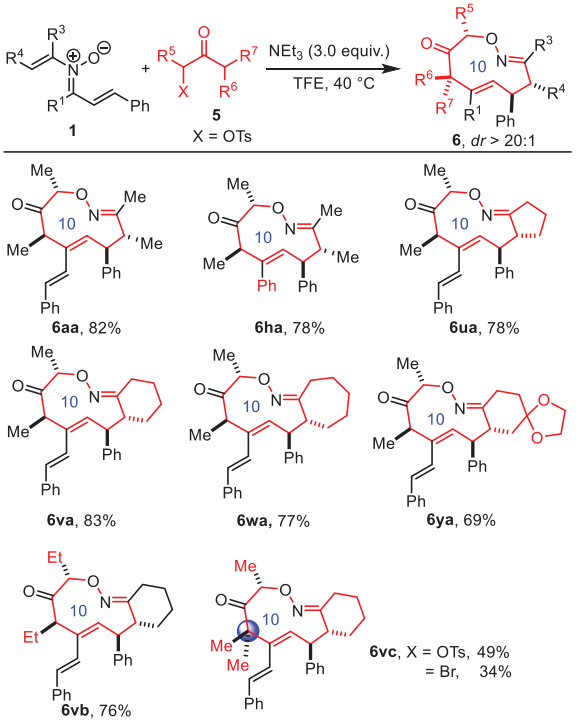


Scheme 3. Substrate scope for α-bromohydroxymates **2**. Reaction conditions: **1** (0.2 mmol), **2b**-**2l** (0.4 mmol, 2.0 equiv.), CuOTf (20 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), r.t., 5−24 h; isolated yield; *dr* = diastereomeric ratio.

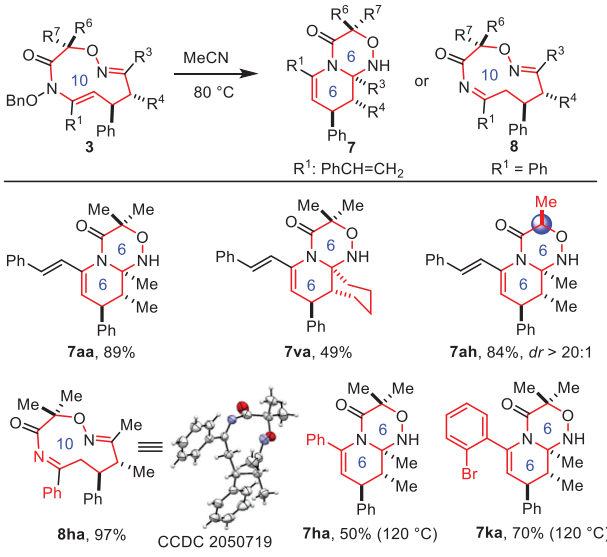


Scheme 4. Substrate scope for α-bromo aryloxyamides **2**. Reaction conditions: **1** (0.2 mmol), **2m**-**2p** (0.4 mmol, 2.0 equiv.), CuOTf (20 mol%), K_2CO_3 (0.4 mmol, 2.0 equiv.), MeCN (2.0 mL), 80 °C, 24 h; isolated yield. *dr* = diastereomeric ratio.

of the substituted groups in **6aa** were determined by its NOESY spectra. Thus, various *N*-vinyl nitrones **1** and α-tosyloxy ketones **5** were evaluated. Chalcone-derived *N*-vinyl nitrone or *N*-vinyl moieties with linear or cyclic vinyl groups all tolerated the reaction conditions affording **6ha**, **6ua-6wa**, and **6ya** in good yields. Interestingly, when α-tosyloxy ketones were varied from R^5, R^6, and R^7 groups, products **6vb** and **6vc** were obtained in 76% and 49% yields, respectively. Moreover, α-tosyloxy ketone **5c** was replaced



