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Highly Regio-, Diastereo-, and Enantioselective Mannich Reaction of Allylic Ketones and Cyclic Ketimines: Access to Chiral Benzosultam

Baokun Qiao,[†] Yin-Jun Huang,[†] Jing Nie,[†] and Jun-An Ma*[,†,‡]

[†]Department of Chemistry, Tianjin University, and Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. of China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. of China

Supporting Information

ABSTRACT: An organocatalytic asymmetric Mannich reaction of allylic ketones with cyclic *N*-sulfonyl α-iminoester has been developed. By using a saccharide-derived chiral tertiary amino-thiourea catalyst, a range of allylic ketones and *N*-sulfonyl ketimines reacted smoothly to afford tetrasubstituted α-amino esters in high yields with good to excellent regio-, diastero-, and enantioselectivities.

Chiral benzosultam is an important structural unit present in many biologically active molecules such as γ-secretase inhibitors, aldose reductase inhibitors, or HIV-1 inhibitors.[1,2] Benzosultams can also be used as chiral auxiliaries and fluorinating reagents in organic synthesis (Figure 1).[3] Catalytic

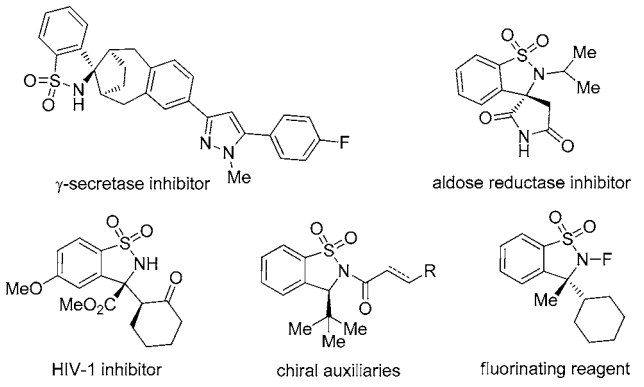

Figure 1. Selected bioactive and chemical benzosultams.

asymmetric transformation of *N*-sulfonyl ketimines represents a direct and feasible method for the construction of optically active benzosultams. In this context, transition-metal-catalyzed asymmetric allylation and arylation of cyclic ketimines for the preparation of optically active benzosultams have been developed.[4] Additionally, organocatalytic aymmetric methods have also been demonstrated to deliver these chiral structures.[2e,5] For example, Nakamura and co-workers disclosed a cinchona alkaloid sulfonamide-catalyzed enantioselective decarboxylative Mannich reaction of *N*-sulfonyl ketimines with β-ketoacids (Figure 2a),[5a] while the Loh and Wang

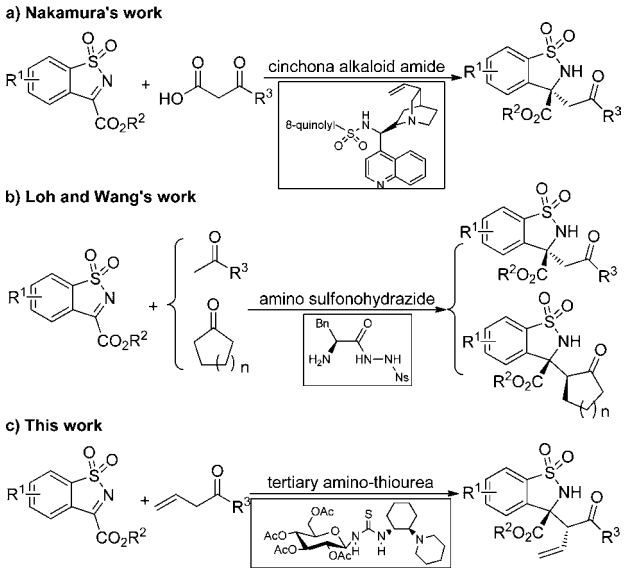

Figure 2. Organocatalytic asymmetric Mannich reactions of cyclic ketimines for the synthesis of chiral benaosultams.

