Asymmetric Synthesis

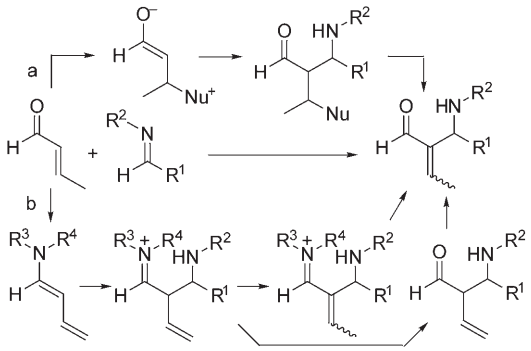
DOI: 10.1002/anie.200603973

# A Way to Highly Enantiomerically Enriched aza-Morita–Baylis–Hillman–Type Products**

*Naoto Utsumi, Haile Zhang, Fujie Tanaka,* and Carlos F. Barbas, III**

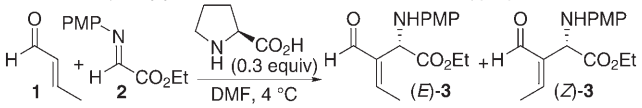
Enantiomerically enriched β-amino carbonyl compounds bearing an α-alkylidene group can be prepared by aza-Morita-Baylis-Hillman (aza-MBH) reactions and are versatile chiral building blocks for pharmaceutical candidates and other important compounds.[1,2] Consequently, the development of efficient methods for enantioselective aza-MBH reactions is of interest.[1] For example, quinidine derivatives,[1a–c] 1,1′-bi-2-naphthol (binol) derivatives containing a pyridyl group,[1d,e] phosphinyl derivatives,[1f–i] and thiourea derivatives[1j] have been used as catalysts for enantioselective aza-MBH reactions. These methods are, however, typically limited to the reactions of cyclic enones (such as 2-cyclopenten-1-one) or of β-unsubstituted acyclic enones and related esters (such as methyl vinyl ketone and methyl acrylate). There have been no reports of highly enantioselective aza-MBH reactions of β-substituted α,β-unsaturated acyclic carbonyl compounds.[3] It has been demonstrated that aza-MBH and MBH reactions of β-substituted acyclic enones are more problematic than those of β-unsubstituted enones.[3,4] This may be related to a relatively slow Michael addition of a nucleophilic reagent (or Lewis base) to β-substituted enones because of steric interaction between the nucleophilic reagent and the β substituent on the enones.[4] To overcome this difficulty, we propose an alternative route to access aza-MBH-type products with β-substituted α,β-unsaturated carbonyl moieties: Mannich-type reaction of in situ generated enamines of β-substituted α,β-unsaturated carbonyl compounds followed by isomerization of the double bond (Scheme 1). Here we report the catalytic enantioselective formation of aza-MBH-type products from β-substituted α,β-unsaturated aldehydes and α-imino esters protected with a *p*-methoxyphenyl (PMP) group through a Mannich-type reaction/isomerization sequence.

We used (*S*)-proline to demonstrate the Mannich/isomerization sequence as it is a good asymmetric catalyst for Mannich-type reactions of alkyl aldehydes.[5] We reasoned that isomerization of the double bond of the Mannich products should occur spontaneously, because epimerization at the α-position of the aldehyde group of Mannich products generated from alkyl aldehydes is facile.[5] In the case of Mannich products generated from β-substituted α,β-unsaturated aldehydes, the acidity of the proton at the α-position of the aldehyde group of the product is increased by the presence of a neighboring alkene; this increased acidity should favor the isomerization of the double bond. Table 1 shows the results of the (*S*)-proline-catalyzed reaction



***Scheme 1.*** a) An aza-MBH reaction route. b) Formation of aza-MBH-type products through Mannich-type reaction/isomerization.

