Chinese Chemical Letters 34 (2023) 108121

Contents lists available at ScienceDirect

Chinese Chemical Letters

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# Organocatalytic enantioselective construction of bicyclic $\gamma$-butrolactones

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ARTICLE INFO

*Article history:*
Received 9 October 2022
Revised 23 December 2022
Accepted 27 December 2022
Available online 29 December 2022

*Keywords:*
Organocatalyst
Asymmetric synthesis
Bicyclic $\gamma$-butyrolactone
Diamine
Cyclization

ABSTRACT

An enantioselective organo-catalyzed reaction of furanones with $\alpha,\beta$-unsaturated ketones has been established herein, which provides an efficient access to chiral bicyclic $\gamma$-butyrolactones in good yields, enantioselectivities and diastereoselectivities. Further transformations of product are demonstrated. A diamine mediated catalytic cycle is proposed.



Bicyclic $\gamma$-butyrolactone compounds with multiple chiral centres are key structural motifs of a variety of biologically active terpenoids and drug molecules, as well as important intermediates in the synthesis of complex natural products [1–5]. Representative examples such as Podophyllotoxin [6–11], Vorapaxar [12–15], Sempervivum lactone [16] and Gracilin A (Fig. 1) [17–19]. Podophyllotoxin, a naturally occurring aryltetralin cyclolignan, belongs to a family of important products that exhibit various biological properties (*e.g.*, cytotoxic, insecticidal, antifungal, antiviral, anti-inflammatory, neurotoxic, immunosuppressive, antirheumatic, antioxidative, antispasmogenic, and hypolipidemic activities) [20]. Podophyllotoxin tinctureis commonly used as a first-line agent for the treatment of condyloma acuminatum [21,22]. The two main semi-synthesized podophyllotoxin-derivatives, namely, etoposide [23–26], teniposide [27–29], were used in frontline cancer therapy against various cancer as topoisomerase II inhibitors [30–32]. Vorapaxar is a first-in-class, potent and orally-active protease-activated receptor 1 (PAR-1) antagonist that used for patients with heart attack or arterial blockage to reduce the risk of death such as cardiovascular disease and stroke [33,34]. Originally isolated and characterized from the Mediterranean sponge *Spongionella gracilis1e*, Gracilin A, was shown to have antioxidant [35] or neuroprotective [36] properties. There are many natural products of bicyclic $\gamma$-butyrolactone showing diverse structural features and interesting biological activities [37,38].

Currently, multiple strategies of merging five-membered rings with six-membered rings have been developed for the synthesis of chiral bicyclic $\gamma$-butyrolactones, including enzymes catalysts [39,40], oxidation catalysis by chiral metal complexes [41–47], organocatalyzed electrooxidation [48,49], *etc.* [3,50–56]. The enzymatic catalysis of the stereotactic transformations of *meso*–compounds into chiral synthons has long been reported, with horse liver alcohol dehydrogenase (HLADH) and pig liver esterase (PLE) proving particularly valuable in this regard (Scheme 1a) [39,40]. Metal oxidation systems involve the use of a metal mediator, especially for the noble metal catalyst, such as the Rh, Ru, Ir and Pt complex (Scheme 1b) [41–47]. A water-soluble artificial xanthine organocatalyst with an oxidation cofactor regeneration system was reported for the synthesis of target compounds in high yields with high *er* values (Scheme 1c) [48,49]. Despite formidable advances have been achieved for the synthesis of chiral bicyclic $\gamma$-butyrolactones, all of them used pre-assembled chiral substrates to construct the skeleton of this class of compounds, which has the disadvantages of high cost and numerous steps, and cannot be used to rapidly construct chiral bicyclic $\gamma$-butyrolactones in a sin-

