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# Direct $\beta$ -selectivity of $\alpha,\beta$ -unsaturated $\gamma$ -butyrolactam for asymmetric conjugate additions in an organocatalytic manner†

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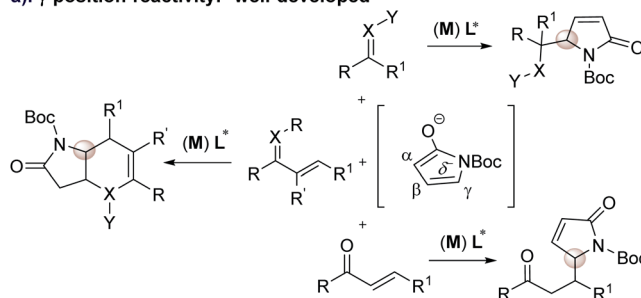
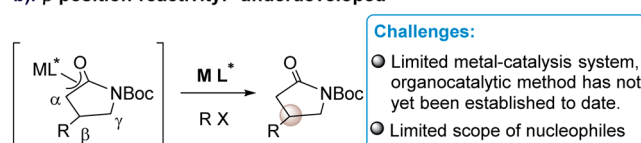
The  $\beta$ -selective asymmetric addition of  $\gamma$ -butyrolactam with cyclic imino esters catalyzed by a bifunctional chiral tertiary amine has been developed, which provides an efficient access to optically active  $\beta$ -position functionalized pyrrolidin-2-one derivatives in both high yield and enantioselectivity (up to 78% yield and 95 : 5 er). This is the first catalytic method to access chiral  $\beta$ -functionalized pyrrolidin-2-one *via* a direct organocatalytic approach.

Metal-free organocatalytic asymmetric transformations have successfully captured considerable enthusiasm of chemists as powerful methods for the synthesis of various kinds of useful chiral compounds ranging from the preparation of biologically important molecules through to novel materials.<sup>1</sup> Chiral pyrrolidin-2-ones have been recognized as important structural motifs that are frequently encountered in a variety of biologically active natural and synthetic compounds.<sup>2</sup> In particular, the  $\beta$ -position functionalized pyrrolidin-2-one backbones, which can serve as key synthetic precursors for inhibitory neurotransmitters  $\gamma$ -aminobutyric acids (GABA),<sup>3</sup> selective GABA<sub>B</sub> receptor agonists<sup>4</sup> as well as antidepressant rolipram analogues,<sup>5</sup> have attracted a great deal of attention. Therefore, the development of highly efficient, environmentally friendly and convenient asymmetric synthetic methods to access these versatile frameworks is particularly appealing.

As a direct precursor to pyrrolidin-2-one derivatives, recently,  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam has emerged as the most attractive reactant in asymmetric organometallic or organocatalytic reactions for the synthesis of chiral  $\gamma$ -position functionalized pyrrolidin-2-ones (Scheme 1). These elegant developments have been achieved in the research area of catalytic asymmetric vinylogous aldol,<sup>6</sup> Mannich,<sup>7</sup> Michael<sup>8</sup> and annulation reactions<sup>9</sup> in the presence of either metal catalysts or organocatalysts (a, Scheme 1). These well-developed catalytic asymmetric methods have been related to the  $\gamma$ -functionalized  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam to

date. However, in sharp contrast, the approaches toward introducing C-3 chirality at the  $\beta$ -position of butyrolactam through a direct catalytic manner are underdeveloped (b, Scheme 1)<sup>10</sup> in spite of the fact that  $\beta$ -selective chiral functionalization of butyrolactam can directly build up  $\alpha,\beta$ -functionalized pyrrolidin-2-one frameworks.

