Asymmetric Mannich-Type Reaction of Aromatic α-Amido Sulfone with Malonate Using Guanidine–Thiourea Bifunctional Organocatalyst

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Abstract: Asymmetric Mannich-type reaction of aromatic α-amido sulfone with malonate, catalyzed by a guanidine–thiourea bifunctional organocatalyst, affords β-amino acid derivatives in high yield with good to excellent enantioselectivity.

Key words: organocatalyst, bifunction, guanidine, thiourea, Mannich-type reaction

Bifunctional catalysts have received considerable attention in the field of asymmetric synthesis and have been applied to various reactions, including carbon–carbon bond-forming reactions, over the last few decades. Chiral bifunctional catalysts are especially attractive, since they can activate multiple reactants simultaneously, and the reaction center is highly controlled. Therefore, high reaction rates and excellent stereoselectivity of the product can be obtained. We have recently developed guanidine–thiourea bifunctional organocatalysts **1** (Figure 1) and applied them to a series of asymmetric Henry and aza-Henry reactions.[1] In these reactions, the guanidinium group and thiourea group selectively coordinate to nucleophiles (nitroalkanes) and electrophiles (aldehydes or imines) through ionic and hydrogen-bonding interaction, respectively, and the transition state is controlled by the amino acid derived chiral spacer. This concept is expected to be applicable to a wide range of catalytic asymmetric reactions, with the use of appropriate combinations of electrophiles and nucleophiles.

The catalytic asymmetric Mannich-type reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[2] In this reaction, an enolizable carbonyl compound attacks an imine acceptor, affording synthetically useful β-amino acid derivatives.[3] In this context, a number of studies have been reported on asymmetric Mannich-type reaction using metal catalysts[4] and/or organocatalysts.[5] During these studies, it was found that α-amido sulfone is a useful and stable precursor for in situ preparation of the imine acceptor.[6] Thus, practical catalytic asymmetric Mannich-type reactions using α-amido sulfone have been investigated, for example with Cinchona alkaloid and proline-type catalysts, though with only limited success so far.[7] We envisaged that imine acceptors might be easily generated from the corresponding α-amido sulfone under phase-transfer conditions using guanidine–thiourea bifunctional organocatalysts **1**. Then, the generated imine should interact effectively with the thiourea group, and stereoselective nucleophilic attack with malonate should be guided by interaction with the guanidine group. Herein, we report the asymmetric Mannich-type reaction of a variety of aromatic α-amido sulfones with malonates using catalyst **1**.

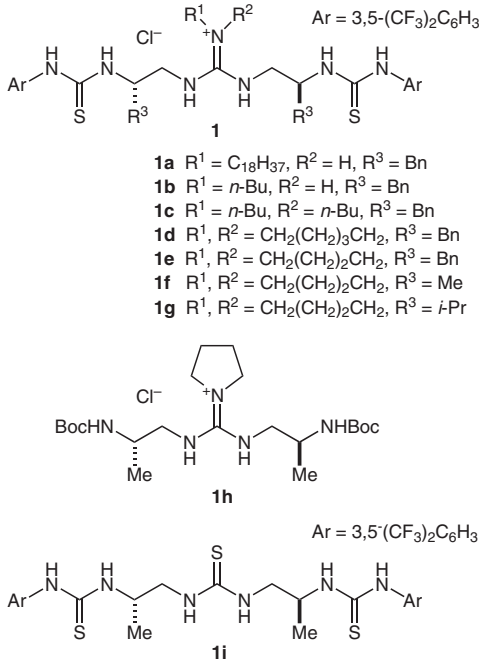

Figure 1 Structures of guanidine–thiourea bifunctional catalyst **1**

In an initial study, we investigated the catalytic activity and enantioselectivity in the reaction of α-amido sulfone **2a** with malonate **3a** catalyzed by **1** in the presence of Cs_2CO_3 in toluene (Table 1).[7a] First, we focused on the effects of the R^1 and R^2 groups of **1** on guanidine. Both the monosubstituted guanidine **1a** and **1b**, and the bis-substituted guanidine **1c** and **1d** gave **4a** in good yield with moderate enantioselectivity (entries 1–4). A marked improvement of enantioselectivity was obtained with catalyst **1e**, which has a pyrrolidine substituent on guanidine (entry 5). Encouraged by these results, we next explored the chiral spacer, that is, the R^3 group. We found that catalyst **1f**, having an alanine-derived chiral spacer (R^3 = Me), gave the best results in terms of enantioselectivity (entry 6). On the other hand, the catalyst **1g** (R^3 =