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https://doi.org/10.1016/j.cclet.2022.108121
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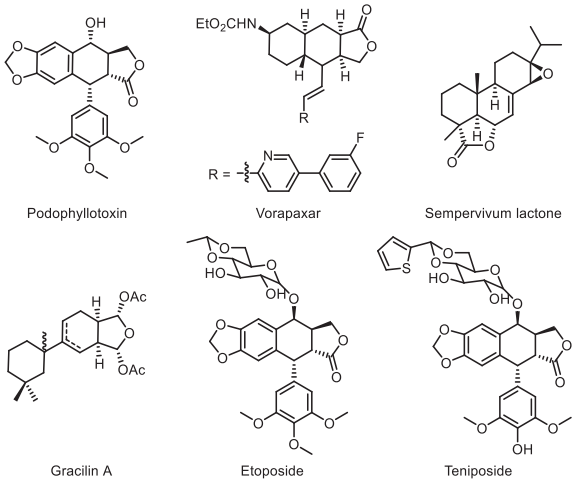
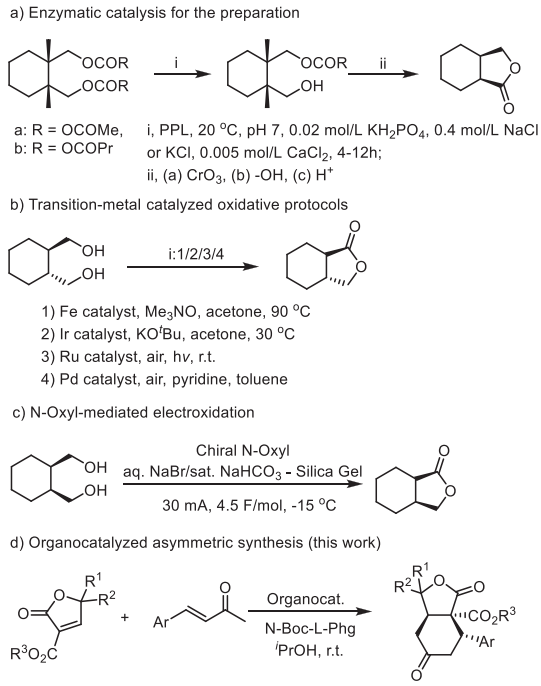



**Fig. 1.** Representative bicyclic $\gamma$-butyrolactones.

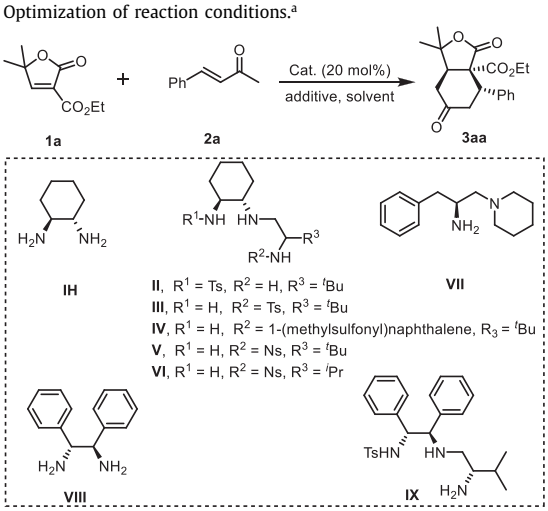



**Scheme 1.** Synthesis of chiral bicyclic $\gamma$-butyrolactones.

gle step reaction. Inspired by recently reported organocatalyst promoted asymmetric synthesis [57–75], we envisioned that a suitable organocatalyst could be employed successfully in the asymmetric cascade Michael reaction and cyclization of $\alpha,\beta$-unsaturated ketones with furanones, but it remains to be disclosed. Herein, we report the establishment of an organo-catalyzed asymmetric reaction of furanones with $\alpha,\beta$-unsaturated ketones (Scheme 1d). Notable features of our study include: (1) the first example of organo-catalyzed asymmetric Michael addition/cyclization reaction of furanone with $\alpha,\beta$-unsaturated ketones; (2) the protocol provides an efficient method to approach diverse chiral bicyclic $\gamma$-butyrolactones in good yields, enantioselectivities and diastereoselectivities.

