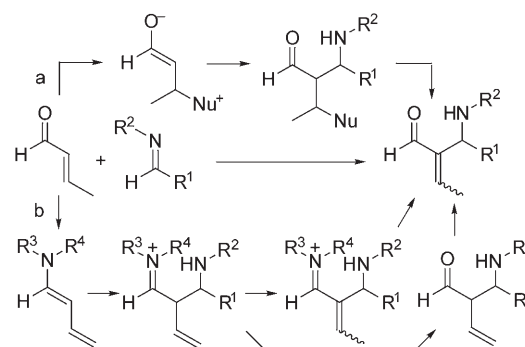


A Way to Highly Enantiomerically Enriched aza-Morita–Baylis–Hillman–Type Products**

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 derivative-s,^[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



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

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

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)	<i>t</i> [h]	Yield ^[a] [%]	<i>E/Z</i> ^[b]	<i>ee</i> ^[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 ¹H 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

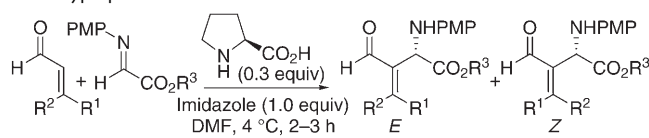
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between crotonaldehyde (**1**) and imine **2**. As expected, the reaction afforded aza-MBH-type product **3**^[6] (entry 1). ROESY analysis of **3** indicated that the major isomer of **3** was an *E*-configured enal. We reasoned that since imidazole 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] [%]	<i>E/Z</i> ^[c]	<i>ee</i> ^[d] [%]
1	Me	H	<i>i</i> Pr	4	68	16:1	99
2	Et	H	Et	5	58	10:1	99
3	<i>n</i> Pr	H	Et	6	50	8:1	97
4	<i>i</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

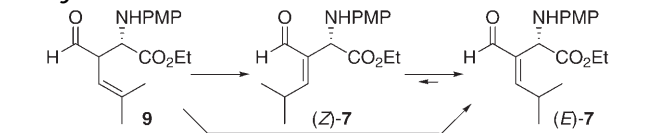
[a] Typical conditions: A mixture of aldehyde (1.5 mmol, 5 equiv), imine (0.3 mmol, 1.0 equiv), (*S*)-proline (0.09 mmol, 0.3 equiv, 30 mol% to the imine), and imidazole (0.3 mmol, 1.0 equiv) in DMF (0.6 mL) was stirred at 4 °C. [b] Yield of isolated product containing the *E* and *Z* isomers. [c] Determined by ¹H 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 R¹ groups (with R² = H) in Table 2 had faster *Z* to *E* isomerization rates than the products with larger R¹ 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 ¹H 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]



<i>t</i> [min]	7/9 ^[b]	(<i>E</i>)- 7 /(<i>Z</i>)- 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 CDCl₃, and changes in the ratios were monitored by ¹H 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 [D₆]DMSO was analyzed by ¹H 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**.

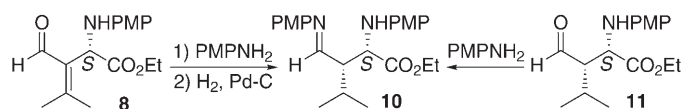
Table 4: ¹H NMR Analysis of the reaction affording **7** in [D₆]DMSO.

<i>t</i>	Relative amount of 7 ^[a]	(<i>E</i>)- 7 /(<i>Z</i>)- 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.

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