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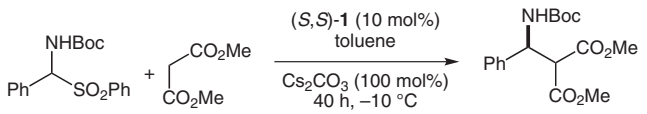
Table 1 Mannich-type Reaction of **2a** and **3a** in the Presence of (*S*,*S*)-**1**[a]



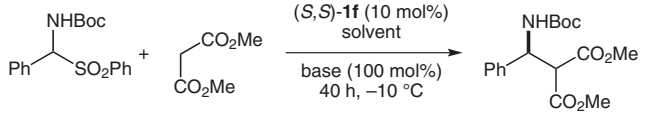
2a **3a** (1.2 equiv) **4a**

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1a**	88	33
2	**1b**	86	36
3	**1c**	86	50
4	**1d**	89	40
5	**1e**	96	76
6	**1f**	89	84
7	**1g**	98	51
8	**1h**	92	31
9	**1i**	84	6

[a] Reaction were carried out on 0.1 mmol scale in toluene (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

i-Pr) gave only moderate enantioselectivity (entry 7). To confirm the bifunctional role of the guanidine and thiourea groups in catalyst **1f**, catalysts **1h** and **1i**, lacking the thiourea or guanidine group, were examined. In these cases, the Mannich product **4a** was obtained in 92% and 84% yield, but the enantioselectivity was only 31% and 6% ee, respectively. Therefore, the guanidine and thiourea groups in catalyst **1f** appear to act cooperatively in the asymmetric reaction (entries 8 and 9). The reaction conditions were further optimized, focusing on the solvent and base, and we found that the enantioselectivity was improved under biphasic solvent conditions. In the case of toluene–H_2O (4:1) with Cs_2CO_3 (1 equiv), the Mannich product **4a** was obtained in 89% yield with 94% ee (Table 2, entry 5).

Table 2 Screening Reaction Conditions of **2a** and **3a** with (*S*,*S*)-**1f**[a]



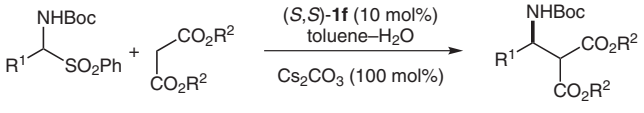
2a **3a** (1.2 equiv) **4a**

Entry	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	Cs_2CO_3	85	35
2	THF	Cs_2CO_3	85	1
3	MeCN	Cs_2CO_3	92	5
4[d]	toluene	Cs_2CO_3	82	83
5	toluene–H_2O = 4:1	Cs_2CO_3	89	94
6	toluene–H_2O = 4:1	K_2CO_3	81	92
7	toluene–H_2O = 4:1	CsOH	77	91
8	toluene–H_2O = 4:1	KOH	54	90

[a] Reaction were carried out on 0.1 mmol scale.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] MS 4 Å (50 mg) was added.

