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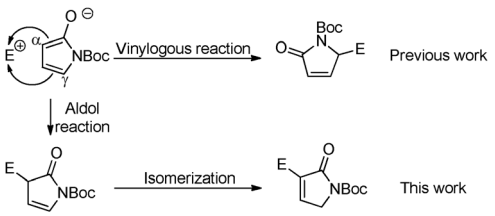
Direct asymmetric aldol addition–isomerization of α,β-unsaturated γ-butyrolactam with aryl α-ketoesters: synthesis of MBH-type products†

Jinlong Zhang, Xihong Liu, Xiaojuan Ma and Rui Wang*

A highly efficient direct asymmetric aldol addition–isomerization reaction at the α-position of α,β-unsaturated γ-butyrolactam and aryl α-ketoesters by using a bifunctional thiourea catalyst was achieved. Morita–Baylis–Hillman type adducts containing a quaternary stereocenter can be obtained in high yields and with excellent enantioselectivities (up to 99% ee).

Nitrogen-containing heterocycles are present in a variety of complex natural and non-natural compounds.[1] Many of these molecules display marvelous biological properties and pharmacological properties, which undoubtedly contribute greatly to their importance in the field of organic chemistry. Recently, α,β-unsaturated γ-butyrolactam has appeared as one of the efficient chemical precursors to a diverse array of attractive nitrogen heterocyclic ring systems in various chemical reactions.[2] Among the established strategies, the catalytic direct vinylogous reactions that could be utilized as effective protocols for carbon–carbon bond formation are more attractive.[3] And, significant progress has also been made in asymmetric direct vinylogous Mannich and Michael reactions.[4] These processes underwent a γ-deprotonation pathway to generate the dienolate intermediate and reaction at the γ-position of the activated dienolate and carbon electrophiles. Here we report a direct asymmetric aldol addition[5,6]–isomerization reaction at the α-position of the activated dienolate generated from α,β-unsaturated γ-butyrolactam and aryl α-ketoesters[7] catalyzed by a bifunctional thiourea catalyst[8] for the synthesis of Morita–Baylis–Hillman (MBH)[9] type products (Scheme 1).

Although the catalytic asymmetric MBH reaction has been extensively studied by employing either chiral amines[10] or phosphines[11] as the catalysts, the electrophiles employed in the MBH reactions are mostly aldehydes and imines, and the use of ketones as electrophiles is very limited.[12] Recently, isatin derivatives have emerged as new electrophilic components for MBH reactions.[13]



Scheme 1 The aldol addition–isomerization at the α-position of α,β-unsaturated γ-butyrolactam.

Preliminary results were achieved in the report of Zhou and co-workers in the asymmetric MBH reaction of isatins and acrolein involving alkaloid catalyst systems, which was also the first time that the ketone has been used as the electrophile.[14a] Furthermore, enantioselective MBH reactions with isatins and activated alkenes have been well developed, using cinchona, phosphinothiourea or phosphine–squaramide as the chiral catalyst.[14] To the best of our knowledge, the MBH reaction of aryl α-ketoesters and activated alkenes has rarely been reported and its enantioselective versions still represent a challenging task regarding the low reactivity and steric hinderance.[15] In view of this limitation, an alternative approach is needed to obtain chiral MBH-type products. The present study provides a convenient approach to MBH-type products containing a quaternary stereocenter[16] through a direct aldol addition–isomerization sequence, providing useful β-hydrogen esters containing a butyrolactam, which are ubiquitous building blocks for many natural products.[17]

Our initial investigations were carried out using a series of quinine and cyclohexanediamine derived catalysts **1a–1h** (Fig. 1) for the model reaction of ethyl phenylglyoxylate **3a** and α,β-unsaturated γ-butyrolactam **2a**. As summarized in Table 1, excellent enantioselectivity could be attained in CH_2Cl_2 at 30 °C in the presence of various thiourea and quinine derivatives. The product yield of the reaction was, however, found to be critically dependent on the structure of the catalysts. Reactions with thioureas **1a–1d** or quinine **1e** afforded **4a** in higher yields than thiourea **1a** and quinine derivatives **1f–1h**. The nitrogen Lewis base of the thiourea catalysts and the hydroxy group of the quinine derivatives played significant

Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, State Key Laboratory of Applied Organic Chemistry and Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou, 730000, China. E-mail: wangrui@lzu.edu.cn

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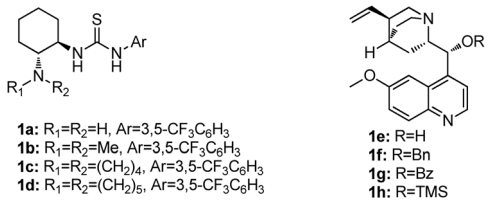


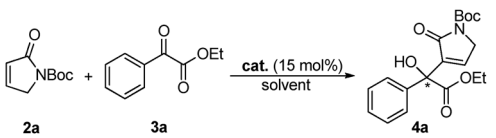
Fig. 1 The structures of screened organocatalysts.

roles in the direct aldol addition–isomerization reaction. Then the reaction solvents were examined with thiourea **1b**.[18] As expected, the use of polar solvents (THF, CH_3OH and MeCN), which reduced the activity of the catalyst, resulted in poor yields of **4a** (Table 1, entries 9–11). In contrast, **1b** in solvents (CH_2Cl_2, toluene) efficiently promoted the reaction, affording **4a** in moderate yields and with excellent enantioselectivities (Table 1, entries 2 and 12). Next, the effects of the temperature were investigated (Table 1, entries 2, 13 and 14). Either at lower (0 °C) or higher temperature (reflux), a decreased yield was observed due to the low catalyst activity and side reactions. When the catalyst loading was reduced to 10 mol% and 5 mol%, the same excellent enantioselectivity was obtained, but more reaction time was needed for completion of the reaction (Table 1, entries 15 and 16). **1b** at a 15 mol% loading was selected for further studies in terms of efficiency.

With the optimal reaction conditions established, the substrate scope of this bifunctional thiourea catalyzed direct aldol addition–isomerization reaction was extended (Table 2). The reactions with diethyl benzoylphosphinate, benzil and trifluorophenylethanone could afford the products with no enantioselectivities (Table 2, **4b–4d**). When *tert*-butyl phenylglyoxylate was used as a reaction substrate, good yield and moderate enantioselectivity were achieved (Table 2, **4e**). The results showed that ethyl arylglyoxylates were the best substrates for the present catalyst system. Subsequently, various derivatives obtained from aryl α-ketoesters were involved. The position of the substituent on the aromatic ring of the aryl α-ketoester had very little effect on the enantioselectivity. The electron-donating substituents at different positions afforded the products in greater than 99% ee and good yield (except for the sterically hindered ethyl 2-methylphenylglyoxylate, which provided the product in a moderate yield, **4f–4j**). Moreover, electron-withdrawing substituents also provided the products in high enantioselectivities and good yields (Table 2, **4k–4p**). In addition, ethyl 2-naphthylglyoxylate afforded the product with high enantioselectivity and moderate yield (Table 2, **4q**).

At the end of the reactivity assessment of aryl α-ketoesters, we evaluated the reactivity of β,γ-unsaturated α-ketoester **3r** in the reaction with α,β-unsaturated γ-butyrolactam (Scheme 2). It is noteworthy that the process underwent direct vinylogous