***Table 1:*** Evaluation of the reaction conditions for the reaction between crotonaldehyde (**1**) and imine **2** to afford aza-MBH-type product **3**.



| Entry | Aldehyde **1** (equiv) | Imidazole (equiv) | *t* [h] | Yield[a] [%] | *E*/*Z*[b] | *ee*[c] [%] |
|---|---|---|---|---|---|---|
| 1 | 5 | 0 | 6 | 35 | 12:1 | 96 |
| **2**[d] | **5** | **1.0** | **2** | **65** | **15:1** | **98** |
| 3 | 5 | 0.3 | 6 | 47 | 15:1 | 97 |
| 4 | 5 | 5.0 | 2 | 49 | 14:1 | 97 |
| 5 | 1.2 | 1.0 | 5 | 50 | 20:1 | 98 |
| 6 | 10 | 1.0 | 2 | 57 | 10:1 | 98 |
| **7**[e] | **10** | **1.0** | **2** | **70** | **17:1** | **98** |
| 8[f] | 15 | 1.0 | 2 | 71 | 13:1 | 97 |
| 9[g] | 5 | 1.0 | 2 | 61 | 17:1 | 99 |

[a] Yield of isolated **3** including *E* and *Z* isomers. [b] Determined by $^1$H NMR spectroscopic analysis of the isolated **3**. [c] Determined by chiral-phase HPLC of (*E*)-**3**. [d] A mixture of aldehyde **1** (1.5 mmol, 5 equiv), imine **2** (0.3 mmol, 1.0 equiv), (*S*)-proline (0.09 mmol, 0.3 equiv, 30 mol% to the imine), and imidazole (0.3 mmol, 1.0 equiv) in DMF (0.6 mL) was stirred at 4 °C. [e] Aldehyde **1** was added portionwise: 5 equiv at 0 min and 5 equiv at 30 min. [f] Aldehyde **1** was added portionwise: 5 equiv at 0 min, 5 equiv at 30 min, and 5 equiv at 1 h. [g] Dimethyl sulfoxide (DMSO) was used as the solvent.

[*] Dr. N. Utsumi, Dr. H. Zhang, Prof. Dr. F. Tanaka, Prof. Dr. C. F. Barbas, III
The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2583
E-mail: ftanaka@scripps.edu
carlos@scripps.edu

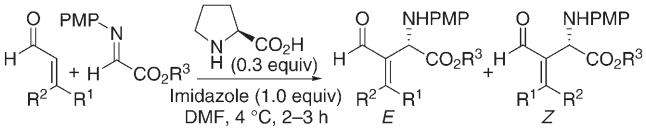
[**] This study was supported in part by The Skaggs Institute for Chemical Biology.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

between crotonaldehyde (**1**) and imine **2**. As expected, the reaction afforded aza-MBH-type product **3**[6] (entry 1). ROESY analysis of **3** indicated that the major isomer of **3** was an *E*-configured enal. We reasoned that since imidazole catalyzes the *syn–anti* isomerization of aldol and Mannich products,[7] it should accelerate the isomerization of the Mannich product of crotonaldehyde and should improve the formation of **3**. In fact, the addition of imidazole (1 equiv) improved both the reaction rate and the yield (Table 1, entry 2), although the addition of excess imidazole increased formation of by-products and decomposition of the product (entry 4). The enantioselectivities of the reactions that afforded **3** were excellent and the stereochemistry of the major enantiomer of **3** was the same irrespective of the presence or absence of imidazole. Further evaluation of the reaction conditions (see also the Supporting Information) showed that the reaction with (*S*)-proline (0.3 equiv) and imidazole (1 equiv) in DMF at 4 °C gave the best results with respect to reaction rate, cleanness of the reaction, and yield (entries 2 and 7).

A series of aza-MBH-type products, **4**–**8**, were also obtained with high enantioselectivities under the optimized conditions (Table 2). In these cases, the *E* isomer was also the major product.

***Table 2:*** Reactions catalyzed by (*S*)-proline and imidazole to afford aza-MBH-type products.[a]



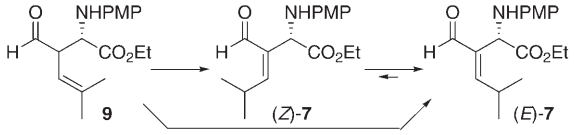

| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Yield[b] [%] | *E*/*Z*[c] | *ee*[d] [%] |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | *i*Pr | **4** | 68 | 16:1 | 99 |
| 2 | Et | H | Et | **5** | 58 | 10:1 | 99 |
| 3 | *n*Pr | H | Et | **6** | 50 | 8:1 | 97 |
| 4 | *i*Pr | H | Et | **7** | 40[e] | 4:1 (19:1)[g] | 98[f] (98)[g] |
| 5 | Me | Me | Et | **8** | 39 | – | 92 |
| 6[h] | Me | Me | Et | **8** | 44 | – | 91 |

