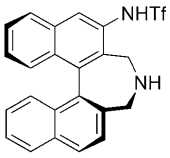
Organocatalysis

DOI: 10.1002/anie.200805628

A Designer Axially Chiral Amino Sulfonamide as an Efficient Organocatalyst for Direct Asymmetric Mannich Reactions of N-Boc-Protected Imines**

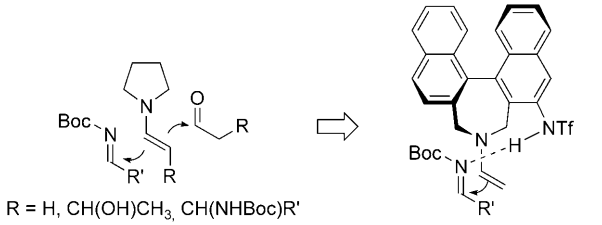
*Taichi Kano, Yukako Yamaguchi, and Keiji Maruoka**

Asymmetric Mannich reactions are the most powerful and versatile tools for synthesizing optically active β-amino carbonyl compounds, which are highly attractive chiral building blocks for biologically and pharmaceutically important compounds.[1] Recently, a large number of small organic molecules, such as proline and its derivatives, were found to successfully catalyze direct asymmetric Mannich reactions between aldehydes and *N*-*p*-methoxyphenyl-protected imines.[2,3] However, strong oxidizing agents such as ceric ammonium nitrate are required to remove the *p*-methoxyphenyl (PMP) group on the nitrogen atom of the Mannich products, and a method that would allow for the easy removal of the N-protecting group under mild conditions would offer a significant synthetic advantage. Recently, the research groups of List[4] and Córdova[5] independently reported the proline-catalyzed *syn*-selective direct asymmetric Mannich reaction between aldehydes and imines protected with a readily cleavable *tert*-butoxycarbonyl (Boc) group. Furthermore, in 2008, List and co-workers demonstrated that proline can also catalyze the direct asymmetric Mannich reaction between acetaldehyde and N-Boc-protected imines to provide the simplest Mannich products as versatile chiral building blocks, albeit in low to moderate yields.[6] Since the enamine intermediate generated from the pyrrolidine-type secondary amine catalyst is highly nucleophilic, it is difficult to suppress undesired side reactions, including aldol reactions and further reactions of the Mannich product (Scheme 1). Very recently Hayashi et al. reported the efficient direct asymmetric Mannich reaction of acetaldehyde, although the N-Boc group on most imines was replaced with an *N*-benzoyl group.[7]



(*S*)-**1**

We previously designed and synthesized the axially chiral bifunctional amino sulfonamide (*S*)-**1** as an organocatalyst, which successfully catalyzed the *anti*-selective direct asymmetric Mannich reactions of *N*-PMP-protected α-imino esters[8] and *syn*-selective asymmetric cross-aldol reactions.[9] This catalyst has a highly acidic triflamide group to activate electrophiles and a less nucleophilic dibenzylic secondary amine moiety compared to pyrrolidine-type catalysts. These characteristic features of (*S*)-**1** should suppress the side reactions, and the hitherto difficult direct Mannich reaction between acetaldehyde and N-Boc-protected imines could be achieved. Here we report the direct asymmetric Mannich reaction between acetaldehyde and N-Boc-protected imines catalyzed by the axially chiral bifunctional amino sulfonamide (*S*)-**1**. In addition, we also describe the highly *anti*- and enantioselective Mannich reaction of N-Boc-protected imines with other aldehydes—which has previously only been reported in a few cases.[3e,10]



Scheme 1. Strategy to suppress undesired side reactions. Tf = trifluoromethanesulfonyl.

