Stereodivergent synthesis of vicinal quaternary-quaternary stereocenters and bioactive hyperolactones

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Although great success has been achieved in asymmetric Claisen rearrangement for the synthesis of chiral γ,δ-unsaturated carbonyl compounds bearing vicinal tertiary-quaternary stereocenters, the development of asymmetric versions for stereodivergent construction of adjacent quaternary-quaternary stereocenters remains a formidable challenge because of the high steric hindrance. Here we report a catalytic enantioselective dearomatization Claisen rearrangement of allyl furyl ethers catalyzed by chiral N,N′-dioxide-NiII complex catalysts. A variety of chiral γ,δ-unsaturated carbonyl compounds bearing vicinal quaternary-quaternary stereocenters were obtained with excellent outcomes under mild conditions. Furthermore, we disclosed that by matching the configuration of the catalysts and the alkene unit of the substrates, four stereoisomers of the products could be prepared in excellent yields and stereoselectivities. Finally, the fascination of this strategy was demonstrated by stereodivergent synthesis of bioactive natural products hyperolactones B, C, and their epimers. A possible catalytic model was proposed to explain the origin of the asymmetric induction.
The Claisen rearrangement of allyl vinyl ethers is one of the most reliable and useful methods for synthesizing γ,δ-unsaturated carbonyl compounds, valuable intermediates in natural product construction\(^\text{1–4}\). On the basis of chiral Lewis acids\(^\text{5–10}\), Jacobsen's guanidinium salts\(^\text{11}\), N-heterocyclic carbenes\(^\text{12}\), or transition metals\(^\text{13–15}\) catalysts, various of linear and cyclic vinyl units have been transformed via catalytic asymmetric Claisen rearrangement to afford chiral γ,δ-unsaturated carbonyl compounds bearing vicinal tertiary-quaternary stereocenters (Fig. 1a). However, the direct and catalytic stereoselective assembly of these compounds with two adjacent quaternary-stereocenters remains scarce, because of the inherent steric congestion in the formation of C–C bond. To obtain vicinal quaternary-quaternary arrays and accomplish the total synthesis of several natural products, chiral starting materials were usually conducted through this type of reaction. Zhai and co-workers reported the total synthesis of (−)-Jiadifenin, in which the key intermediate was acquired on the basis of Ireland–Claisen rearrangement of chiral acetal precursor\(^\text{16}\). Nakamura developed a stereoselective Ireland–Claisen Rearrangement for the synthesis of the CDE ring system of antitumor and chiral building blocks for oxygenated Terpenoids\(^\text{17,18}\). In regard of catalytic asymmetric methodology, in 2010, the Jacobsen group reported the only catalytic example to produce the vicinal quaternary-quaternary array\(^\text{19}\). However, limited substrates were evaluated though good results were obtained, which restricted further application in the total synthesis of natural products. Although great achievement has been made in asymmetric Claisen rearrangement, the direct catalytic stereodivergent accessing to optically pure γ,δ-unsaturated carbonyl compounds bearing two adjacent quaternary stereocenters is yet to be described and would be of great value for the natural product-oriented asymmetric synthesis.

The hyperolactones A–C\(^\text{20,21}\) and (−)-biyouyanagin A\(^\text{22}\) are a family of spirolactone natural products isolated from Hypericum chinese \(L\), which possess significant activity against HIV replication (Fig. 1b). These compounds contain a mutual spiro-lactone fragment with two chiral vicinal quaternary carbon centers. Besides, the configuration of hyperolactones A, C, and (−)-biyouyanagin A is (S,S), while the configuration of hyperlactone B is (R,S), which varies from the spirocyclic center. Because of their anti-HIV biological activities and unique structures, synthetic chemists have developed many methodologies for their total syntheses\(^\text{22–32}\). Particularly, Kraus utilized a tandem Claisen rearrangement to realize the synthesis of racemic hyperolactones \(\text{C}\)\(^\text{33}\). Though, the yield was only 25% even heating the reaction mixture in a sealed tube at 130 °C for 15 h, which indicated the challenge of the construction of adjacent quaternary stereocenters. Motivated by these initial results, we try to establish a general and efficient asymmetric Claisen rearrangement methodology for the synthesis of the family compounds of hyperlactone. Besides, we envision that by matching the configuration of the chiral catalysts and the substrates, all of the four stereoisomers might be accessible (Fig. 1c).

