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Organocatalytic Direct Asymmetric Vinylogous Michael Reaction of an α,β-Unsaturated γ-Butyrolactam with Enones

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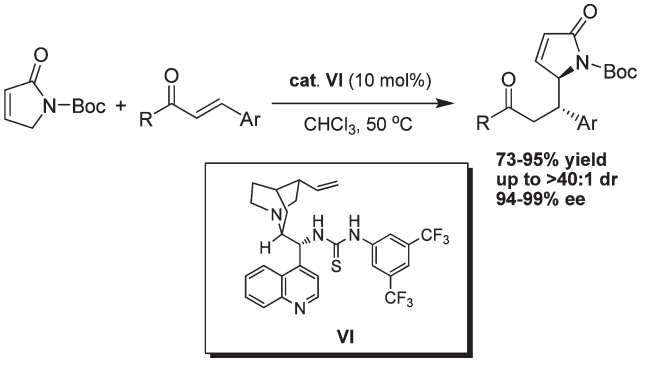

An organocatalytic asymmetric direct vinylogous Michael addition of α,β-unsaturated γ-butyrolactam to enones has been achieved with a simple bifunctional thiourea-tertiary amine catalyst, affording the γ-substituted butyrolactam products with high diastereo- and enantioselectivity (up to >40:1 dr and 94−99% ee).

Catalytic asymmetric vinylogous reactions have been demonstrated as effective protocols for carbon−carbon bond formation at the γ-position, which enables access to a diverse array of chiral γ-functionalized products from the combination of various donors and acceptors.[1] Although significant progress has been made in vinylogous aldol,[2] Mannich,[3] and Michael[4] reactions by employing masked dienol ethers, the direct approaches are still highly valuable from the standpoint of atom economy. Accordingly, this issue has attracted much research interest recently.[5,6]

Chiral γ-butyrolactams are ubiquitous building blocks for many natural products.[7] Despite their synthetic utility, α,β-unsaturated γ-butyrolactams have not been well explored in the direct catalytic asymmetric reactions.[8] Very recently, Shibasaki and co-workers[9] pioneered the research on direct catalytic asymmetric vinylogous Mannich and Michael reactions of α,β-unsaturated γ-butyrolactams by using a chiral dinuclear nickel complex. Chen and co-workers[10] reported the first organocatalytic conjugate addition reaction of α,β-unsaturated γ-butyrolactams to α,β-unsaturated aldehydes via iminium catalysis. Herein, we disclose an efficient conjugate addition of α,β-unsaturated γ-butyrolactams to enones catalyzed by a bifunctional alkaloid-derived thiourea organocatalyst, which affords the desired products in up to >40:1 dr and 94−99% ee.

Chiral cinchona alkaloids and amine thioureas have previously been utilized as effective bifunctional organocatalysts for the conjugate addition of various carbon nucleophiles to α,β-unsaturated carbonyls via acid−base cooperative activation.[11] Accordingly, our initial investigation began with screening this type of organocatalysts (**I**−**VI**, Figure 1). As

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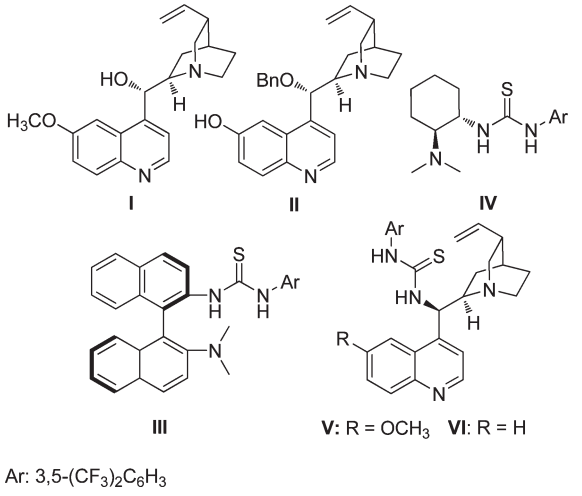
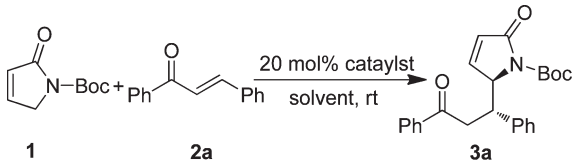


FIGURE 1. Organocatalysts for screening.