group developed a chiral amino sulfonohydrazide-promoted asymmetric alkylation of *N*-sulfonyl ketimines with unmodified ketones for the synthesis of enantiomeric pure benzosultams (Figure 2b).[2e] Recently, β,γ-unsaturated allylic ketones, bearing one potential enolization, were used as highly active nucleophiles in several catalytic asymmetric reactions.[6]

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Encouraged by these investigations, we envisioned that allylic benzosultams with two stereocenters, including a quaternary chiral center, could be constructed by an organocatalytic asymmetric Mannich reaction of allylic ketones with cyclic ketimines (Figure 2c). By screening various organocatalysts, we found that in the presence of saccharide-derived amino-thioureas, this Mannich reaction proceeded well with excellent regiocontrol to give a series of benzosultam derivatives with high diastereo- and enantioselectivities. Herein, we report our preliminary results on this subject.

We began our investigations with the asymmetric Mannich reaction of allylic phenyl ketone **1a** and ketimine **2a** in dichloromethane in the presence of saccharide-derived amino-thioureas **I**–**VI** (Figure 3), which were prepared previously by

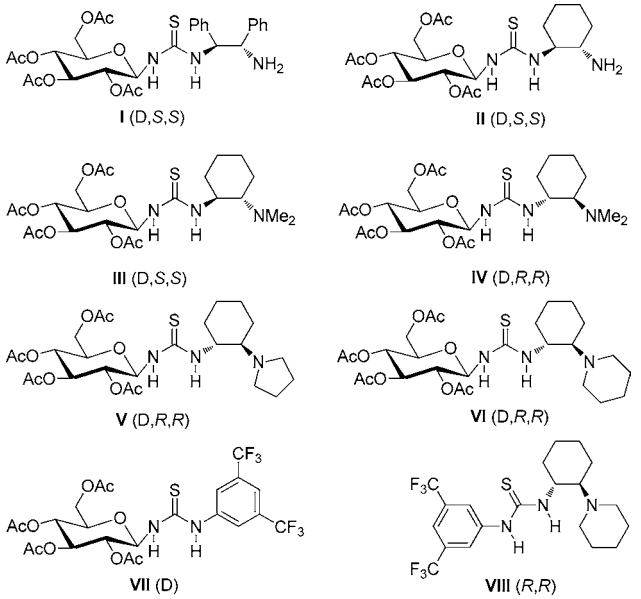
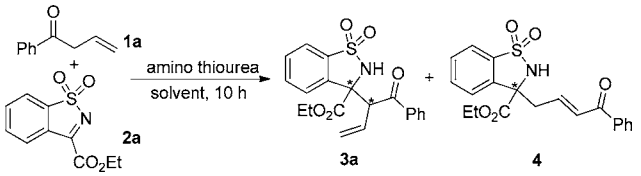


Figure 3. Structures of amino-thiourea catalysts tested.

our group.[7] The results are summarized in Table 1. First, (D,*S*,*S*)-saccharide-derived primary amino-thioureas **I** and **II** were utilized as chiral catalysts. The reactions led directly to Mannich adduct **3a** in low yields with poor *ee* values and good diastereoselectivities. In addition, vinylogous conjugate Mannich adduct **4** could also be detected (Table 1, entries 1 and 2). Considering tertiary amine thioureas to be a class of effective bifunctional catalysts,[8] subsequently we tested (D,*S*,*S*)-saccharide-derived tertiary amino-thiourea **III** and found that it gave good regioselectivity and moderate enantioselectivity (Table 1, entry 3). Notably, the catalyst **IV** led to a very exciting yield with high regio-, diastereo-, and enantioselectivity (Table 1, entry 4). These results indicated that the (*R*,*R*)-configuration of the 1,2-diaminocyclohexane derived tertiary amino combined with the *β*-D-glucopyranose to display a strong stereocontrolling ability. Next, both catalysts **V** and **VI** bearing a cyclic tertiary amine moiety were texted (Table 1, entries 5 and 6), and it was found that catalyst **VI** gave a better *ee* value (Table 1, entry 6). However, catalyst **VII**, which does not contain any amino substituent, showed no catalytic activity (Table 1, entry 7). Additionally, catalyst **VIII**, which does not bear a saccharide moiety, delivered moderate regio- and enantioselectivity. These results indicated that both the (D)-saccharide framework and tertiary amino moiety of the thiourea catalysts were critical for this asymmetric Mannich reaction. Among the catalysts tested,