Herein, we report the application of chiral \(N,N’\)-dioxide-Ni\(^\text{II}\) complex catalysts in the catalytic asymmetric dearomatization Claisen rearrangement of allyl furyl ethers. A series of γ,δ-unsaturated carbonyl compounds bearing two adjacent quaternary stereocenters were obtained in up to 99% yield, 19:1 dr, and 99% ee under mild reaction conditions. Moreover, the catalytic reaction shows a broad substrate scope, which may lead to the discovery of new bioactive molecules. Furthermore, four stereoisomers could be obtained and stereodivergent synthesis\(^\text{34–48}\) of natural products hyperlactone B, C could be achieved as well.

**Results**

**Optimization of reaction conditions.** Initially, we selected compound \(1\text{a}\) with \(E\)-configuration as the model substrate to optimize the reaction conditions. The classical catalysts of Cu (OTf)\(_2\)/BOX and Ni(OTf)\(_2\)/BOX yielded trace amount of the

![Fig. 1 Asymmetric Claisen rearrangement of allyl vinyl ethers and representative natural products containing adjacent quaternary stereocenters.](image-url)

- **a** Previous work for the catalytic asymmetric Claisen rearrangement of allyl vinyl ethers.
- **b** The structures of natural products hyperolactones A–C and (−)-biyouyanagin A.
- **c** Our catalytic asymmetric Claisen rearrangement strategy for stereodivergent construction of adjacent quaternary stereocenters.
Table 1 Optimization of the reaction conditions

| Entry | 1    | Metal source/Ligand  | Yield (%) | dr  | ee  |
|-------|------|----------------------|-----------|-----|-----|
| 1     | 1a   | Cu(OTf)2/BOX         | trace     | -   | -   |
| 2     | 1a   | Ni(OTf)2/BOX         | trace     | -   | -   |
| 3     | 1a   | Yb(OTf)3/L-PiMe2     | 47(3:1)   | 3:1 | 33  |
| 4     | 1a   | Ni(OTf)2/L-PiMe2     | 85        | 5:1 | 98  |
| 5     | 1a   | Ni(OTf)2/L-PiMe3     | 85        | 5:1 | 98  |
| 6     | 1a   | Ni(OTf)2/L-RaMe2     | 90        | 2:1 | 94  |
| 7     | 1b   | Ni(OTf)2/L-PiMe2     | 90        | 8:1 | 98  |
| 8     | 1c   | Ni(OTf)2/L-PiMe2     | 90        | 5:1 | 98  |
| 9     | 1b   | Ni(BF4)2·6H2O/L-PiMe2| 96        | 8:1 | 98  |
| 10    | 1b   | Ni(BF4)2·6H2O/L-PiMe2| 96        | 10:1| 99  |
|       | 1b   | Ni(BF4)2·6H2O/L-PiMe2| 94        | 5:1 | 99  |
| 11    | 1e   | Ni(BF4)2·6H2O/L-PiMe2| 90        | 1.5:1|99 |

*Unless otherwise noted, the reactions were performed with 1 (0.1 mmol), and metal source/Ligand (1:1, 10 mol%), in DCE (1.0 mL) at 70 °C for 4 h
bIsolated yield
cThe dr value was determined by 1H NMR and HPLC analysis
dDetermined by HPLC analysis on chiral stationary phases
eAt 35 °C for 4 days