Initially, model reaction by condensation of $\gamma$-bis-methyl-$\alpha$-ethylfuranone **1a** and benzal acetone **2a** was used to optimize the reaction condition. The corresponding results are shown in Table 1. We firstly investigated the activity of catalysts **I-IX**, a range of chiral primary amine catalysts. We envisaged that a catalyst with

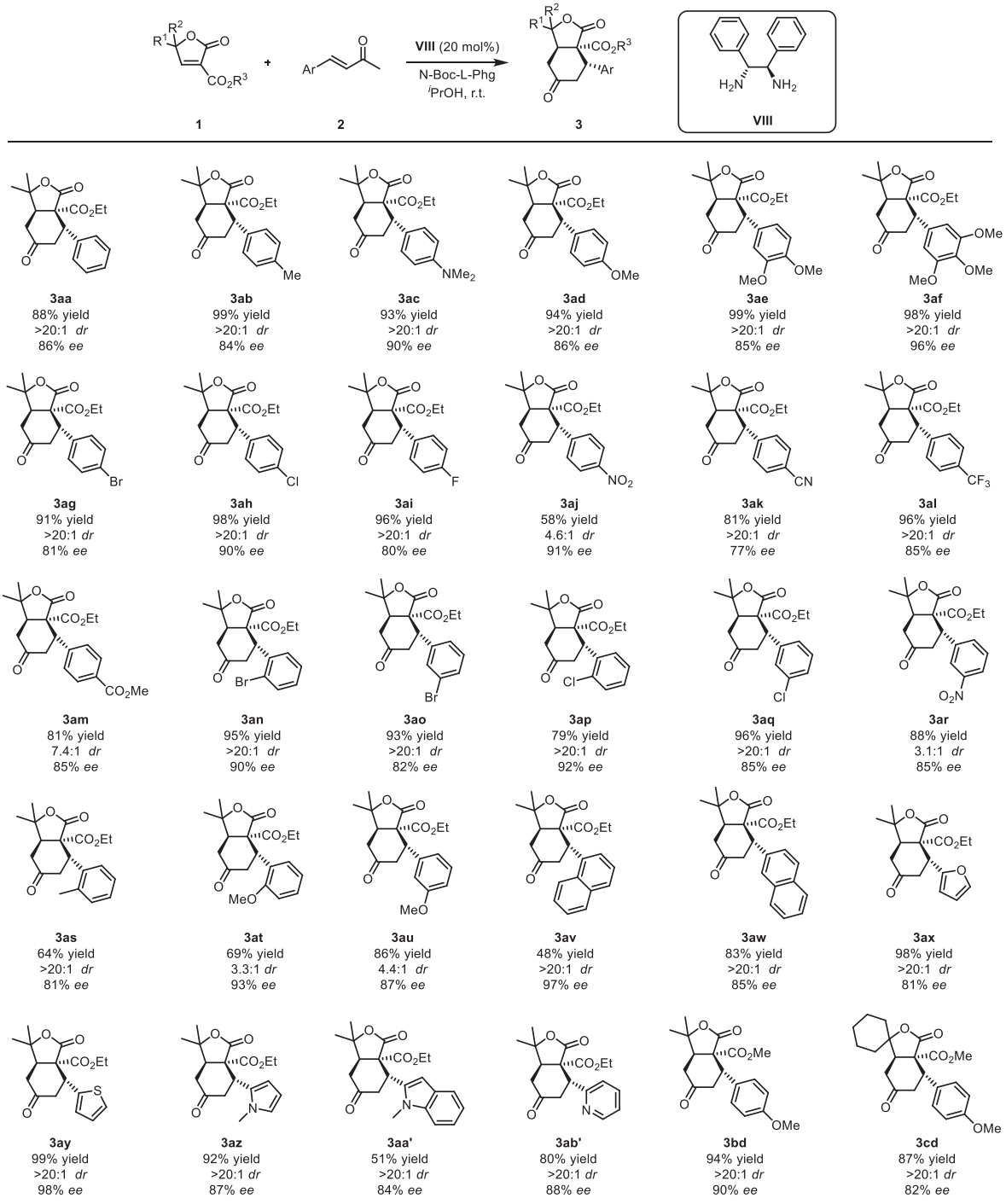
**Table 1**
Optimization of reaction conditions.[a]




