

# Bifunctional Amino Sulfonohydrazide Catalyzed Direct Asymmetric Mannich Reaction of Cyclic Ketimines with Ketones: Highly Diastereo- and Enantioselective Construction of Quaternary Carbon Stereocenters

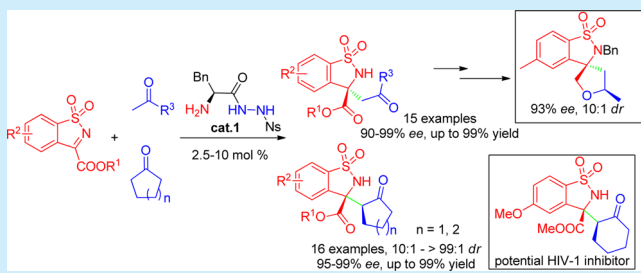
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## S Supporting Information

**ABSTRACT:** A bifunctional amino sulfonohydrazide which contains multiple sites for hydrogen bonding with substrates was found to enhance reactivity and enantioselectivity in the direct asymmetric Mannich reaction of *N*-sulfonyl cyclic ketimines with ketones. In this efficient transformation, not only methyl ketones but also cyclic ketones can be employed to provide a general methodology to construct tetrasubstituted  $\alpha$ -amino ester in a stereoselective manner. The synthetic utility of a substituted amino ester product is demonstrated by the synthesis of biologically active spirotetrahydrofuran.



Amino acids as important organocatalysts have received considerable attention since the pioneering work of List and Barbas, III.<sup>1</sup> However, the limitations of amino acids as organocatalysts have also been recognized gradually. Typically, high catalyst loadings and low catalytic activity restricted the applications of amino acids as catalysts for large scale synthesis. It is well-known that a carboxylic acid proton in the amino acid plays a critical role in enhancing the reactivity and stereoselectivity of the catalyst.<sup>2</sup> Accordingly, increasing the acidity of an amino acid based catalyst became a common approach to improve catalytic activity.<sup>3</sup> In contrast, the effect of increasing the H-bonding sites of amino acid derived catalysts is less explored.<sup>4</sup> Therefore, we envisage that amino sulfonohydrazide (**cat.1**) which contains multiple sites for hydrogen bonding with substrates may enhance the reactivity and enantioselectivity of reaction. To illustrate, we attempted the direct Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones. Here, we found that the direct Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones could indeed be catalyzed by amino sulfonohydrazide with an increase in catalytic activity and high enantioselectivity (Scheme 1).

The asymmetric Mannich reaction of *N*-sulfonyl ketimines is an efficient and direct method for enantioselective synthesis of benzosultams containing quaternary stereocenters,<sup>5</sup> which are widely found in biologically active molecules and serve as useful chiral auxiliaries in asymmetric transformations (Figure 1).<sup>6,7</sup> Recently, transition-metal-catalyzed asymmetric allylation and arylation of cyclic ketimines have been reported by the Lam, Xu,

## Scheme 1. Our Strategy to Enhance the Catalytic Activity of Amino Acid Catalyst (Ns = 2-Nitrobenzene-1-sulfonyl)

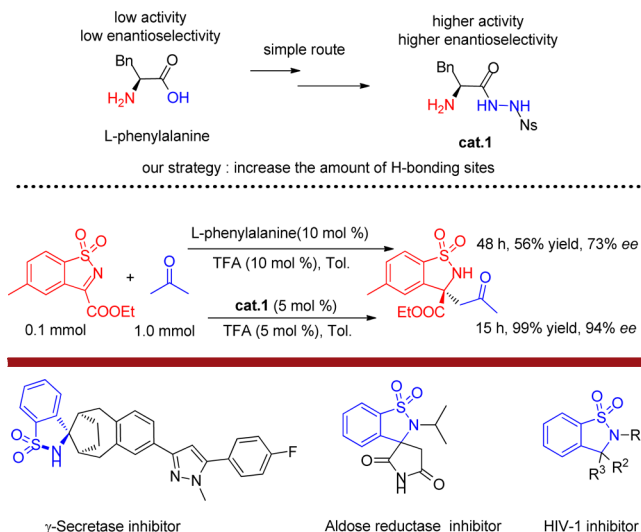


Figure 1. Biologically active sultams.