So far, only a few metal-catalytic enantioselective  $\beta$ -selective functionalized reactions have been reported. For examples, a rhodium/diene complex catalyzed efficient asymmetric  $\beta$ -selective arylation<sup>10a</sup> and alkenylation<sup>10b</sup> have been reported by Lin group (a, Scheme 2). Procter and co-workers reported an efficient Cu(I)-NHC-catalyzed asymmetric silylation of unsaturated lactams (b, Scheme 2).<sup>10c</sup> Despite these creative works, considerable challenges still exist in the catalytic asymmetric  $\beta$ -selective functionalization of  $\gamma$ -butyrolactam. First, the

a).  $\gamma$ -position reactivity: well-developedb).  $\beta$ -position reactivity: underdeveloped

## Challenges:

- Limited metal-catalysis system, organocatalytic method has not yet been established to date.
- Limited scope of nucleophiles

Scheme 1 Different reactive position of  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam in catalytic asymmetric reactions.

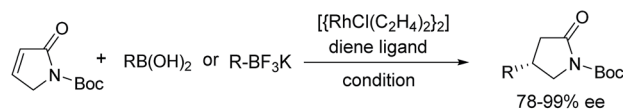
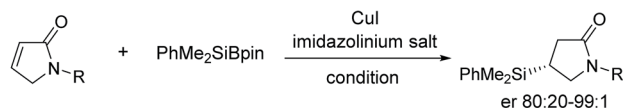
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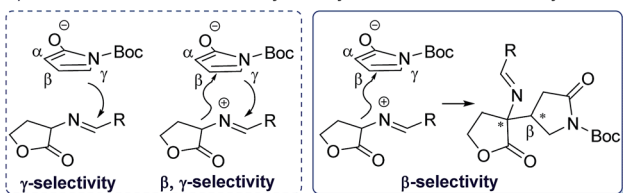
† Electronic supplementary information (ESI) available. CCDC 1475321. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra05264f

‡ These authors contributed equally to this work.



a) Rhodium/Diene-Catalyzed Asymmetric  $\beta$ -Selective Arylation/Alkenylationb) Cu(I)-NHC Catalyzed Asymmetric  $\beta$ -Selective Silyl Transfer Reaction

## c) This work: Chiral Amine Catalyzed Asymmetric Reaction of Butyrolactam



Scheme 2  $\beta$ -Selective functionalization of  $\gamma$ -butyrolactam via metal- (previous work) or organo- (this work) catalytic approach.

scope of nucleophiles is limited to arylboronic acids, potassium alkenyltrifluoroborates and  $\text{PhMe}_2\text{SiBpin}$  reagents. Second, the catalytic system and activation mode is restricted to metal/chiral ligands. To our knowledge, an efficient catalytic method to access chiral  $\beta$ -functionalized pyrrolidin-2-one *via* a direct organocatalytic approach has not yet been established. Therefore, the development of organocatalytic asymmetric  $\beta$ -selective functionalization of  $\gamma$ -butyrolactam are highly desirable. In conjunction with our continuing efforts in building upon chiral precedents by using chiral tertiary amine catalytic system,<sup>11</sup> we rationalized that the activated  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam might serve as a  $\beta$ -position electron-deficient electrophile. This  $\gamma$ -butyrolactam may react with a properly designed electron-rich nucleophile to conduct an expected  $\beta$ -selective functionalized reaction of  $\gamma$ -butyrolactam under a bifunctional organocatalytic fashion, while avoiding the direct  $\gamma$ -selective vinylogous addition reaction or  $\beta,\gamma$ -selective annulation as outlined in Scheme 2. Herein we report the  $\beta$ -selective asymmetric addition of  $\gamma$ -butyrolactam with cyclic imino esters<sup>12</sup> catalyzed by a bifunctional chiral tertiary amine, which provides an efficient and facile access to optically active  $\beta$ -position functionalized pyrrolidin-2-one derivatives with both high diastereoselectivity and enantioselectivity.