| Entry | Cat. | Additive | Solvent | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | **I** | N-Boc-L-Phg | $^i$PrOH | 70 | 67 |
| 2 | **II** | N-Boc-L-Phg | $^i$PrOH | 50 | 43 |
| 3 | **III** | N-Boc-L-Phg | $^i$PrOH | 60 | 46 |
| 4 | **IV** | N-Boc-L-Phg | $^i$PrOH | 28 | 38 |
| 5 | **V** | N-Boc-L-Phg | $^i$PrOH | 50 | 44 |
| 6 | **VI** | N-Boc-L-Phg | $^i$PrOH | 55 | 53 |
| 7 | **VII** | N-Boc-L-Phg | $^i$PrOH | 30 | 26 |
| 8[d] | **VIII** | N-Boc-L-Phg | $^i$PrOH | 89 | 86 |
| 9 | **IX** | N-Boc-L-Phg | $^i$PrOH | 35 | 62 |
| 10 | **VIII** | $PhCO_2H$ | $^i$PrOH | 32 | 81 |
| 11 | **VIII** | AcOH | $^i$PrOH | 30 | 46 |
| 12 | **VIII** | $CF_3CO_2H$ | $^i$PrOH | 35 | 29 |
| 13 | **VIII** | *p*-TsOH | $^i$PrOH | 10 | 70 |
| 14 | **VIII** | N-Boc-L-Phg | DMSO | 0 | – |
| 15 | **VIII** | N-Boc-L-Phg | PhMe | 62 | 79 |
| 16 | **VIII** | N-Boc-L-Phg | MeOH | 45 | 78 |
| 17 | **VIII** | N-Boc-L-Phg | EtOH | 50 | 83 |
| 18 | **VIII** | N-Boc-L-Phg | THF | 10 | 74 |
| 19 | **VIII** | – | $^i$PrOH | 0 | – |
| 20 | **–** | N-Boc-L-Phg | $^i$PrOH | 0 | – |

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), cat. (20 mol%), additive (20 mol%), $^i$PrOH (1 mL), at room temperature for 7 days.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Diastereoselectivity > 20:1. N-Boc-L-Phg = Boc-L-Phenylglycinol.

neighboring bulky substituents of the primary amine group could improve the enantioselectivity. Therefore, the (1*S*,2*S*)-cyclohexane-1,2-diamine **I** was chosen as the catalytic backbone, which is readily available from cheap amino acids, and the *tert*–butyl group was introduced into the catalyst backbone to investigate the effect of secondary and tertiary amines on enantioselectivity and product yield (Table 1, entries 1–9). Unfortunately, changing the substituent groups at the $R^1$ and $R^2$ positions of catalyst **II** and **III**, which with a *tert*–butyl group at the $R^3$ position, did not improve the enantioselectivity (Table 1, entries 2 and 3). Moreover, the catalysts **IV**, **V**, **VI** and **VII** with different substituents also failed to increase the efficiency (Table 1, entries 4–7). To our delight, the use of (1*R*,2*R*)−1,2-diphenylethane-1,2-diamine **VIII** as catalyst resulting in good yield, enantioselectivity and diastereoselectivity (Table 1, entry 8). Next, the tridentate $N_3$-catalyst **IX** provided ineffective (Table 1, entry 9). Subsequently, we optimized the reaction by using various additives in the presence of catalyst **VIII** and found that both weak acid additives AcOH and $PhCO_2H$ and stronger acid $CF_3CO_2H$ and *p*-TsOH gave lower enantioselectivity and yields than N-Boc-L-Phg (Table 1, entries 10–13). Further screening of the solvent indicated that $^i$PrOH is better than DMSO, PhMe, MeOH, EtOH, and THF (Table 1, entries 14–18). Finally, control experiments




**Scheme 2.** Scope of various $\alpha,\beta$-unsaturated ketones and $\gamma$-butenolides.

demonstrated that the organo-catalyst and acid additive are both essential for the success of this transformation (Table 1, entries 19 and 20).