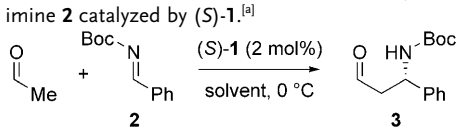
We first examined the reaction between acetaldehyde and the benzaldehyde-derived N-Boc-protected imine **2** in the presence of (*S*)-**1** at 0 °C, and the results are summarized in Table 1. The reaction with five equivalents of acetaldehyde in $CHCl_3$ gave the corresponding product **3** in low yield but excellent enantioselectivity (Table 1, entry 1). It is important to note that the side product **4** arising from the Mannich reaction between **2** and **3** was also obtained in 15% yield during the reaction. Therefore, an increased amount of acetaldehyde was used, which consequently improved the yields of **3** (Table 1, entries 2 and 3). The reaction using CH_2Cl_2 and THF as solvents provided similar results (Table 1, entries 4 and 5), while the reaction in toluene was less satisfactory in terms of the yield (Table 1, entry 6). Under solvent-free conditions, the desired product was obtained in higher yield and excellent enantioselectivity (Table 1, entry 7). Accordingly, the solvent-free conditions were selected for further studies.

[*] Dr. T. Kano, Y. Yamaguchi, Prof. K. Maruoka
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[**] This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" from the Ministry of Education, Culture, Sports, Science, and Technology (Japan). Y.Y. is grateful to the Japan Society for the Promotion of Science for Young Scientists for a research fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805628.

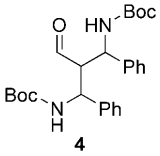
Table 1: Direct Mannich reactions between acetaldehyde and N-Boc-protected imine **2** catalyzed by (*S*)-**1**.[a]



2 **3**

Entry	CH_3CHO [equiv]	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	5	$CHCl_3$	8	36	99
2[d]	10	$CHCl_3$	3	43	99
3	36	$CHCl_3$	4	76	99
4	36	CH_2Cl_2	4	78	99
5	36	THF	4	81	99
6	36	toluene	4	33	99
7	36	–	4	87	99

[a] Unless otherwise specified, the reaction between acetaldehyde and N-Boc-protected imine **2** (0.25 mmol) was carried out in a solvent (500 μL) in the presence of (*S*)-**1** (0.005 mmol) at 0 °C. [b] Yield of isolated product. [c] The *ee* value of **3** was determined by HPLC analysis on a chiral stationary phase. [d] Use of 5 mol% of (*S*)-**1** and 2.5 mL of $CHCl_3$.

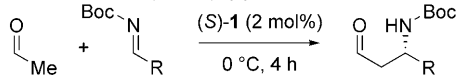


4

We then applied our system to the reaction between acetaldehyde and various N-Boc-protected imines, and the results are shown in Table 2. In general, these direct asymmetric Mannich reactions proceeded smoothly, and the desired products were obtained in good yields and excellent enantioselectivity in all the cases examined. An N-Boc-protected aliphatic imine was also applicable to this reaction system when the imine was added slowly by syringe pump. It should be noted that most of the (*S*)-**1** was recovered by a single separation by column chromatography at the end of the reaction and was reusable without further purification.

A proline-catalyzed direct asymmetric Mannich reaction between aldehydes and N-Boc-protected aromatic imines is known to give the corresponding *syn*-β-amino-β-aryl aldehyde preferentially with excellent enantioselectivity.[4,5] To the best of our knowledge, however, a general method for obtaining the opposite *anti*-β-amino-β-aryl aldehyde remains unattainable, although a few exceptional examples that give *anti*-Mannich adducts were reported by using an N-Boc-protected aromatic imine.[10] Accordingly, we next examined the reaction between various aldehydes and N-Boc-protected imines, and attempted to expand the substrate scope of our *anti*-selective Mannich reaction catalyzed by (*S*)-**1**.