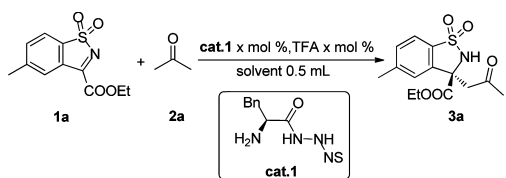
Zhang and Hayashi groups,<sup>5a-d</sup> whereas the enantioselective Mannich reaction of *N*-sulfonyl ketimines with aldehydes or

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ketones has not been explored yet. In particular, utilizing a ketone as a nucleophile in the asymmetric Mannich reaction of cyclic ketimines was scarce in literature.<sup>8</sup> In this context, we first developed the highly diastereo- and enantioselective direct Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones by virtue of the efficient amino sulfonylhydrazide catalyst.

We initially investigated the reaction between acetone and **1a** in the presence of 10 mol % of **cat.1** in various solvents at rt (Table 1). Nonpolar solvent toluene was found to be the optimal

Table 1. Optimization of the Direct Mannich Reaction<sup>a</sup>



entry	solvent	x	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	MTBE	10	86	80
2	CHCl <sub>3</sub>	10	92	90
3	toluene	10	99	94
4 <sup>d</sup>	toluene	10	71	93
5 <sup>e</sup>	toluene	5	73(99)	93(94)
6 <sup>f</sup>	toluene	2.5	57(85)	84(87)
7	toluene	1	34	70
8 <sup>g</sup>	toluene	5	99	95

<sup>a</sup>The reaction of **1a** (0.1 mmol) with **2a** (1 mmol) was performed in the presence of **cat.1** (x mol %) and TFA (x mol %) in solvent (0.5 mL) at rt for 8 h. <sup>b</sup>Yield of isolated product. <sup>c</sup>The ee value of the product **3a** was determined by HPLC on a chiral stationary phase. <sup>d</sup>The reaction was carried out without TFA as additive. <sup>e</sup>The numbers in parentheses were obtained when the reaction was carried out in 0.5 mL of toluene for 15 h. <sup>f</sup>The numbers in parentheses were obtained when the reaction was carried out in 0.2 mL of toluene for 72 h. <sup>g</sup>The reaction was performed on 0.3 mmol scale under standard conditions (see details in Supporting Information) (MTBE = methyl *tert*-butyl ether).

solvent for this reaction with respect to both catalytic activity and asymmetric induction (Table 1, entries 1–3). On the other hand, acid additive had a great influence on catalytic activity. In the absence of trifluoroacetic acid, the yield was decreased from 99% to 71% (Table 1, entry 4). The catalyst loading had a great effect on the yield of this reaction, since the byproduct of this process was increased when lowering the catalyst loading. But a higher concentration and prolonged reaction time provided the product with a good yield and excellent enantioselectivity (Table 1, entries 5–7). After different reaction conditions were screened, the best result was obtained when 5 mol % catalyst was employed. To our delight, upon scaling up to 0.3 mmol, the enantioselectivity and yield of the reaction were maintained (Table 1, entry 8).