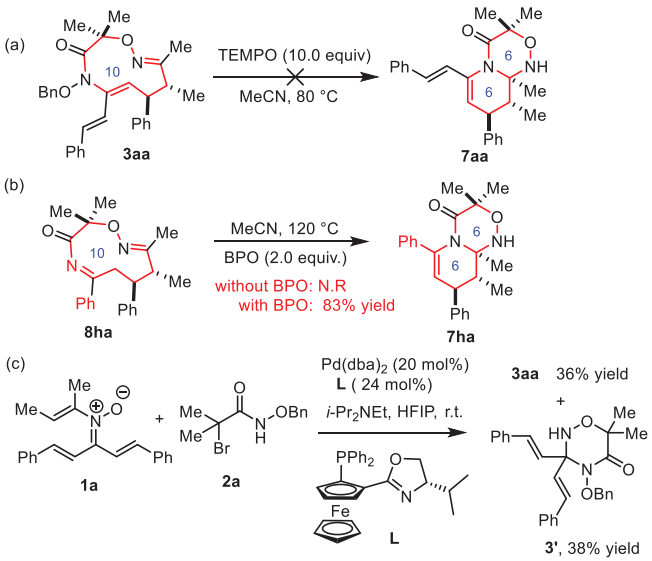
Scheme 5. Substrate scope for α-tosyloxy ketones **5**. Reaction conditions: **1** (0.2 mmol), **5** (0.4 mmol, 2.0 equiv.), NEt_3 (0.4 mmol, 2.0 equiv.), TFE (2.0 mL), 40 °C, 24 h, isolated yield.



Scheme 6. Thermal conversions of ten-membered lactams **3** to bicyclo[4.4.0] skeletons **7**.

by α-bromo ketone also afforded product **6vc** in 34% yield with all carbon center in the ten-membered ring.

With the ten-membered lactams **3** in hand, we are interested in their properties under the thermal conditions (see Table S4 for optimizations in Supporting information). When compound **3aa** was heated in MeCN at 80 °C for 12 h, a bicyclo[4.4.0] skeleton product **7aa** containing three continuous stereocenters was obtained in 89% yield as single isomer, which was confirmed by X-ray diffraction analysis (CCDC 2050717). As shown in Scheme 6, The reaction tolerated ten-membered lactams **3va** and **3ah**, and delivered **7va** and **7ah** in 49% and 84% yields in high diastereoselectivity, respectively. The relative configuration of **7ah** bearing four stereocenters

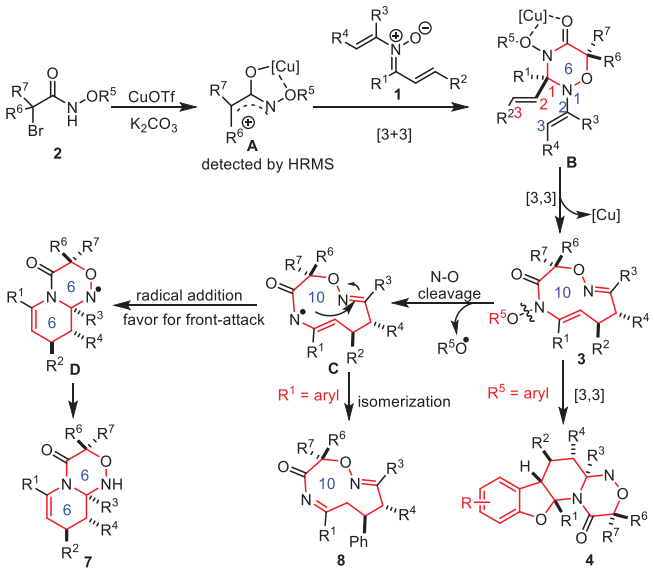


Scheme 7. Control experiments.

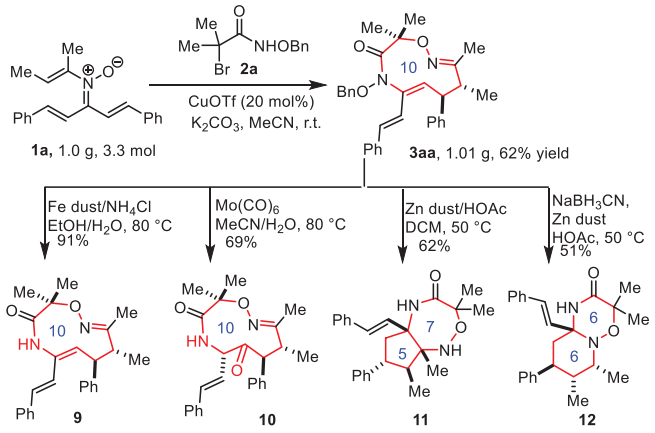
was determined by X-ray diffraction analysis (CCDC 2050718). To our surprise, lactam **3ha** with a phenyl at the R^1 group did not afford the desired piperidine **7ha** at 80 °C, however, a novel ten-membered lactam **8ha** was obtained in 97% yield. The structure of **8ha** was determined by X-ray diffraction analysis, showing an outside N-O bond cleavage. It was pleased to find that when lactams **3ha** and **3ka** were carried out at 120 °C, the desired bicyclo[4.4.0] products **7ha** and **7ka** were obtained in 50% and 70% yields, respectively. These results indicated that the R^1 group in the ten-membered ring had a great effect on the formation of compounds **7** and **8** at the thermal conditions.