To begin our initial investigation, several bifunctional organocatalysts<sup>13</sup> were firstly screened to evaluate their ability to promote the  $\beta$ -selective asymmetric addition of  $\gamma$ -butyrolactam **2a** with cyclic imino ester **3a** in the presence of 15 mol% of catalyst loading at room temperature in  $\text{CH}_2\text{Cl}_2$  (entries 1–6, Table 1). These results indicated that chiral catalyst (DHQD)<sub>2</sub>AQN **1f** is the best catalyst in terms of chemical yield and enantioselectivity, furnishing the products with excellent diastereoselectivity in 71% yield and 77 : 23 er (entry 6). Subsequently, a survey of other solvents was carried

Table 1 Optimization of reaction conditions<sup>a</sup>

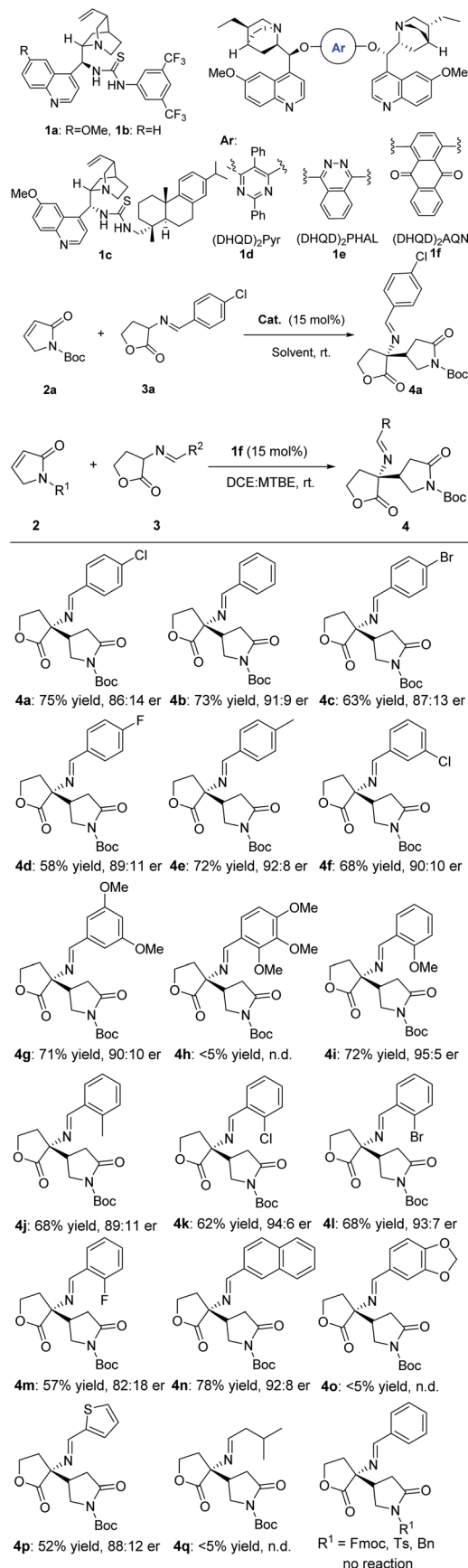
Entry	Cat.	Solvent	Yield <sup>e</sup>	er <sup>f</sup>
1	<b>1a</b>	$\text{CH}_2\text{Cl}_2$	70%	40 : 60
2	<b>1b</b>	$\text{CH}_2\text{Cl}_2$	<5%	57 : 43
3	<b>1c</b>	$\text{CH}_2\text{Cl}_2$	70%	65 : 35
4	<b>1d</b>	$\text{CH}_2\text{Cl}_2$	68%	70 : 30
5	<b>1e</b>	$\text{CH}_2\text{Cl}_2$	58%	63 : 47
6	<b>1f</b>	$\text{CH}_2\text{Cl}_2$	71%	77 : 23
7	<b>1f</b>	DCE	72%	80 : 20
8	<b>1f</b>	$\text{CHCl}_3$	70%	80 : 20
9	<b>1f</b>	MTBE	68%	79 : 21
10	<b>1f</b>	Toluene	63%	78 : 22
11	<b>1f</b>	THF	45%	76 : 24
12	<b>1f</b>	MeOH	32%	62 : 38
13 <sup>b</sup>	<b>1f</b>	DCE : MTBE	75%	87 : 13
14 <sup>c</sup>	<b>1f</b>	DCE : MTBE	72%	87 : 13
15 <sup>d</sup>	<b>1f</b>	DCE : MTBE	70%	85 : 15