With optimal reaction conditions in hand, we then evaluated the generality of this protocol. The results for the Mannich-type reaction of selected aromatic α-amido sulfones **2** and malonates **3a** or **3b** are summarized in Table 3. Excellent enantioselectivity and yield were obtained for a series of α-amido sulfones bearing *para* substituents on the aromatic ring (entries 4, 5, 8, and 9). The reactions with *meta*- or *ortho*-toluyl-, naphthyl- and furyl-group-substituted α-amido sulfones also gave products in high yield with good enantioselectivity (entries 2, 3, and 10–12). In some cases, selectivities were varied depending on the solvents ratio. As shown in entries 5, 9, and 10 (in Table 3), the selectivities were increased up to 90%, 85%, and 80% ee, respectively, by changing the ratio of solvents (toluene–H_2O) from 4:1 to 19:1. Interestingly,

Table 3 Mannich-type Reaction of **2** and **3** in the Presence (*S*,*S*)-**1f**[a]

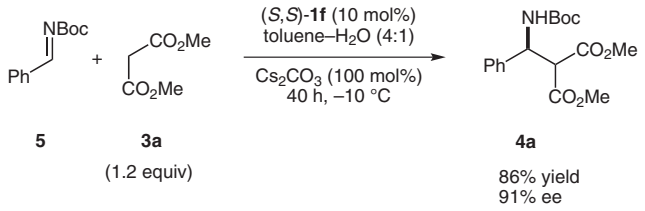


2a–j **3a**,**b** (1.2 equiv) **4b–m**

Entry	R^1	R^2	Time (h)	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**2a** Ph	**3b** Bn	120	–10	**4b** 86	81
2	**2b** 2-MeC_6H_4	**3a** Me	46	r.t.	**4c** 84	80
3	**2c** 3-MeC_6H_4	**3a** Me	48	r.t.	**4d** 96	86
4[d]	**2d** 4-MeC_6H_4	**3a** Me	43	–10	**4e** 89	97
5[d]	**2d** 4-MeC_6H_4	**3b** Bn	120	0	**4f** 87	90
6	**2e** 2-ClC_6H_4	**3a** Me	44	r.t.	**4g** 84	52
7	**2f** 3-ClC_6H_4	**3a** Me	67	–10	**4h** 83	59
8	**2g** 4-ClC_6H_4	**3a** Me	45	–10	**4i** 95	92
9[d]	**2g** 4-ClC_6H_4	**3b** Bn	120	0	**4j** 90	85
10[d]	**2h** 1-naphthyl	**3a** Me	72	0	**4k** 87	80
11	**2i** 2-naphthyl	**3a** Me	72	–15	**4l** 86	90
12	**2j** 2-furyl	**3a** Me	72	0	**4m** 92	80

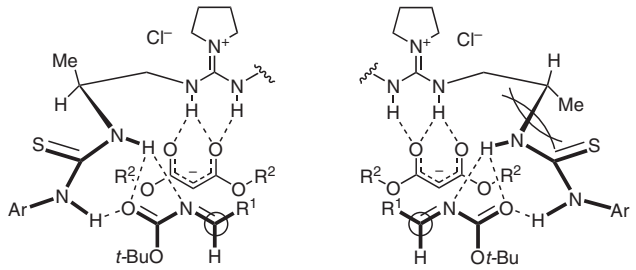
[a] Reaction were carried out on 0.1 mmol scale in toluene (0.8 mL) and H_2O (0.2 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Reaction were carried out in toluene (0.95 mL) and H_2O (0.05 mL).

only moderate enantioselectivity was obtained in the case of *meta*- or *ortho*-chloro-substituted aromatic α-amido sulfones **2e** and **2f** (entries 6 and 7), which presumably interact poorly with the thiourea group because of the steric and electronic effects.



Scheme 1 Mannich-type reaction of **5** with **3a** in presence of (*S*,*S*)-**1f**

In this reaction, we found that the benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**5**) from the α-amido sulfone with malonate **3a** also gave **4a** in 86% yield with 91% ee under the same reaction conditions as in Table 2, entry 5 (Scheme 1). The absolute stereochemistry of **4** was found to be 2*S*, and a possible transition state for this reaction was proposed to account for this enantioselectivity. As shown in Figure 2, malonate coordinates with guanidine as an enolate form, at the same time, the thiourea part of the catalyst interacts with imine, which is generated in situ from α-amido sulfone, and is activated via a double hydrogen-bonding interaction. Then, nucleophilic attack of the malonate on the imine from the preferential transition state TS-1, which avoids the steric repulsion between the methyl group in the chiral spacer and the R^2 group in malonate, results in the formation of (2*S*)-**4**.