To better understand the thermal conversion of ten-membered lactams **3**, control experiments were performed (Scheme 7). It was found that addition of radical trapping reagents TEMPO to compound **3aa** at the thermal conditions inhibited the formation of **7aa** with the recovery of **3aa** only (Scheme 7a). Heating **8ha** at 120 °C for 12 h did not afford **7ha**, however, adding radical initiator BPO to **8ha** delivered **7ha** in 83% yield (Scheme 7b). Interestingly, when nitrone **1a** reacted with **2a** in the presence of $Pd(dba)_2$ and P,N-ligand **L** in HFIP at room temperature, **3aa** was obtained in 36% yield accompanied by cycloadduct **3'** in 38% yield, which indicated that the first step of **1a** reacting with **2a** was [3 + 3] cycloaddition process.

To study the role of copper(I), high resolution mass spectrum (HRMS) trace experiments were carried out (see Scheme S3 in Supporting information). It was found that the copper(I) catalyst played as Lewis acid to promote the [3 + 3] cycloaddition and aza-Claisen rearrangement to form ten-membered ring. Based on the experimental studies, the mechanism for the formation of compounds **3**, **4**, **7**, and **8** from *N*-vinyl nitrones **1** and α-bromohydroxamates **2** was proposed in Scheme 8. The active aza-oxyallylic cations generated from α-bromohydroxamates **2** in the presence of base coordinate with CuOTf to form copper(I) intermediate **A**. Then, **A** undergoes [3 + 3] cycloaddition with *N*-vinyl nitrones **1** to give intermediate **B**. Intermediate **B** occurs stereodefined [3,3]-rearrangement through chair transition state to give ten-membered lactams **3** with high diastereoselectivity and release Cu(I) to finish the catalytic cycle. When the R^5 was an aryl group, a further [3,3]-rearrangement of **3** gave compound **4**. When the R^5 was not an aryl group under the thermal conditions, homolytic cleavage of the outside N-O bond to form diradical intermediate **C**



Scheme 8. Proposed mechanism.



Scheme 9. Gram scale preparation of **3aa** and its diverse transformations.

and $R^5O^{\bullet}$. Then, intermediate **C** underwent isomerization to give compound **8**. Alternatively, **C** underwent radical addition to the C=N bond to result in compound **7** *via* intermediate **D**.

To show the utility of this cascade reaction to access ten-membered lactams, gram scale preparation of **3aa** was carried out. As shown in Scheme 9, 1.0 g of *N*-vinyl nitrone **1a** reacting with **2a** delivered ten-membered lactam **3aa** in 62% yield (1.01 g). Interestingly, the treatment of **3aa** with Fe/NH_4Cl reductive conditions afforded **9** in 91% yield by N-O bond reductive cleavage. When **3aa** reacted with $Mo(CO)_6$ in a mixture of MeCN/water open to air, compound **10** bearing a ketone with three stereocenters was obtained in 69% yield as single isomer. Treating **3aa** with Zn dust and HOAc resulted in bicyclo[5.3.0] scaffold **11** in 62% yield with 3:1 diastereomers, while bicyclo[4.4.0] scaffold **12** was obtained in 51% yield by treating with $NaBH_3CN$, Zn dust, and HOAc. The structures of **9**, **10**, **11**, and **12** were all determined by X-ray diffraction analysis (CCDC: 2050720-2050723). These versatile and fantastic conversions of ten-membered lactams provide a good approach to access these fused *N*-heterocycles containing multiple stereocenters that are difficult to prepare by other possible methods.