<sup>a</sup> Reaction conditions: unless specified, a mixture of **2a** (0.2 mmol), **3a** (0.3 mmol) and a catalyst (15 mmol%) in a solvent (2.0 mL) was stirred at rt. for 48 h. <sup>b</sup> The reaction was carried out in 2.2 mL a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1). <sup>c</sup> The reaction was carried out in 2.2 mL a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1) for 24 h. <sup>d</sup> The reaction was carried out in 2.2 mL a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1) and 10 mol% of catalyst was used. <sup>e</sup> Isolated yields. <sup>f</sup> Determined by chiral HPLC, the product was observed with >99 : 1 dr by <sup>1</sup>H NMR and HPLC. Configuration was assigned by X-ray crystal data of **4a**.

out with catalyst **1f** (entries 7–12). We found that a substantial change of the solvent has a significant effect on the reaction. Among the solvents tested, dichloroethane appeared to be the most suitable reaction media, giving the product with 80 : 20 er (entry 7). Screening of solvents revealed a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1) offered a better yield and enantioselectivity (75% yield, and 87 : 13 er) (entry 13).

The results of experiments under the optimized conditions that probed the scope of the reaction are summarized in Scheme 3. The catalytic  $\beta$ -selective asymmetric addition of  $\gamma$ -butyrolactam **2a** with cyclic imino esters **3a** in the presence of 15 mol% (DHQD)<sub>2</sub>AQN **1f** was performed. A variety of phenyl-substituted cyclic imino esters including those bearing electron-withdrawing and electron-donating substituents on the aryl ring, heterocyclic were also examined. The electron-neutral, electron-rich, or electron-deficient groups on the *para*-position of phenyl ring of the cyclic imino esters afforded the products **4a–4m** in 57–75% yields and 82 : 18 to 95 : 5 er values. It appears that either an electron-withdrawing or an electron-donating at the *meta*- or *ortho*-position of the aromatic ring had little influence on the yield and stereoselectivity. Similar results on the yield and enantioselectivities were obtained with 3,5-dimethoxy substituted cyclic imino ester (71% yield and 91 : 9 er). It was notable that the system also demonstrated a good tolerance to naphthyl substituted imino ester (78% yield and 92 : 8 er value). The 2-thienyl substituted cyclic imino ester proceeded smoothly under





Scheme 3 Substrate scope of the asymmetric reaction of  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactam **2** to cyclic imino esters **3**. <sup>a</sup>Reaction

standard conditions as well, which gave the desired product **4p** in good enantioselectivity (88 : 12 er), although yield was slightly lower. However, attempts to extend this methodology to aliphatic-substituted product proved unsuccessful due to the low reactivity of the substrate **3q**. It is worth noting that the replacement of Boc group with 9-fluorenylmethyl, tosyl or benzyl group as the protection, no reaction occurred. The absolute and relative configurations of the products were unambiguously determined by X-ray crystallography (**4a**, see the ESI†).

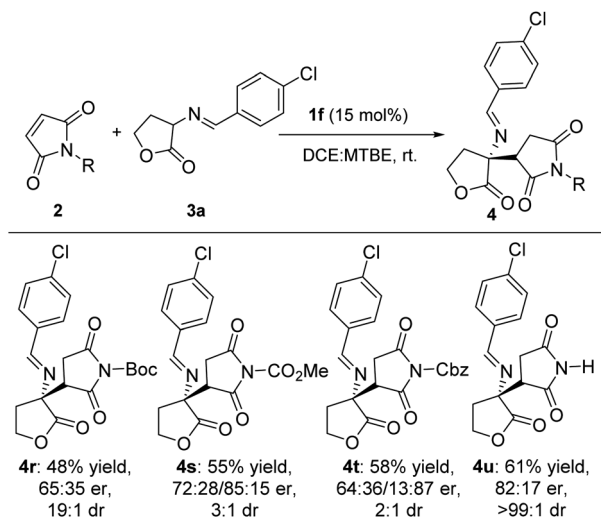
We then examined the substrate scope of the imide derivatives (Scheme 4). Investigations with maleimides **4r–4u** gave 48–61% yield of corresponding products as lower er and dr values than most of  $\gamma$ -butyrolactams. As for methyl substituted maleimides, the reaction failed to give any product.