TABLE 1. Selected Studies of the Direct Vinylogous Michael Reaction of α,β-Unsaturated γ-Butyrolactam 1 with Chalcone 2a[a]



entry	catalyst	solvent	time	yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	CH_2Cl_2	10 d	30	15:1	42
2	**II**	CH_2Cl_2	10 d	45	12:1	44
3	**III**	CH_2Cl_2	10 d	trace	nd[e]	nd
4	**IV**	CH_2Cl_2	10 d	68	10:1	94
5	**V**	CH_2Cl_2	10 d	75	> 30:1	97
6	**VI**	CH_2Cl_2	10 d	75	> 30:1	98
7	**VI**	toluene	10 d	65	18:1	97
8	**VI**	CH_3CN	10 d	45	12:1	94
9	**VI**	THF	10 d	74	10:1	94
10	**VI**	$CHCl_3$	10 d	85	> 30:1	99
11	**VI**	$Cl(CH_2)_2Cl$	10 d	70	> 30:1	98
12[f]	**VI**	$CHCl_3$	60 h	90	15:1	97
13[g]	**VI**	$CHCl_3$	72 h	90	> 30:1	98

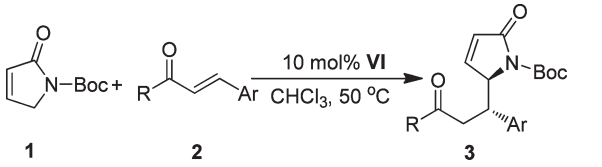
[a]Unless otherwise noted, the reaction was performed with 0.2 mmol of **1**, 0.1 mmol of **2a**, and 20 mol % of catalyst in 0.2 mL solvent. [b]Isolated yield after purification by column chromatography. [c]Determined by ^{1}H NMR analysis of crude mixture. [d]Determined by HPLC analysis using Daicel chiral IC column. [e]Not determined. [f]The reaction was carried out at 50 °C. [g]The reaction was carried out at 50 °C, and 10 mol % of catalyst was used.

shown in Table 1, the catalytic activity and enantioselectivity varied significantly when different catalysts were applied. In the presence of catalysts **I**−**III** (Table 1, entries 1−3), poor reactivities and diastereo- and enantioselectivities were observed for the reaction of α,β-unsaturated γ-butyrolactam **1** with chalcone **2a**. In contrast, amine thioureas **IV**−**VI** showed promising results (entries 4−6). The cinchona alkaloid-based thiourea catalysts[12] proved to be more effective: the catalyst **VI** gave the addition product with 75% yield, > 30:1 diastereoselectivity, and 98% ee after 10 days at ambient temperature (entry 6) in CH_2Cl_2.

The influence of different solvents on the reaction catalyzed by **VI** was therefore investigated (Table 1, entries 6−11). $CHCl_3$ proved to be the best reaction medium (entry 10), which further enhanced the yield to 85% and the ee value to 99% and maintained the dr value as > 30:1. Reaction temperature and catalyst loading had a dramatic influence on the efficiency of the process. Elevation of the reaction temperature from ambient temperature (entry 10) to 50 °C (entry 12) significantly shortened the reaction time from 10 days to 60 h and improved the yield from 85% to 90%, while the diastereo- and enantioselectivities were slightly decreased from > 30:1 dr to 15:1 dr and from 99% ee to 97% ee, respectively. When the catalyst loading was lowered to 10 mol %, the diastereo- and enantioselectivities were further improved to > 30:1 dr and 98% ee, with a slightly extended reaction time of 72 h (entry 13).

Applying the conditions described in Table 1, entry 13 as the optimal compromise between reactivity and stereoselectivity, the generality of this protocol was demonstrated by evaluating a variety of enones (Table 2). The enone substrates with either an electron-withdrawing or electron-donating group at the *ortho*-, *meta*-, or *para*-position of Ar and R were examined. High diastereo- and enantioselectivities (from 10:1 to > 40:1 dr and from 94 to 99% ee) were achieved for these enone substrates (Table 2, entries 1−16). A heterocyclic system (thiophene as an example) was also applicable,