Fig. 2 Substrate scope with variations at the furan unit. Unless otherwise noted, the reactions were performed with 1, Ni(BF4)2·6H2O/L-PiMe2 (1:1, 10 mol%), in DCE at 35 °C for 4 days. Isolated yield. The dr value was determined by 1H NMR and HPLC analysis. The ee value was determined by HPLC analysis on chiral stationary phases. The reaction of 2b and 2k were scaled up to 1.0 mmol. The reaction of 2n-2p were performed at 35 °C for 8 days.
Ni(BF$_4$)$_2$·6H$_2$O (10 mol%) catalyzed the reaction of ethyl substituted substrate $1q$ and $1r$ in excellent yields, stereoselectivities (Fig. 3b, up to 85% yield and 99% ee). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($97%$ yield, 12:1 dr and 93% ee). Halogen substitution on the aryl ring ($2u$, $2v$) improved the diastereoselectivity ($2v$, $2w$) while keeping the enantioselectivity ($2v$, $2w$, 92% yield, 15:1 dr). With Ni(BF$_4$)$_2$·6H$_2$O catalyst, a wide range of substrates with varied substituents on furan unit were tolerated in the reaction, furnishing the corresponding products in excellent yields, diastereo- and enantioselectivities (up to 99% yield, 12:1 dr and 99% ee). 1-Naphthyl substituted furan substrate ($2p$) was also obtained in excellent results (up to 96% yield, 9:1 dr and 99% ee) after prolonging the reaction time. To demonstrate the utility of this Claisen rearrangement, preparative-scale synthesis of the products $2b$ and $2k$ was carried out. Delightedly, the reactivity and stereocontrol were maintained, which indicated that this method could tolerate the gram-scale chemical production. Furthermore, the absolute configuration of $2g$ was determined to be $(S,S)$ by the X-ray diffraction of the related spirolactone derivative $3g$ (See Supplementary Fig. 7). The compounds $2b$ and $2n$ exhibited a similar Cotton effect in their circular dichroism (CD) spectra (See Supplementary Figs. 64–75).

The substrates with variation at the alkene unit were also examined (Fig. 3). Under the optimized reaction conditions, ethyl substituted substrate $1q$ and $E$-isobutyl substituted substrate $1r$ were transformed into the desired products $2q$ and $2r$ in excellent yields and enantioselectivities (Fig. 3a, up to 85% yield and 99% ee). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr). The latter showed relatively lower diastereoselectivity ($2q$) than $1q$ ($96%$ yield, 13:1 dr).
62% ee. In addition, the 2-naphthyl substituent alkene E-1x′ was found suitable for this reaction, delivering the product 2x′ in 82% yield with 8:1 dr and 83% ee. Furthermore, terminal monophenyl substituted alkene substrate E-1y could afford the desired product 2y in 97% yield with 95% ee and 12:1 dr in the presence of Ni(BF_4)₂/L-PiMe₂ catalyst. Both E-1z and Z-1z′ with terminal disubstituent were suitable in this reaction to afford the corresponding products 2z and 2z′ in excellent results (Fig. 3c, up to 96% yield, 99% ee and 9:1 dr).

**Asymmetric synthesis of four stereoisomers.** To examine our initial stereodivergent assumption and the purpose of synthesizing natural products hyperolactones B and C, we prepared the E-1b, 1n and Z-1b′, 1n′ and treated them under the optimal reaction conditions (Fig. 4). As expected, the E-substrates preferably afforded (S,S)-configuration products 2b and 2n, while the Z-substrates yielded the (S,R)-configuration products 2b′ and 2n′ (The configuration of the products were confirmed by CD spectra and NOE spectra analysis of hyperolactones, see Supplementary Figs. 64–79). Besides, by alternating the absolute configuration of N,N′-dioxide ligand L-PiMe₂, the corresponding enantiomers were available in comparable results. Thus, all four stereoisomers of such γ,δ-unsaturated carbonyl compounds containing vicinal quaternary-quaternary centers could be obtained with this kind of easily available chiral catalyst.