With the optimal conditions in hand, structural diversity of $\alpha,\beta$-unsaturated ketones were then examined. As demonstrated in Scheme 2, a wide range of aryl $\alpha,\beta$-unsaturated ketones substituted with either electron-withdrawing and electron-donating group on the aromatic ring and heteroaromatic $\alpha,\beta$-unsaturated ketones were found to be well tolerated in this transformation. For example, the $\alpha,\beta$-unsaturated ketones holding electron-releasing substituents, such as alkyl, amine and ether, smoothly reacted with furanone **1a**, affording **3ab**-**3af** in excellent yields with good to excellent diastereo- and enantioselectivity. Electron-deficient $\alpha,\beta$-unsaturated ketones containing halide, nitro, cyano, trifluoromethyl and ester functional groups were all successfully applied in this approach (**3ag**-**3ar**). With the variation of the steric effect at the phenyl ring, the stereoselectivities remained excellent (**3as**-**3aw**). The *dr* values of products **3aj** and **3ar** were 4.6:1 and 3:1 when the aryl possessed the 4-nitro and 3-nitro groups substituent, respectively. Noteworthy, the heterocyclic unsaturated ketones also proceeded smoothly with good to excellent enantioselectivities (**3ax**-**3ab'**). Alkyl substituted $\alpha,\beta$-unsaturated ketones were not suitable in this transformation resulting in low yields. Furthermore, the $\alpha$-methyl ester substituted furanone was applicable to this asymmetric synthesis, affording the corresponding product **3bd**. The cyclohexyl substituted at the $\gamma$-position of furanone also worked well

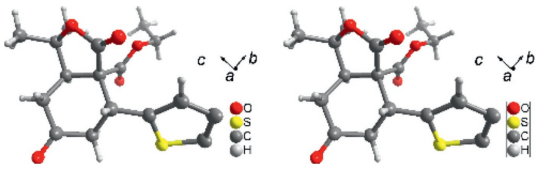
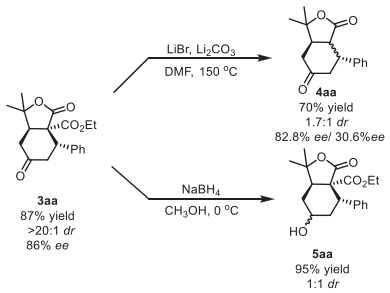
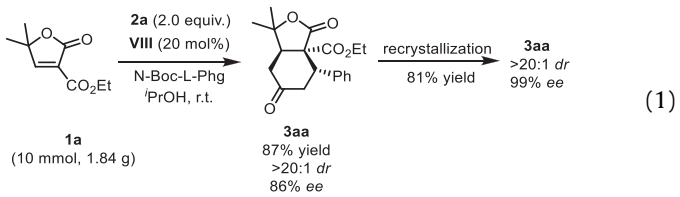


**Fig. 2.** X-ray structures of **3ae** (left, CCDC: 2111451) and **3ay** (right, CCDC: 2111452).




**Scheme 3.** Further transformation.

to yield the product **3cd**. In addition, the optimized conditions were applied in a scale up process (10 mmol) in which the chemical and optical yields were sustained well. It should be noted that the *ee* value could be easily improved to 99% after recrystallization (Eq. 1).