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	solvent	α/γ[b] (**3a**/**4**)	yield (%)[c]	*ee* (%)[d]	dr[e]
1	**I** (10)	CH_2Cl_2	1.5:1	35	3 (+)	10:1
2	**II** (10)	CH_2Cl_2	1.5:1	42	5 (+)	10:1
3	**III** (10)	CH_2Cl_2	4:1	60	35 (+)	10:1
4	**IV** (10)	CH_2Cl_2	>20:1	91	93 (−)	>20:1
5	**V** (10)	CH_2Cl_2	>20:1	90	94 (−)	>20:1
6	**VI** (10)	CH_2Cl_2	>20:1	93	94 (−)	>20:1
7	**VII** (10)	CH_2Cl_2	–	0	–	–
8	**VIII** (10)	CH_2Cl_2	4:1	81	52 (−)	17:1
9	**VI** (10)	$CHCl_3$	>20:1	78	92 (−)	>20:1
10	**VI** (10)	CH_3CN	>20:1	75	90 (−)	>20:1
11	**VI** (10)	Et_2O	>20:1	83	95 (−)	>20:1
12	**VI** (10)	toluene	>20:1	94	93 (−)	>20:1
13	**VI** (10)	THF	>20:1	94	96 (−)	>20:1
14	**VI** (5)	THF	>20:1	94	96 (−)	>20:1
15	**VI** (2)	THF	>20:1	84	96 (−)	>20:1
16[f]	**VI** (10)	THF	>20:1	83	96 (−)	>20:1
17[g]	**VI** (10)	THF	>20:1	46	96 (−)	>20:1

[a]The reaction was carried out with 0.11 mmol of **1a**, 0.1 mmol of **2a** in 2.0 mL solvent at room temperature. [b]α/γ determined by ^{1}H NMR analysis. [c]Isolated yield of the major adduct **3a**. [d]ee determined by HPLC methods. [e]dr determined by ^{1}H NMR analysis. [f]The reaction was carried out at 0 °C. [g]The reaction was carried out at −20 °C.

catalyst **VI** revealed the best catalytic activity and asymmetric induction ability (Table 1, entry 6). To further optimize the reaction conditions, the reaction was performed in different solvents with catalyst **VI** (Table 1, entries 9–13), and the use of THF gave the best results (Table 1, entry 13). Subsequently, we attempted to reduce the amount of the catalyst **VI** (Table 1, entries 14 and 15). In the presence of 5.0 mol % **VI**, the reaction performed equally well with excellent regio-, diastereo-, and enantioselectivity (Table 1, entry 14). Even at a loading of 2.0 mol %, **3a** was still obtained in a good yield without compromising any regio- and stereoselectivity (Table 1, entry 15). The decrease of the reaction temperature led to the lower reactivity (Table 1, entries 16 and 17).

With the optimized protocol in hand, we performed the organocatalytic asymmetric Mannich reactions between allylic ketones **1** and cyclic ketemines **2** in THF by using 5 mol % of (D,*R*,*R*)-saccharide-derived tertiary amino-thiourea catalyst **VI** at room temperature, and the substrate scope of the Mannich adducts was explored (Scheme 1). Various allylic phenyl ketones (**1a**–**l**) bearing different electronic and steric substituents on the phenyl ring were all tolerated in this reaction. The Mannich adducts **3a**–**l** could be obtained in 89–99% yields with 88–96% *ee* and 18:1 to >20:1 dr. The major stereoisomer of **3b** proved to be crystalline, thus allowing the determination of the absolute configuration of two adjacent stereogenic centers by means of X-ray crystallographic analysis.[9] In addition, other aromatic ketones, such as 1-naphthyl-, 2-naphthyl-, and 2-thiophenyl-substituted allylic ketones **1m**–**o**, were also good substrates, thus giving the desired products **3m**–**o** in high yields with high diastereo- and enantioselectivies.