The chloride product **4a** ((*R*)-*tert*-butyl 4-((*R*)-3-((*E*)-(4-chlorobenzylidene)amino)-2-oxotetrahydrofuran-3-yl)-2-oxopyrrolidine-1-carboxylate) was recrystallized and the corresponding single crystal was subjected to X-ray analysis to determine the absolute structure. Based on this result and our previous work, a plausible catalytic mechanism involving multisite interactions was assumed to explain the high stereoselectivity of this process (Fig. 1). Similar to the conformation reported for the dihydroxylation and the asymmetric direct aldol reaction, the transition state structure of the substrate/catalyst complexes might be presumably in the open conformation. The acidic  $\alpha$ -carbon atom of cyclic imino ester **3a** could be activated by interaction between the tertiary amine moiety of the catalyst and the enol of **3a** *via* a hydrogen bonding. Moreover, the enolate of **3a** in the transition state might be in part stabilized through the  $\pi$ - $\pi$  stacking between the phenyl ring of **3a** and the quinoline moiety. Consequently, the *Re*-face of the enolate is blocked by the left half of the quinidine moiety. The steric hindrance between the *Boc* group of **2a** and the right half of the quinidine moiety make the *Re*-face of **2a** face to the enolate of **3a**. Subsequently, the attack of the incoming nucleophiles forms the *Si*-face of enolate of **3a** to *Re*-face of **2a** takes place, which is consistent with the experimental results.

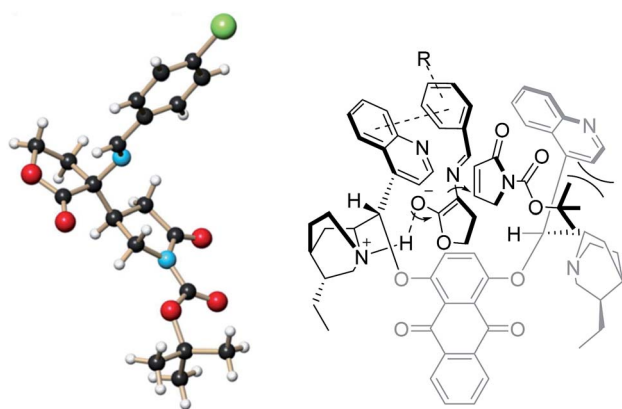
In conclusion, we have disclosed the  $\beta$ -selective asymmetric addition of  $\gamma$ -butyrolactam with cyclic imino esters catalyzed by a bifunctional chiral tertiary amine, which provides an efficient and facile access to optically active  $\beta$ -position functionalized pyrrolidin-2-one derivatives with high diastereoselectivity and enantioselectivity. To our knowledge, this is the first catalytic method to access chiral  $\beta$ -functionalized pyrrolidin-2-one *via* a direct organocatalytic approach. Current efforts are in progress to apply this new methodology to synthesize biologically active products.

conditions: unless specified, a mixture of **2** (0.2 mmol), **3** (0.3 mmol) and **1f** (15.0 mmol%) in 2.2 mL a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1) was stirred at rt. <sup>b</sup>Isolated yields. <sup>c</sup>Determined by chiral HPLC, all products were observed with >99 : 1 dr by <sup>1</sup>H NMR and HPLC. Configuration was assigned by comparison of HPLC data and X-ray crystal data of **4a**.





**Scheme 4** Substrate scope of the asymmetric reaction of maleimides to cyclic imino esters. <sup>a</sup>Reaction conditions: unless specified, a mixture of 2 (0.2 mmol), 3 (0.3 mmol) and 1f (15.0 mmol%) in 2.2 mL a mixture of dichloroethane and methyl *tert*-butyl ether (volume ratio = 10 : 1) was stirred at rt. <sup>b</sup>Isolated yields. <sup>c</sup>Determined by <sup>1</sup>H NMR and chiral HPLC.



**Fig. 1** Proposed transition state for the reaction.

## Conflicts of interest

There are no conflicts to declare.

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