TABLE 2. Enantioselective Direct Vinylogous Michael Reaction of α,β-Unsaturated γ-Butyrolactam 1 with Chalcones 2 Catalyzed by VI[a]



entry	R, Ar, **2**	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph, Ph, **2a**	72	90	> 30:1	98
2	Ph, 4-$NO_2C_6H_4$, **2b**	48	90	25:1	95
3	Ph, 4-CNC_6H_4, **2c**	48	92	15:1	98
4	Ph, 4-FC_6H_4, **2d**	72	86	18:1	97
5	Ph, 4-$CF_3C_6H_4$, **2e**	48	89	20:1	96
6	Ph, 4-ClC_6H_4, **2f**	72	83	> 25:1	97
7	Ph, 2-ClC_6H_4, **2g**	60	93	> 30:1	96
8	Ph, 3-ClC_6H_4, **2h**	60	88	15:1	97
9	Ph, 2,4-$Cl_2C_6H_4$, **2i**	48	90	> 40:1	94
10	Ph, 4-$CH_3OC_6H_4$, **2j**	84	78	16:1	96
11	Ph, 4-$CH_3C_6H_4$, **2k**	84	81	> 25:1	96
12	4-$CH_3OC_6H_4$, Ph, **2l**	84	73	> 30:1	95
13	4-BrC_6H_4, Ph, **2m**	60	95	> 25:1	96
14	4-$CH_3OC_6H_4$, 4-CNC_6H_4, **2n**	60	88	15:1	98
15	4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, **2o**	60	83	10:1	98
16	2-BrC_6H_4, 4-CNC_6H_4, **2p**	48	93	> 20:1	98
17	thienyl, thienyl, **2q**	84	78	15:1	99
18	CH_3, Ph	84	trace	nd[e]	nd
19	*t*-Bu, Ph	84	trace	nd	nd

[a]Unless otherwise noted, the reaction was performed with 2.0 equiv of **1** (0.1 mmol, 0.5 M), 1.0 equiv of **2**, and 0.1 equiv of catalyst in 0.2 mL of $CHCl_3$ at 50 °C. [b]Isolated yield after purification by column chromatography. [c]Determined by ^{1}H NMR analysis of crude mixture. [d]Determined by HPLC analysis using Daicel chiral IC or OD-H column. [e]Not determined.

(12) For the original report on the application of cinchona alkaloid-based thiourea catalysts for the activation of chalcones, see: Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

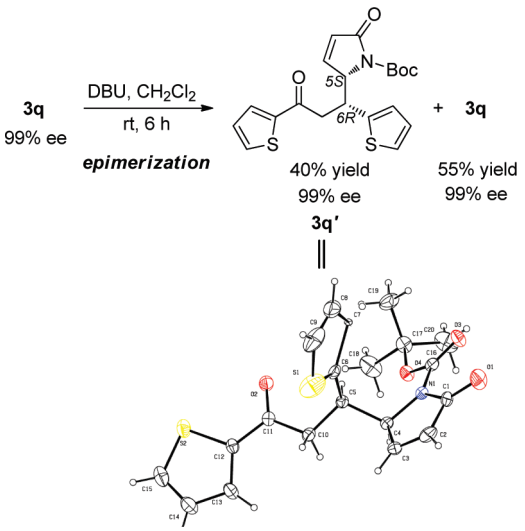


FIGURE 2. X-ray crystallographic structure of **3q**′.

affording the vinylogous product with 15:1 dr and 99% ee (entry 17). However, when R was an aliphatic moiety (e.g., CH_3 or *t*-Bu), the reaction did not occur, presumably owing to the low reactivity of the enone substrate (entries 18 and 19).

The absolute configuration of the reaction products was derived from the single crystal structure of **3q**′ (Figure 2). We failed to obtain a single crystal of product **3q**, although numerous conditions for the crystal growth were attempted. However, we found that the chiral center of C5 in **3q** was epimerized under basic conditions, such as in the presence of DBU,[13] and the diastereoisomer **3q**′ could be easily isolated from **3q** (scheme in Figure 2). Fortunately, we were able to obtain a single crystal of **3q**′ by slow evaporation of a mixture of ethyl acetate and hexane. The X-ray structural analysis (Figure 2) indicates that the absolute configuration of **3q**′ is (5*S*,6*R*), and therefore the absolute configuration of the adduct **3q** could be concluded as (5*R*,6*R*).[14]

Two possible routes for the formation of C−C bond could therefore be envisioned, representing two distinct activation models for the interaction of tertiary amine/thiourea organocatalyst with the electrophile and the nucleophile (Figure 3). According to the mechanistic studies by Pápai and coworkers[15] for conjugate additions, the transition state **B** should be more favorable to explain the stereoselective outcome. The carbonyl group of the chalcone was activated by the N-H proton of ammonium through hydrogen bond, while the thiourea coordinated to γ-butyrolactam. Therefore, the desired product (5*R*,6*R*)-**3q** could be obtained by the *si*-face attack of the activated enone (pathway **B** in Figure 3).