With the optimized conditions in hand, a wide variety of cyclic *N*-sulfonyl ketimines **1** were tested to examine the reaction scope (Table 2). Good to excellent enantioselectivities were obtained with aromatic sulfamide-derived imines bearing either electron-withdrawing or -donating substituents (up to 99% yield, up to 99% ee; Table 2). Variation of the substituent position on aromatic rings of cyclic ketimines **1** resulted in no significant change in the enantioselectivity of this process, but led to a decrease in the product yield. Notably, when the 4-position of **1**, close to the reaction site, was substituted by a fluorine atom, the adduct **3fa** was still obtained with 90% ee and 70% yield (Table 2,

Table 2. Direct Mannich Reaction of Cyclic *N*-Sulfonyl Ketimines with Methyl Ketones Catalyzed by Amino Sulfonylhydrazide<sup>a</sup>

entry	3	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>3aa</b>	5-Me	Et	Me	99	95
2 <sup>d</sup>	<b>3ba</b>	5-Me	Me	Me	98(87)	99(96)
3	<b>3ca</b>	—	Et	Me	90	94
4 <sup>d</sup>	<b>3da</b>	—	Me	Me	99(82)	96(92)
5	<b>3ea</b>	5-F	Me	Me	99	91
6 <sup>e</sup>	<b>3fa</b>	4-F	Me	Me	70	90
7 <sup>d</sup>	<b>3ga</b>	5-OMe	Me	Me	89(87)	94(92)
8 <sup>d</sup>	<b>3ha</b>	5- <i>t</i> -Bu	Me	Me	99(97)	96(93)
9	<b>3ia</b>	5-Cl	Me	Me	95	95
10 <sup>e</sup>	<b>3ja</b>	7-Cl	Me	Me	60	90
11	<b>3ka</b>	5-CF <sub>3</sub>	Me	Me	81	90
12	<b>3la</b>	5-OCF <sub>3</sub>	Me	Me	97	90
13	<b>3ma</b>	6-Me	Me	Me	99	95
14 <sup>e</sup>	<b>3na</b>	5,6-(CH <sub>3</sub> ) <sub>4</sub>	Me	Me	87	97
15 <sup>f,g</sup>	<b>3bb</b>	5-Me	Me	Ph	90(72)	80(98)

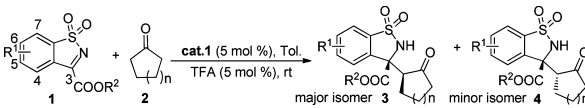
<sup>a</sup>The reaction of **1** (0.3 mmol) with **2** (3.0 mmol) was performed in the presence of **cat.1** (0.015 mmol) and TFA (0.015 mol) in toluene (1.5 mL) at rt for 30 h. <sup>b</sup>The product was isolated by flash chromatography. <sup>c</sup>The ee value of the product was determined by HPLC on a chiral stationary phase. <sup>d</sup>The numbers in parentheses were obtained when the catalyst loading was lowered to 2.5 mol % (see details in Supporting Information). <sup>e</sup>The numbers in parentheses were obtained when chloroform (1.5 mL) was used as solvent. <sup>f</sup>MTBE (1.5 mL) was used as solvent. <sup>g</sup>The numbers in parentheses were obtained when the product was treated with ethanol.

entry 6). The exchange of the methyl ester group for ethyl group in **1** had little influence on both yield and enantioselectivity. Remarkably, high levels of asymmetric induction continued to be observed when reactions were performed with only 2.5 mol % of the catalyst (Table 2, **3ba**, **3da**, **3ga**, and **3ha**). Replacing acetone with less reactive acetophenone as a nucleophile still furnished the adduct **3bb** with moderate ee (80%) and excellent yield (90%) (Table 2, entry 15). Moreover, the enantioselectivity could be further improved by washing the product with EtOH, giving a white solid with 98% ee after concentrating the filtrate. To the best of our knowledge, this is the first example utilizing acetophenone as a direct nucleophile to construct a chiral quaternary carbon center.