Finally, some prepared *N*-heterocycles were tested for anti-inflammatory activity by using RAW264.7 cells. As shown in Fig. 1a, most of the viability of cells treated with various *N*-heterocycles alone were similar or better than commercial anti-inflammatory drug indometacin. The LPS (1 μg/mL) stimulation for 24 h could markedly improve NO production, and compound **3ba** and **7aa** showed better NO inhibitory activity compared to indometacin at the concentration of 25 μmol/L (Fig. 1b). These preliminary results demonstrated that the designed ten-membered lactams or 5,6,6-perifused benzofurans and bicyclo[4.4.0] skeletons could prevent inflammatory response in RAW264.7 cells LPS-induced and might serve as good potent anti-inflammatory agents.

In summary, we have identified a modular synthesis of a range of valuable ten-membered *N*-heterocycles containing two or more continuous stereocenters in high diastereoselectivity through a formal [7 + 3] higher order cycloaddition reaction from *N*-vinyl-α,β-unsaturated nitrones and α-bromohydroxymates or α-tosyloxy ketones. Initial studies have shown that the obtained ten-membered *N*-heterocycles can be used as useful precursors for rapidly access highly functionalized benzofurans, bicyclo[4.4.0], and bicyclo[5.3.0] skeleton *N*-heterocyclic structures that are difficult to be prepared by traditional methods. The reaction shows a broad substrate scope and tolerated various sensitive functional groups. This mild and simple transformation provides a general approach to ten-membered rings and its fused *N*-heterocyclic derivatives. In addition, biological tests reveal that some of these designed ten-membered lactams and their derivatives including perifused benzofurans, bicyclo[4.4.0], and bicyclo[5.3.0] skeletons displayed their bioactivity as potent anti-inflammatory agents. We anticipate that this novel assembly higher-order [7 + 3] cycloaddition may provoke new developments in the formation of related medium-sized rings and the present protocol will find broad applications in synthetic and pharmaceutical chemistry.

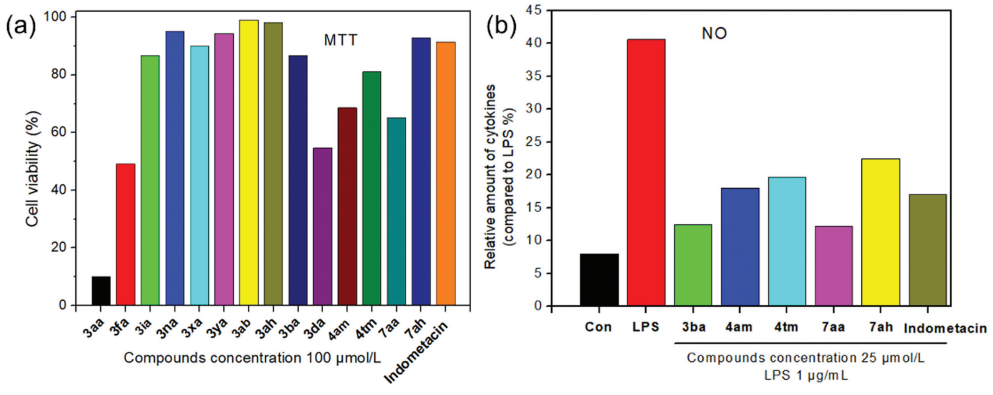


Fig. 1. Biological studies. (a) The effect on the cell viability. (b) The effect on LPS-induced NO production.

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.

CRediT authorship contribution statement

Yan Luo: Writing – original draft, Methodology, Investigation. **Yan-Jiao Lu:** Methodology, Formal analysis, Data curation. **Mei-Mei Pan:** Methodology, Investigation, Data curation. **Yu-Feng Liang:** Investigation, Data curation. **Wei-Min Shi:** Resources, Data curation. **Chun-Hua Chen:** Supervision, Methodology, Investigation, Conceptualization. **Cui Liang:** Supervision, Resources, Data curation. **Gui-Fa Su:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Dong-Liang Mo:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Acknowledgments

Financial support from the National Natural Science Foundation of China (No. 22071035), the Natural Science Foundation of Guangxi (Nos. 2023GXNSFDA026025, 2022GXNSFBA035494), Guangxi Minzu University Scientific Research Funds for Talent Introduction (2022KJQD14), and the Student Innovation Training Program (No. 202310602014), are greatly appreciated.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110207.

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