Table 2: Direct Mannich reactions between acetaldehyde and various N-Boc-protected imines catalyzed by (*S*)-**1**.[a]

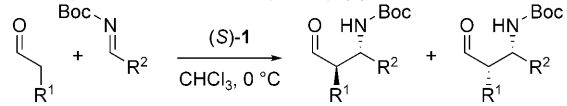


Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	87	99
2	2-naph	82	99
3	4-$MeOC_6H_4$	92	99
4	4-ClC_6H_4	73	99
5	2-furyl	70	98
6[d,e]	cyclohexyl	70	99

[a] Unless otherwise specified, the reaction between acetaldehyde (500 μL) and an N-Boc-protected imine (0.25 mmol) was carried out in the presence of (*S*)-**1** (0.005 mmol) at 0 °C. [b] Yield of isolated product. [c] The *ee* value of the Mannich product was determined by HPLC analysis on a chiral stationary phase. [d] THF used as solvent. [e] The N-Boc-protected imine was added by syringe pump over 0.5 h. Stirring was then continued for 3 h.

We executed the direct asymmetric Mannich reaction between various aldehydes and N-Boc-protected imines. As shown in Table 3, the corresponding *anti*-Mannich adducts were obtained with good *anti* selectivity and excellent enantioselectivity in all the cases examined under the optimized conditions. When a solution of the N-Boc-protected imine was added more slowly to the reaction mixture by syringe pump, the catalyst loading could be reduced to 1 mol% without loss of stereoselectivity (Table 3, entries 3 and 4). In addition, N-Boc-protected heteroaromatic imines as well as an N-Boc-protected aliphatic imine were found to be applicable to the present reaction system (Table 3, entries 8–10).

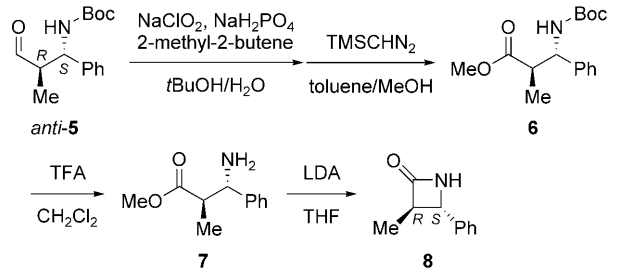
Table 3: *anti*-Selective Mannich reactions between various aldehydes and N-Boc-protected imines catalyzed by (*S*)-**1**.[a]



Entry	R^1	R^2	Cat. [mol%]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Me	Ph	5	92	7.7:1	99
2	*i*Pr	Ph	5	77	8.8:1	99
3[e]	Bu	Ph	5	93	16:1	99
4[f]	Bu	Ph	1	88	15:1	99
5	Bn	Ph	5	80	15:1	99
6	Bu	4-$MeOC_6H_4$	5	91	8.2:1	98
7	Bu	4-ClC_6H_4	5	78	11:1	99
8	Bu	2-furyl	5	88	7.5:1	99
9	Bu	3-pyridyl	5	92	16:1	99
10[e,g]	Me	cyclohexyl	10	66	>20:1	99

[a] Unless otherwise specified, the reaction between an aldehyde (0.75 mmol) and an N-Boc-protected imine (0.25 mmol) was carried out in $CHCl_3$ in the presence of (*S*)-**1** at 0 °C. The N-Boc-protected imine was added by syringe pump over 4 h. Stirring was then continued for 1 h. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] The *ee* value of the *anti* isomer was determined by HPLC analysis on a chiral stationary phase. [e] Stirred for 2 h after addition of the N-Boc-protected imine. [f] The N-Boc-protected imine was added by syringe pump over 12 h. Stirring was then continued for 1 h. [g] 1.25 mmol propanal was used.

To assign the absolute configuration of the obtained *anti*-β-amino aldehyde and to extend the synthetic utility of this asymmetric transformation, the optically enriched *anti*-β-amino aldehyde *anti*-**5** was successfully converted into the corresponding β-lactam (Scheme 2). Thus, treatment of *anti*-**5** with $NaClO_2$, followed by addition of $TMSCHN_2$, resulted in clean formation of the corresponding methyl ester **6** (97% yield over two steps). Subsequent removal of the N-Boc protecting group and treatment of the resulting β-amino ester



Scheme 2. Determination of the absolute configuration of *anti*-**5**. TMS = trimethylsilyl, TFA = trifluoroacetic acid, LDA = lithium diisopropylamide.