After demonstrating the direct Mannich reaction of *N*-sulfonyl ketimines with methyl ketones, we applied our catalytic system to more challenging substrates, such as cyclohexanone and cyclopentanone. Pleasingly, the high levels of enantioselectivity and excellent yields were maintained in both cases (Table 3). In addition, most products were obtained with high control of the diastereoselectivity (up to >99:1). For electron-rich ketimines, the desired products can be obtained with lower diastereoselectivity. When the reactions were carried out at 0 °C the satisfactory diastereoselectivity can be obtained for these ketimines (Table 3, entries 7, 8, 12, 14).

The performance of our amino sulfonylhydrazide catalyst **cat.1** for enantioselective catalysis on a preparative scale was explored next. Using 5 mol % **cat.1**, 2.4 g of ketimine **1b** was reacted with 10 equiv of acetone at rt over 24 h to afford the product in 81% yield and 99% ee (Scheme 2). To demonstrate the synthetic

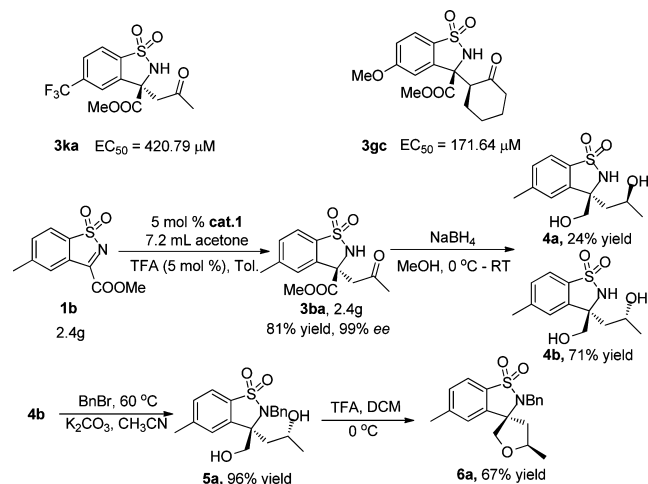
**Table 3. Direct Mannich Reaction of Cyclic *N*-Sulfonyl Ketimines with Cyclic Ketones Catalyzed by Amino Sulfonohydrazide<sup>a</sup>**



entry	3	R <sup>1</sup>	R <sup>2</sup>	n	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	dr (3:4) <sup>d</sup>
1	3ac	5-Me	Et	2	99	99	19:1
2	3bc	5-Me	Me	2	98	98	16:1
3	3cc	—	Et	2	86	98	14:1
4	3dc	—	Me	2	99	98	19:1
5	3ec	5-F	Me	2	99	96	18:1
6	3fc	4-F	Me	2	75	97	33:1
7 <sup>e</sup>	3gc	5-OMe	Me	2	88	99	10:1
8 <sup>e</sup>	3hc	5- <i>t</i> -Bu	Me	2	99	99	25:1
9	3ic	5-Cl	Me	2	95	97	18:1
10 <sup>f</sup>	3jc	7-Cl	Me	2	73	95	36:1
11	3kc	5-CF <sub>3</sub>	Me	2	93	97	15:1
12 <sup>e</sup>	3lc	5-OCF <sub>3</sub>	Me	2	99	98	39:1
13	3mc	6-Me	Me	2	99	96	14:1
14 <sup>e,f</sup>	3nc	5,6-(CH <sub>2</sub> ) <sub>4</sub>	Me	2	99	99	17:1
15	3bd	5-Me	Me	1	88	98	>99:1
16	3dd	—	Me	1	82	97	43:1

<sup>a</sup>The reaction of **1** (0.3 mmol) with **2** (3.0 mmol) was performed in the presence of **cat.1** (0.015 mmol) and TFA (0.015 mol) in toluene (1.5 mL) at room temperature for 30 h. <sup>b</sup>The product was isolated by flash chromatography. <sup>c</sup>The *ee* value of the product was determined by HPLC on a chiral stationary phase. <sup>d</sup>The *dr* (*dr* = 3:4) value was determined by <sup>1</sup>H NMR. <sup>e</sup>The reaction was conducted at 0 °C for 40 h. <sup>f</sup>Chloroform (1.5 mL) was used as solvent.