[a] Typical conditions: A mixture of aldehyde (1.5 mmol, 5 equiv), imine (0.3 mmol, 1.0 equiv), (*S*)-proline (0.09 mmol, 0.3 equiv, 30 mol% to the imine), and imidazole (0.3 mmol, 1.0 equiv) in DMF (0.6 mL) was stirred at 4 °C. [b] Yield of isolated product containing the *E* and *Z* isomers. [c] Determined by $^1$H NMR spectroscopic analysis of isolated products. [d] Determined by chiral-phase HPLC of the *E* isomer. [e] Containing **9** (**7**/**9** = 93:7). [f] 97% *ee* for (*Z*)-**7**. [g] Data after isomerization using imidazole. [h] Aldehyde **1** (10 equiv) was added portionwise: 5 equiv at 0 min and 5 equiv at 30 min.

The *E*/*Z* ratio of products **3**–**7** changed during purification by column chromatography on silica gel. The products with small $R^1$ groups (with $R^2$ = H) in Table 2 had faster *Z* to *E* isomerization rates than the products with larger $R^1$ groups under the same conditions.

In the reaction of (*E*)-4-methylpent-2-enal (Table 2, entry 4), unconjugated product **9** was obtained together with **7**, thus supporting that the C–C bond formation occurred through a Mannich-type reaction of an enamine intermediate without Michael addition of a nucleophile. When a product mixture containing **7** and **9** was treated with imidazole and then analyzed by $^1$H NMR spectroscopy, a decrease in the amount of **9** was observed after 10 min, without formation of significant amounts of by-products, and the *E*/Z ratio of **7** increased with time (Table 3).[8] When the reaction that

***Table 3:*** Isomerization of **7** and **9** with imidazole.[a]




| *t* [min] | **7**/**9**[b] | (*E*)-**7**/(*Z*)-**7** |
|---|---|---|
| 0[c] | 87:13 | 51:49 |
| 10 | >93:7 | 60:40 |
| 30 | –[d] | 82:18 |
| 40 | –[d] | 85:15 |
| 90 | –[d] | 95:5 |

[a] Imidazole (15 equiv) was added to a mixture of **7** and **9** (**7**:**9**, see 0 min) in $CDCl_3$, and changes in the ratios were monitored by $^1$H NMR spectroscopy. [b] For **7**, *E* and *Z* isomers were combined. For **9**, *anti* and *syn* isomers were combined. [c] Before addition of imidazole. [d] Not determined. The chemical shifts of **9** overlapped with those of decomposed products.

afforded **7** in [$D_6$]DMSO was analyzed by $^1$H NMR spectroscopy, only the *Z* isomer was observed (no *E* isomer was present) at 10 min and the amount of *E* isomer increased as the reaction progressed (Table 4). These results suggest that **9** (or its iminium ion with proline) was formed first and then isomerized to **7** (or its iminium ion) and that (*Z*)-**7** was isomerized to (*E*)-**7**.

***Table 4:*** $^1$H NMR Analysis of the reaction affording **7** in [$D_6$]DMSO.

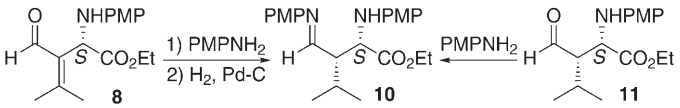
| *t* | Relative amount of **7**[a] | (*E*)-**7**/(*Z*)-**7** |
|---|---|---|
| 10 min | 1 | 0:100 |
| 20 min | 31 | 33:67 |
| 80 min | 97 | 46:54 |
| 24 h | 100 | 84:16 |

[a] The relative amount of **7** was determined by comparing with the amount of **7** at 24 h.

Reactions of non-enolizable aldehydes, such as acrylaldehyde and cinnamaldehyde, did not afford the desired aza-MBH-type product under the conditions used for the reactions shown in Table 2. These results also support the enamine mechanism (Scheme 1, path b) being more feasible than a typical aza-MBH reaction route (Scheme 1, path a) for the reactions affording **3**–**8**.[9]

The absolute stereochemistry at the carbon atom of the product substituted with an amino group was determined to be *S* by the transformation of **8** to **10** and by transformation of **11** to **10**, where **11** was generated from the (*S*)-proline-catalyzed Mannich-type reaction of isovaleraldehyde[5] (Scheme 2).