In conclusion, we have developed an organocatalytic enantioselective direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam with enones by using a cinchona alkaloid-based thiourea. This method enables efficient

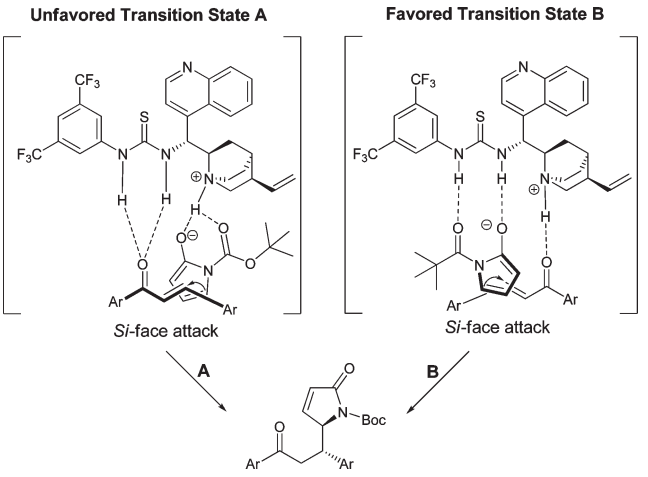


FIGURE 3. Proposed transition states for conjugate addition of α,β-unsaturated γ- butyrolactam to enones catalyzed by **VI**.

access to synthetically versatile γ-substituted butyrolactams in up to >40:1 dr and 94−99% ee. Further studies of α,β-unsaturated γ-butyrolactam as versatile nucleophile in organocatalytic asymmetric reactions, and its applications in natural product synthesis are currently underway in our laboratory.

Experimental Section

Genaral Procedure for Direct Catalytic Asymmetric Vinylogous Michael Reaction of α,β-Unsaturated γ-Butyrolactam. To a solution of chalcone **2a** (0.1 mmol, 1.0 equiv) in $CHCl_3$ (0.2 mL) was added catalyst **VI** (0.01 mmol, 0.1 equiv) followed by α,β-unsaturated γ-butyrolactam **1** (0.2 mmol, 2.0 equiv). The reaction mixture was stirred at 50 °C until the consumption of **2a**, the progress of which was monitored by TLC analysis. The solvent was then removed under vacuum. The residue was purified by silica gel chromatography (hexane/AcOEt = 4/1 to 2/1 as eluent) to afford the desired addition product **3a** (90% yield). $[\alpha]^{20}_D$ = +109 (*c* 1.0, $CHCl_3$); 98% ee, determined by HPLC analysis using Daicel chiral IC column, EtOH flow rate: 0.3 mL/min, detection at 254 nm, t_R (minor) = 19.43 min, t_R (major) = 21.91 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.34 (q, *J* = 7.2 Hz, 2H), 7.27 (dd, *J* = 13.3, 6.8 Hz, 3H), 7.04 (dd, *J* = 6.1, 1.7 Hz, 1H), 6.19 (d, *J* = 6.1 Hz, 1H), 4.87−4.84 (m, 1H), 4.60−4.54 (m, 1H), 3.28 (dd, *J* = 17.2, 9.7 Hz, 1H), 3.04 (dd, *J* = 17.2, 4.6 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 169.2, 149.2, 147.8, 139.2, 136.7, 133.2, 128.9, 128.6, 128.0, 127.9, 127.8, 127.4, 83.6, 66.8, 40.8, 35.1, 28.2; ESI-HRMS calcd for $[C_{24}H_{25}NO_4 + Na]$ 414.1676, found 414.1668.

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Supporting Information Available: Full characterization for the new compounds, crystallographic data of compound **3q**′ in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) As shown in Figure 2, the ee values of isolated **3q**′ (40% yield) and recovered **3q** (55% yield) were both kept as 99% after epimerization, indicating that only the chiral center of C5 in **3q** was epimerised in the presence of DBU. See Supporting Information for characterization details.
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