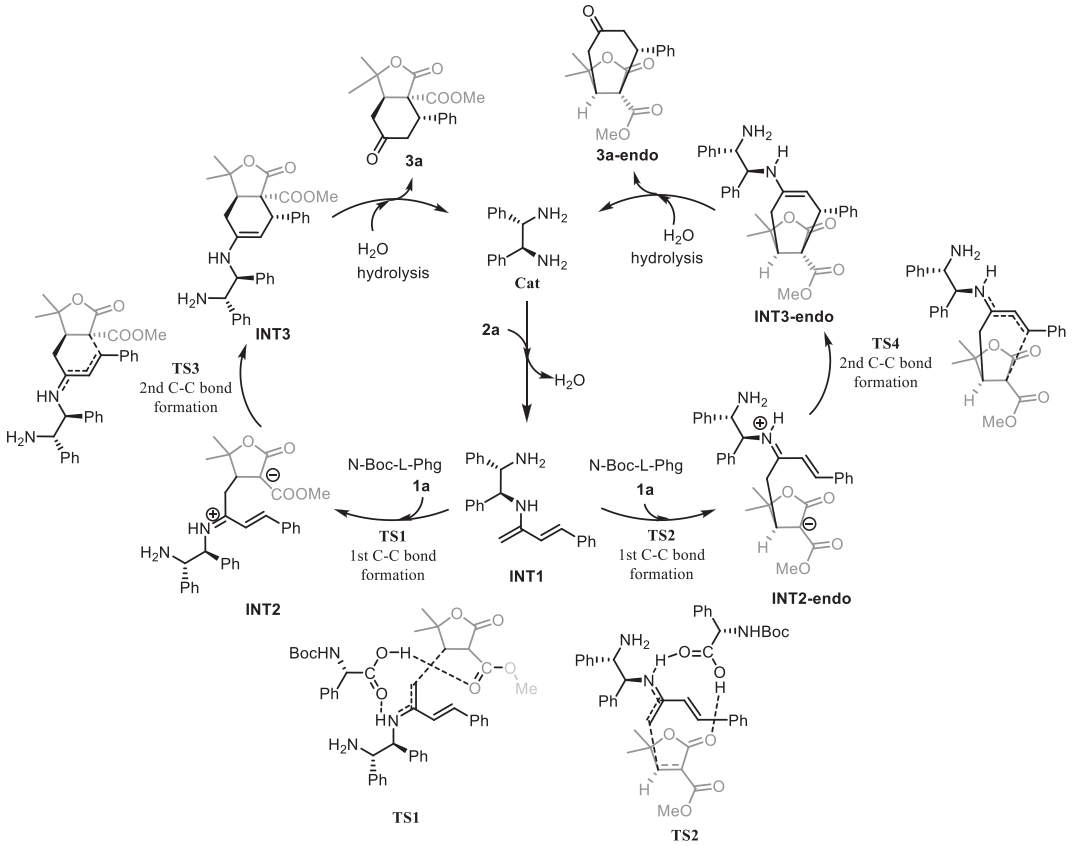



(1)

The absolute configuration was unambiguously confirmed by the X-ray structures of **3ae** and **3ay**. The lactone and six-ring were *syn*-ring fused bicylic butrolactone (Fig. 2). In order to investigate the further transformation of obtained chiral bicyclic $\gamma$-butyrolactones, **3aa** was decarboxylated under certain conditions to obtain **4aa**. Moreover, product **3aa** was reduced to alcohol **5aa** by $NaBH_4$ in methanol (Scheme 3).

As shown in Scheme 4, a mechanism including two Michael addition reactions catalyzed by **Cat** was proposed using **1a** and **2a**. **Cat** can react with **2a** leading to the active enamine intermediate **INT1** catalyzed by weak acid [76]. Subsequently, **INT1** attacks **1a** from the *Re*-face through **TS1** or **TS2** under the concerted catalysis of N-Boc-L-Phg to form the first C–C bond leading to the zwitterionic intermediate **INT2** or **INT2-endo**, which determines the stereoselectivity of this reaction. The $\pi$-$\pi$ stacking interaction between N-Boc-L-Phg and **Cat** or substrate is important to get good stereoselectivity in this reaction, which should be further specified in future. The second C–C bond formation was limited by the first C–C bond. The second C–C bond was formed through **TS3** or **TS4** to yield **INT3** or **INT3-endo**. Hydrolysis of **INT3** or **INT3-endo** leads to **3aa** or **3aa-endo** and **Cat** was regenerated.

In conclusion, we demonstrated the asymmetric construction of bicyclic $\gamma$-butyrolactones from the one-step reaction of furanone with $\alpha,\beta$-unsaturated ketones in the catalytic system of chiral 1,2-diphenylethylenediamine and N-Boc-L-Phg. This is the first asymmetric cascade Michael addition/cyclization reaction of furanone with $\alpha,\beta$-unsaturated ketones, providing bicyclic $\gamma$-butyrolactones in good yields, as well as high enantioselectivities and diastereoselectivities (up to 98% *ee* and >20:1 *dr*).




**Scheme 4.** Proposed reaction mechanism.

## 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.

## Acknowledgments

We thank National Natural Science Foundation of China (Nos. 21877005, 21907059, 22001147), Taishan Scholars Project of Shandong Province (No. tsqn202103027), Distinguished Young Scholars of Shandong Province (Overseas) (No. 2022HWYQ-001), Academic Promotion Programme of Shandong First Medical University (No. 2019LJ003), and Natural Science Foundation of Shandong Province (No. ZR2021MB102) for financial support.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.108121.

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