**Stereodivergent synthesis of hyperolactones.** Subsequently, we tried various reagents to realize the deprotection/lactonization transformation of the product 2b, 2b′, 2n and 2n′. b Formal synthesis of (−)-biyouyanagin A and epi-(−)-biyouyanagin A.

**Fig. 4** Synthesis of all four stereoisomers. Unless otherwise noted, the reactions were performed with 1 (0.1 mmol), and cat* or ent-cat* (10 mol%), in DCE (1.0 mL) at 35 °C for 4 days. Isolated yield. The dr value was determined by 1H NMR and HPLC analysis. The ee value was determined by HPLC analysis on chiral stationary phases. cat* = Ni(BF₂)₂·6H₂O/L-PiMe₂ (1:1), ent-cat* = Ni(BF₂)₂·6H₂O/ent-L-PiMe₂ (1:1).
Fig. 6 Proposed stereochemical model. Substrate 1g was selected for the model analysis.

Proposed stereochemical model. On the basis of our previous works and the absolute configuration of the product 2g, a possible stereocontrol model was proposed in Fig. 6. The chiral N, N'-dioxide coordinates to the nickel(II) center to form octahedral metal complex in which the chiral ligand occupies four sites. The substrate 1g displays the ancillary solvents or anion and could coordinate to the Lewis acid catalyst via a bidentate manner with the oxygen of ether and carbonyl group of the auxiliary ester group. Due to the steric hindrance between alkene unit and the bulky aniline moiety of ligand, the alkene preferentially approaches a position of furan unit from the Re face. Therefore, the E-alkene substrate 1g affords (S,S)-2g and the Z-alkene substrate 1g' affords (S,R)-2g'.

Discussion
In summary, we have developed a catalytic asymmetric dearomatization Claisen rearrangement of allyl furyl ethers for the synthesis of chiral γ,δ-unsaturated carbonyl compounds with two adjacent quaternary-quaternary carbon centers. By adjusting the configuration of the catalysts and alkene units, all four possible product stereoisomers could be prepared in excellent yields and stereoselectivities. In addition, the reaction has a broad substrate scope, which may lead to the discovery of new bioactive molecules. Furthermore, the bioactive natural products hyperolactones B, C, and their epimers could be readily acquired in high efficiency, which are also the key intermediates for the synthesis of natural product (−)-bijouyanagin A and its epimer.

Methods
General procedure for asymmetric Claisen rearrangement. N,N'-Dioxide ligand L-PiMe2 or ent-L-PiMe2 or ent-L-PiMe3 (10 mol%), Ni(BF4)2·6H2O (10 mol%) in CH2Cl2 were stirred at 35 °C for 1 h. Then CH2Cl2 was removed in vacuo. Substrate 1 and DCE were added and the resulting mixture was stirred at 35 °C for 4–8 days. After the reaction completed (monitored by TLC), flash column chromatography was carried out to provide the desired product (Petroleum ether/EtOAc = 20:1 to 10:1).

General procedure for deprotection/cyclization reaction. To a solution of the product 2 (0.1 mmol) in CH3OH/CH2Cl2 (1.5 mL, 2:1, v/v), TMSBr (0.4 mmol, 4.0 equiv.) was added. The reaction mixture was stirred at 30 °C for 8–24 h. Then the reaction was quenched by saturated aq. Na2CO3 (1 mL) and diluted with water (1 mL). The product was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (20 mL) and concentrated in vacuo. The product was purified by column chromatography on silica gel (hexane/EtOAc = 10:1 as eluent).

Data availability. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Crystal data and structure refinement for 3g was displayed in Supplementary Information. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/ under deposition number 1554368. All other data is available from the corresponding author upon reasonable request.

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Author contributions

H.F.Z. performed experiments and prepared the Supplementary Information and Manuscript. Y.W. and C.R.X. took part in the reaction development and synthesized several substrates. X.X. repeated some experiments. L.L.L. helped with modifying the paper and Supplementary Information. X.H.L. and X.M.F. conceived and directed the project.

Additional information

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Competing interests

The authors declare no competing interests.

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