TS-1 (favored) **TS-2** (unfavored)

Figure 2 Plausible transition state of the Mannich-type reaction catalyzed by **1f**

In summary, we have developed an asymmetric Mannich-type reaction of aromatic α-amido sulfone **2** with malonate **3** utilizing guanidine–thiourea bifunctional catalyst **1f**. The key functional groups in **1f** act cooperatively to afford β-amino acid derivatives **4** in high yield with good to excellent enantioselectivity.

Experimental Section

Typical Procedure for the Asymmetric Mannich-type Reaction

To a mixture of (*S*,*S*)-**1f** (8.0 mg, 10 μmol), Cs_2CO_3 (32.6 mg, 0.1 mmol), and α-amido sulfone **2a** (34.7 mg, 0.1 mmol) in toluene–H_2O (0.8/0.2 mL) was added methyl malonate (**3a**, 15.8 μL, 0.12 mmol) at –10 °C. The resulting mixture was stirred vigorously at –10 °C for 40 h. To the reaction mixture was added sat. aq NH_4Cl, and the organic layer was extracted with EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (*n*-hexane–EtOAc = 30:1 to 8:1) to give **4a** (29.3 mg, 89%). The ee of **4a** {94% ee, $[\alpha]_D^{25}$ +16.9 (*c* 1.1, $CHCl_3$)} was determined by means of chiral HPLC analysis (Chiral AD-H, 0.46 cm × 25 cm, *n*-hexane–2-PrOH = 80:20, 0.75 mL/min, t_R (major) = 14.9 min; t_R (minor) = 18.9 min). The absolute configuration of **4a** was assigned as the *S* isomer by comparison of its optical rotation with a literature value.[7c]

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References

(1) (a) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (b) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144. (c) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894. (d) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150. (e) Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623. (f) Takada, K.; Nagasawa, K. *Adv. Synth. Catal.* **2009**, *351*, 345.

(2) (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, **1991**, 893. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044.

(3) (a) Kleinmann, E. F. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (b) Hintermann, T.; Seebach, D. *Chimia* **1997**, *50*, 244. (c) Magriotis, P. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4377. (d) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (e) Ma, J.-A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.

(4) Recent reports on asymmetric Mannich-type reaction by metal catalysts: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (b) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476. (c) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525. (d) Harada, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4365. (e) Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528. (f) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (g) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010. (h) Nakamura, S.; Sano, H.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2007**, *48*, 5565. (i) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 2145. (j) Hamashima, Y.; Sasamoto, N.; Umebayashi, N.; Sodeoka, M. *Chem. Asian. J.* **2008**, *3*, 1443.

(5) Recent reports on asymmetric Mannich-type reaction by organocatalysts: (a) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F. III. *Adv. Synth. Catal.* **2004**, *346*, 1131. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (c) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987. (d) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew.*

Chem. Int. Ed. **2004**, *43*, 4476. (e) Notz, W.; Tanaka, F.; Barbas, C. F. III. *Acc. Chem. Res.* **2004**, *37*, 5801. (f) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (g) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 2896. (h) Okada, A.; Shibuguchi, T.; Oshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564. (i) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (j) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (k) Mitsumori, S.; Zhang, H.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 1040. (l) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (m) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (n) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (o) Zhang, H. L.; Mifsud, M.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 9630. (p) Verkade, J. M.; van Hemert, J. C.; Quaedflieg, P. L. M.; Rutjes, F. J. T. *Chem. Soc. Rev.* **2007**, *37*, 29:. (q) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, *16*, 2571. (r) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2008**, *35*, 5797.

(6) (a) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949. (b) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159.

(7) (a) Fini, F.; Bernardi, L.; Herrera, R. P.; Petterson, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043. (b) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (c) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Petterson, D.; Sgarzoni, V.; Ricci, A. *Chem. Eur. J.* **2007**, *13*, 8338. (d) Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 1620. (e) Los, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998. (f) Wang, J.; Shi, T.; Deng, G.; Jiang, H.; Liu, H. *J. Org. Chem.* **2007**, *73*, 8563. (g) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8700.