***Scheme 2.*** Determination of the absolute stereochemistry.

In summary, highly enantiomerically enriched aza-MBH-type products with β-substituted enal moieties have been prepared for the first time under mild conditions. Our results support that these reactions proceed through a Mannich-type reaction followed by isomerization of the double bond. This type of mechanism might be favorably exploited in other reactions involving enals and enones.

Received: September 27, 2006
Published online: January 29, 2007

**Keywords:** aldehydes · asymmetric synthesis · enamines · imines · organocatalysis

[1] a) M. Shi, Y.-M. Xu, *Angew. Chem.* **2002**, *114*, 4689; *Angew. Chem. Int. Ed.* **2002**, *41*, 4507; b) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 3103; c) D. Balan, H. Adolfsson, *Tetrahedron Lett.* **2003**, *44*, 2521; d) K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680; e) K. Matsui, K. Tanaka, A. Horii, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry* **2006**, *17*, 578; f) M. Shi, L.-H. Chen, C.-Q. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790; g) P. Buskens, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2005**, *127*, 16762; h) Y.-H. Liu, L.-H. Chen, M. Shi, *Adv. Synth. Catal.* **2006**, *348*, 973; i) K. Matsui, S. Takizawa, H. Sasai, *Synlett* **2006**, 761; j) I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701; k) R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, C. W. Lehmann, J. Klankermayer, W. Leitner, *Angew. Chem.* **2006**, *118*, 3772; *Angew. Chem. Int. Ed.* **2006**, *45*, 3689.

[2] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; b) V. K. Aggarwal, A. M. M. Castro, A. Mereu, H. Adams, *Tetrahedron Lett.* **2002**, *43*, 1577.

[3] Routes other than aza-MBH reactions have been developed to access aza-MBH-type products with β-substituted α,β-unsaturated carbonyl moieties, but there has been no report of enantioselective versions of these reactions: a) J. L. G. Ruano, I. Fernandez, M. P. Catalina, J. A. Hermoso, J. Sanz-Aparicio, M. Martinez-Ripoll, *J. Org. Chem.* **1998**, *63*, 7157; b) H.-X. Wei, J. D. Hook, K. A. Fitzgerald, G. Li, *Tetrahedron: Asymmetry* **1999**, *10*, 661; c) B. Trost, C. K. Chung, *J. Am. Chem. Soc.* **2006**, *128*, 10358.

[4] a) Y.-L. Shi, Y.-M. Xu, M. Shi, *Adv. Synth. Catal.* **2004**, *346*, 1220; b) Y.-L. Shi, M. Shi, *Tetrahedron* **2006**, *62*, 461; c) V. K. Aggarwal, I. Emme, S. Y. Fulford, *J. Org. Chem.* **2003**, *68*, 692.

[5] a) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanuvan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624; b) A. Cordova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; c) S. Watanabe, A. Cordova, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2002**, *4*, 4519.

[6] a) Whereas aza-MBH-type product **3** was generated by the formation of a C–C bond at the α-position of aldehyde **1**, for the reaction between two molecules of **1** in the presence of proline, the γ-position of **1** reacted as a nucleophilic carbon atom and [3+3] adducts were formed. This observation supports the proposed formation of an enamine from **1** with proline: B.-C. Hong, M.-F. Wu, H.-C. Tseng, J.-H. Liao, *Org. Lett.* **2006**, *8*, 2217; b) formation of enamine intermediates of β-substituted α,β-unsaturated aldehydes with a pyrrolidine derivative was also suggested in a γ-amination reaction: S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[7] a) D. E. Ward, M. Sales, P. Sasmal, *J. Org. Chem.* **2004**, *69*, 4808; b) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040.

[8] Addition of excess imidazole resulted in a broadening of the $^1$H NMR signals of **9**, but no broadening of the $^1$H NMR signals of **7** was observed with imidazole.

[9] Imidazole has been used or suggested as a nucleophile in MBH reactions in the presence of proline: a) M. Shi, J.-K. Jiang, C.-Q. Li, *Tetrahedron Lett.* **2002**, *43*, 127; b) S.-H. Chen, B.-C. Hong, C.-F. Su, S. Sarshar, *Tetrahedron Lett.* **2005**, *46*, 8899.