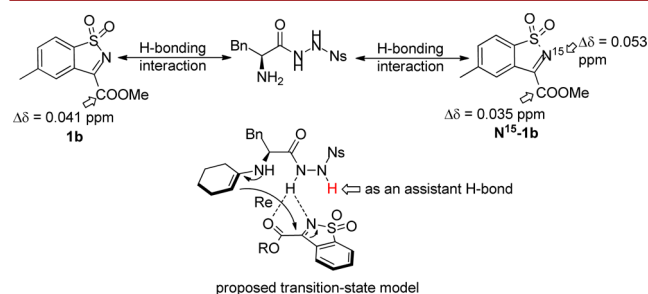
**Scheme 2. Synthetic Utility of the Direct Mannich Reaction and the Biological Activity of the Products**



utility of the product **3ba**, we transformed **3ba** to biologically active spirotetrahydrofuran **6a** via a three-step sequence, which involved sodium borohydride reduction followed by *N*-benzyl protection and then dehydrated etherification. The product **6a** contains a spiro structure, which is an important moiety in a large number of natural products with potent pharmacological properties.<sup>6,9</sup> Furthermore, a biological activity assay indicated that the products **3ka** and **3gc** had potential activity as an HIV-1 inhibitor.<sup>10</sup>

To shed light on the reaction mechanism, we synthesized N<sup>15</sup> isotope labeled substrate N<sup>15</sup>-**1b** and performed <sup>13</sup>C and <sup>15</sup>N

NMR experiments.<sup>11</sup> Initially, interaction between catalyst **cat.1** and **1b**/N<sup>15</sup>-**1b** was observed in the <sup>13</sup>C NMR spectra, where H-bonding induced a downfield shift of 0.041/0.035 ppm of the ester group in **1b** (Figure 2). In addition, when the ester group



**Figure 2. Interaction between **cat.1** and **1b**, and the proposed transition-state model.**

was removed in the control experiments, the reaction did not work and no desired products were obtained.<sup>11</sup> This implied that the ester group was involved in the formation of the hydrogen bond. On the other hand, variation in the <sup>15</sup>N NMR spectra of N<sup>15</sup>-**1b** provided further proof of the H-bonding interaction between **cat.1** and **1b**. Based on these results, other control experiments, the absolute configuration of the product **3fc**, and the previously reported mechanism,<sup>12,13</sup> a possible transition-state model was proposed as shown in Figure 2.

In conclusion, we have developed bifunctional chiral amino sulfonohydrazide organocatalyst **cat.1**, which showed excellent catalytic activity and high stereoselectivity in the direct asymmetric Mannich reaction of *N*-sulfonyl cyclic ketimines with ketones. This method provides a general access to the optically active tetrasubstituted  $\alpha$ -amino esters. With these densely functionalized products, biologically active spirotetrahydrofuran was synthesized in three steps. More importantly, increasing the hydrogen bonding sites for maximum coordination with substrates proved to be an effective strategy to improve the activity of the catalyst in this process. Further application of the chiral amino sulfonohydrazide catalyst is presently under active investigation in our laboratory.

## ■ ASSOCIATED CONTENT

### § Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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- (10) Hu, P.; Wang, X.; Zhang, B.; Zhang, S.; Wang, Q.; Wang, Z. *ChemMedChem.* **2014**, 9, 928 (see Section 1.9 (S15) of the Supporting Information (SI)).
- (11) See section 1.6 (S9–S12) of the SI.
- (12) (a) A series of catalysts were synthesized, and control experiments utilizing these catalysts were also carried out (see section 1.7 (S13) of the SI). (b) The absolute configuration of the products was proven by X-ray crystal structure analysis of product **3fc**. See section 1.8 (S14) of the SI. CCDC 1034439 (**3fc**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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