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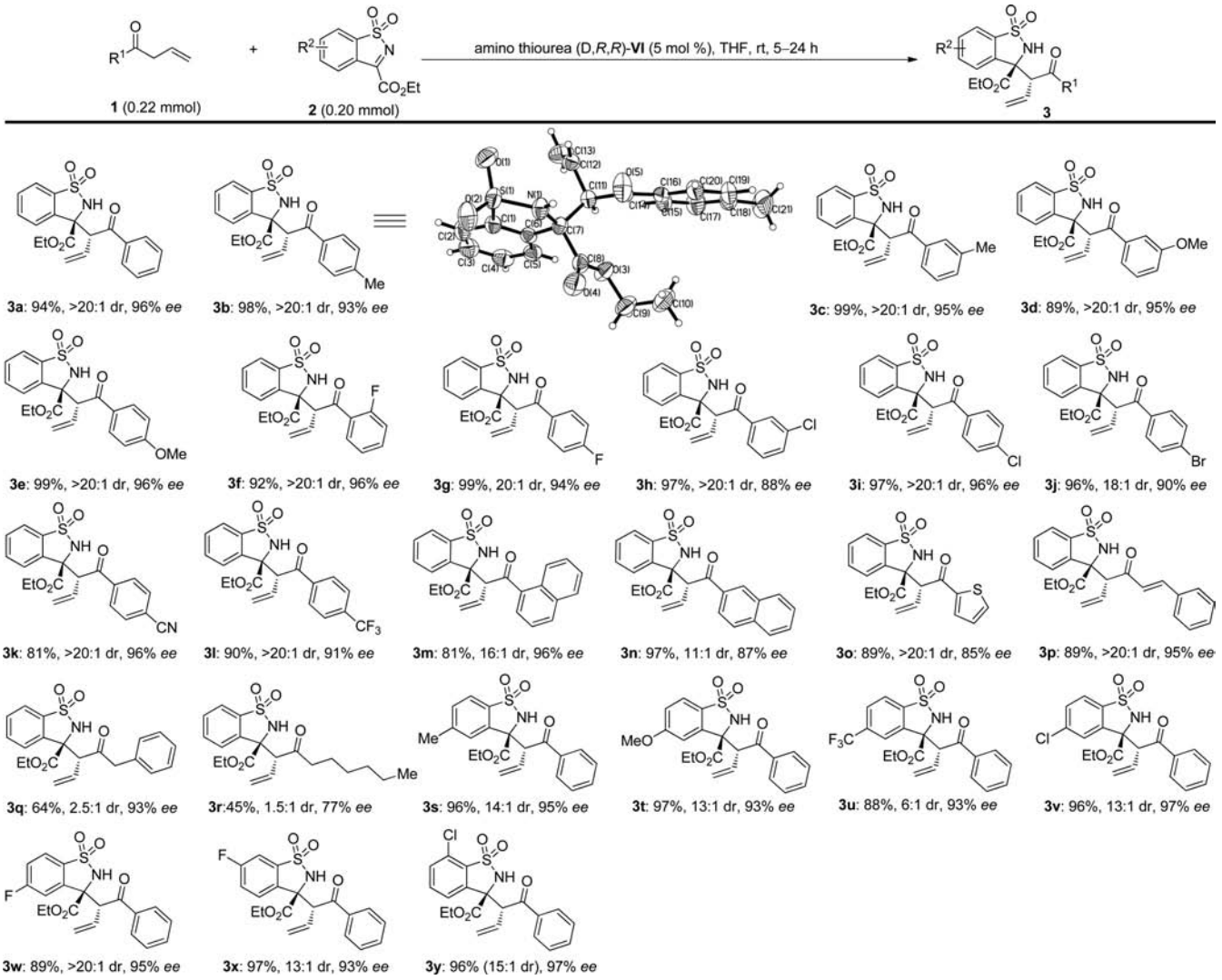
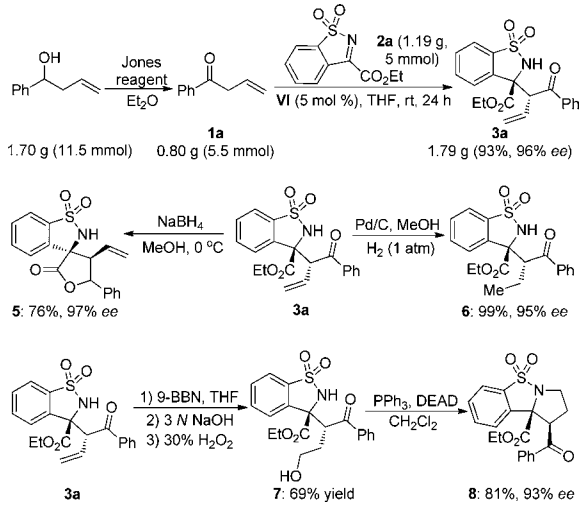
Scheme 1. Substrate Scope of the Mannich Reaction of Allylic Ketones 1 with Ketimines 2