Table 1 Screening of the reaction conditions

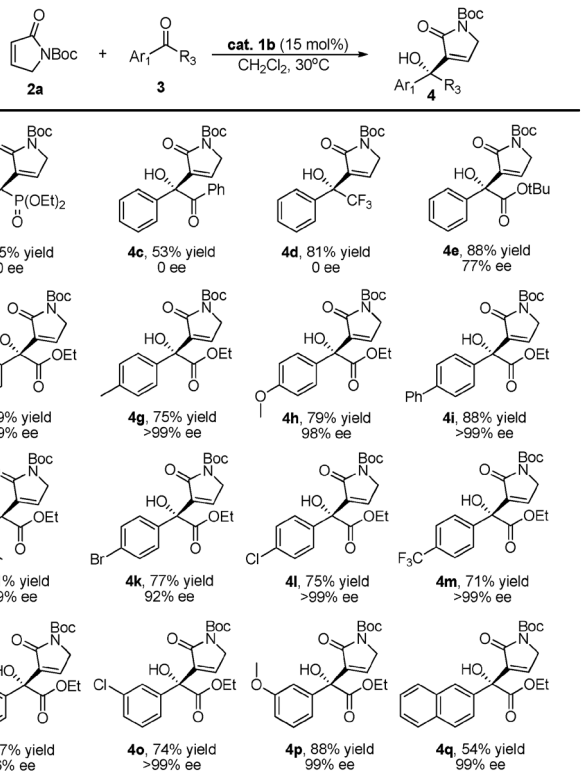


2a 3a 4a

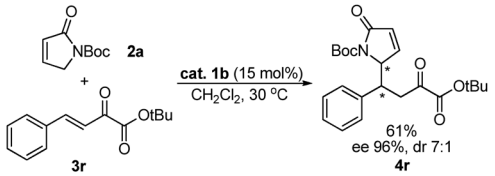
Entry[a]	L (mol%)	Solvent	T (°C)	Yield[b] (%)	ee[c] (%)
1	**1a** (15)	CH_2Cl_2	30	31	99
2	**1b** (15)	CH_2Cl_2	30	78	99
3	**1c** (15)	CH_2Cl_2	30	46	97
4	**1d** (15)	CH_2Cl_2	30	61	95
5	**1e** (15)	CH_2Cl_2	30	65	97
6	**1f** (15)	CH_2Cl_2	30	16	97
7	**1g** (15)	CH_2Cl_2	30	17	97
8	**1h** (15)	CH_2Cl_2	30	20	95
9	**1b** (15)	THF	30	44	97
10	**1b** (15)	CH_3OH	30	65	94
11	**1b** (15)	CH_3CN	30	20	96
12	**1b** (15)	Toluene	30	82	98
13	**1b** (15)	CH_2Cl_2	0	40	99
14	**1b** (15)	CH_2Cl_2	Reflux	71	98
15	**1b** (10)	CH_2Cl_2	30	60	99
16	**1b** (5)	CH_2Cl_2	30	52	99

[a] Reactions were carried out with **2a** (0.1 mmol) and **3a** (0.15 mmol, 1.5 eq.). [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC analysis of the isolated product.

Table 2 Substrate scope for the catalytic direct asymmetric aldol addition–isomerization[a]



[a] Reactions were carried out with **1b** (0.03 mmol, 15 mol%), α-ketoesters **3** (0.3 mmol, 1.5 eq.) and **2a** (0.2 mmol, 1.0 eq.) in CH_2Cl_2 (0.4 ml) at 30 °C. Isolated yields were obtained for all the compounds and ee values determined by chiral HPLC.



Scheme 2 The direct vinylogous Michael addition reaction of α,β-unsaturated γ-butyrolactam to β,γ-unsaturated α-ketoester **3r**.

Michael addition reaction under the established optimal conditions and the product **4r** was obtained with excellent enantioselectivity and high diastereoselectivity (ee 96%, dr 7 : 1). The X-ray analysis of the crystal of **4g** revealed an *R* configuration for the quaternary stereogenic center.[19]

In summary, we have developed a simple bifunctional thiourea catalyzed direct asymmetric aldol addition–isomerization reaction of α,β-unsaturated γ-butyrolactam and aryl α-ketoesters, affording a series of chiral β-hydrogen esters. This method represents the first construction of optically active MBH-type products containing a quaternary chiral carbon center.

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