7 with LDA gave β-lactam **8** without loss of enantiopurity (82% yield over two steps).[11] By comparison of the optical rotation of β-lactam **8** with the literature value,[12] the absolute configuration of *anti*-β-amino aldehyde *anti*-**5** was determined to be 1*S*,2*R*.

In summary, we have developed a highly stereoselective direct asymmetric Mannich reaction between acetaldehyde and N-Boc-protected imines as well as an *anti*-selective direct asymmetric Mannich reaction of N-Boc-protected imines by using the less nucleophilic chiral amino sulfonamide (*S*)-**1** to suppress the undesired side reactions. The present reactions represent a rare example of an efficient direct Mannich reaction of N-Boc-protected imines via an enamine intermediate. Further investigations to expand the scope of this and related reactions are currently underway.

Received: November 18, 2008
Published online: January 28, 2009

Keywords: asymmetric catalysis · diastereoselectivity · enantioselectivity · Mannich reaction · organocatalysis

[1] For reviews, see a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991; c) S. Kobayashi, M. Ueno in *Comprehensive Asymmetric Catalysis Supplement I* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2003**, chap. 29.5; d) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10; e) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; f) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348; g) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541; h) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; i) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29.

[2] For *syn*-selective asymmetric Mannich reactions catalyzed by amines, see a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; b) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; c) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Synlett* **2003**, 1906; d) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624; e) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987; f) N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507; g) A. Münch, B. Wendt, M. Christmann, *Synlett* **2004**, 2751; h) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84; i) I. Ibrahem, ; A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839; A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839; j) S. Fustero, D. Jiménez, J. F. Sanz-Cervera, M. Sánchez-Roselló, E. Esteban, A. Simón-Fuentes, *Org. Lett.* **2005**, *7*, 3433; k) Y. Hayashi, T. Urushima, M. Shin, M. Shoji, *Tetrahedron* **2005**, *61*, 11393; l) P. H.-Y. Cheong, H. Zhang, R. Thayumanavan, F. Tanaka, K. N. Houk, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 811.

[3] For *anti*-selective asymmetric Mannich reactions catalyzed by amines, see a) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749; b) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; c) I. Ibrahem, A. Córdova, *Chem. Commun.* **2006**, 1760; d) G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 7417; e) H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2008**, *130*, 875; f) T. Kano, Y. Hato, A. Yamamoto, K. Maruoka, *Tetrahedron* **2008**, *64*, 1197; g) M. Pouliquen, J. Blanchet, M.-C. Lasne, J. Rouden, *Org. Lett.* **2008**, *10*, 1029.

[4] J. W. Yang, M. Stadler, M. List, *Angew. Chem.* **2007**, *119*, 615; *Angew. Chem. Int. Ed.* **2007**, *46*, 609.

[5] J. Vesely, R. Rios, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 421.

[6] J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453.

[7] Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa, T. Uchimaru, *Angew. Chem.* **2008**, *120*, 9193; *Angew. Chem. Int. Ed.* **2008**, *47*, 9053.

[8] T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408.

[9] T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem.* **2007**, *119*, 1768; *Angew. Chem. Int. Ed.* **2007**, *46*, 1738.

[10] C. Gianelli, L. Sambri, A. Carlone, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8828; *Angew. Chem. Int. Ed.* **2008**, *47*, 8700.

[11] S. Kobayashi, M. Kawamura, *J. Am. Chem. Soc.* **1998**, *120*, 5840.

[12] I. Abrahams, M. Motevalli, A. J. Robinson, P. B. Wyatt, *Tetrahedron* **1994**, *50*, 12755.