It was found find that (*E*)-1-phenylhexa-1,5-dien-3-one could also work well and produce the adduct **3p** in 89% yield with 95% *ee* and >20:1 dr. Moreover, we conducted the reaction of allylic aliphatic ketones with cyclic ketimine **2a**, thereby affording the Mannich products **3q** and **3r** in moderate yields and diastereoselectivties with good to high enantioselectivities. To further define the scope of our methodology, the reactions of other cyclic ketimines with both electron-withdrawing and -donating groups, as well as those bearing various substituents at different positions on the phenyl ring, were tested. All these substrates proceeded efficiently to provide the corresponding adducts **3s**–**y** in high yields with good to high diastereo- and enantioselectivities.

To illustrate the practicability of this highly efficient catalytic asymmetric Mannich reaction, we conducted **1a** with **2a** (5.0 mmol) on a 1 g scale (Scheme 2). Using 5 mol % of the catalyst **VI** under the optimized reaction conditions, the Mannich reaction proceeded smoothly and the corresponding product **3a** could be obtained in 93% yield (1.79 g) with 96% *ee* and >20:1 dr. To further demonstrate the synthetic utility of this protocol, we conducted other transformations by using the product **3a** (Scheme 2). In the presence of 5.0 equiv of $NaBH_4$ in MeOH for 60 min, the adduct **3a** was transformed into the spirobenzosultam derivative **5** in 76% yield with 97% *ee*.

Scheme 2. Scaled-up Reaction and Further Transformation



Reduction of the adduct **3a** with H_2 on Pd/C for 30 min gave **6** in quantitative yield without racemization. In addition, hydroboration–oxidation of **3a** and subsequent Mitsunobu

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cyclization provided the tricyclic product **8** in good yield with high *ee* value.

In conclusion, we have successfully developed an organocatalytic asymmetric Mannich reaction of allylic ketones and cyclic ketimines by using a saccharide-derived chiral tertiary amino-thiourea catalyst. This protocol provides a wide range of tetrasubstituted α-amino esters with high regio-, diastereo-, and enantioselectivities. Moreover, the products obtained can be converted into optically active spiro- and tricyclic benzosultam derivatives from simple modifications. Further development and application of this Mannich reaction, as well as investigation of the mechanism, is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02351.

Experimental details; spectral data of all the new compounds (PDF)

Crystallographic information on **3b** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: majun_an68@tju.edu.cn.

Notes

The authors declare no competing financial interest.

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(9) CCDC 150414A contains the supplementary crystallographic data for the compound **3b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deosit/.

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