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Ba-Catalyzed Direct Mannich-Type Reactions of a β,γ-Unsaturated Ester Providing β-Methyl *aza*-Morita–Baylis–Hillman-Type Products

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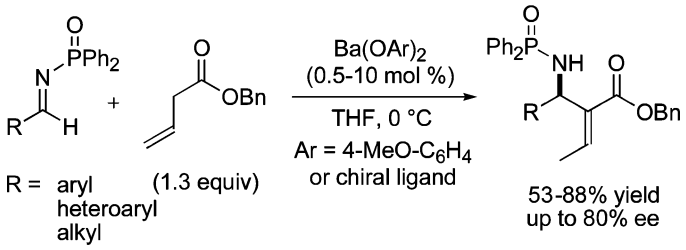
ABSTRACT



Barium-catalyzed direct Mannich-type reactions of a β,γ-unsaturated ester are described. The Ba-catalyst not only promoted the Mannich-type reactions, but also isomerized Mannich adducts to afford β-methyl *aza*-Morita–Baylis–Hillman-type products in 61–88% yield from various aryl, heteroaryl, and alkyl imines. Preliminary trials on enantioselective variants with a chiral biaryldiol ligand gave products in up to 80% ee.

β-Amino carbonyl compounds are important building blocks for the syntheses of natural products and pharmaceuticals. Therefore, tremendous effort has been devoted to the development of synthetic methods for β-amino carbonyl compounds, including enantioselective variants.[1] Of these methods, direct catalytic Mannich-type reactions are attractive in terms of atom economy.[2,3] Many excellent direct catalytic enantio- and diastereoselective Mannich(-type) reactions with ketones and aldehydes as donors have been reported.[3,4] The use of esters as nucleophiles, however, is limited to a glycine Schiff-base[5] and active methylene compounds such as β-keto esters and malonates.[6] Recently, the utility of activated ester equivalent donors such as *N*-acylpyrroles,[7] trichloromethylketones,[8] and *N*-Boc-anilides[9] in direct catalytic Mannich-type reactions was also reported. There remains room for improvement, however, when using esters themselves as donors. Herein, we describe the utility

(1) Reviews: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.

(2) Trost, B. M. *Science* **1991**, *254*, 1471.

(3) Recent reviews on direct Mannich-type reactions: (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (b) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(4) Selected recent direct Mannich-type reactions of ketones and aldehydes: Metal catalysts: (a) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. Organocatalysts: (c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (d) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609. (e) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. For other examples, see reviews in ref 3 and references therein.

(5) (a) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (b) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (c) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794 and references cited therein.

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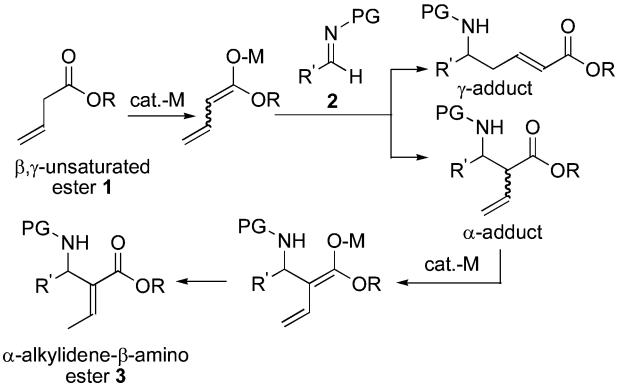
of a β,γ-unsaturated ester as a new donor class in direct catalytic Mannich-type reactions.[10,11] The Ba-catalyst not only promoted the Mannich-type reactions of the β,γ-unsaturated ester, but also isomerized Mannich adducts to afford β-methyl *aza*-Morita−Baylis−Hillman-type products in up to 88% yield.[12] Preliminary studies on enantioselective reactions are also described.

Possible reaction pathways with use of a β,γ-unsaturated ester **1** are shown in Scheme 1. The acidity of the proton at

Scheme 1. Mannich-Type Reaction/Isomerization Sequence with a β,γ-Unsaturated Ester



the α-position of the ester group is increased due to the neighboring C−C double bond. Therefore, a Brønsted basic metal catalyst would readily generate a dienolate in situ from **1**. The dienolate reacts with imine **2** at the α- and/or γ-position. If the catalyst further deprotonates the α-proton from the α-adduct, the C−C double bond would isomerize to give a β-amino ester **3** bearing an α-alkylidene group. Despite recent progress in *aza*-Morita−Baylis−Hillman (*aza*-MBH) reactions including enantioselective variants,[13,14] applicable substrates in *aza*-MBH reactions are mostly limited to cyclic enones, β-unsubstituted acyclic enones, and related esters. *aza*-MBH reactions with β-substituted α,β-unsaturated esters are rare due to their low reactivity.[15] Thus, we decided to search for a suitable catalyst to selectively promote the α-addition/isomerization sequence using β,γ-unsaturated ester **1** to provide an alternative approach for β-substituted *aza*-MBH adducts.[16]

We screened several metal aryloxides for racemic reactions using *N*-diphenylphosphinoyl (*N*-Dpp) imine[17] **2a** and 1.3 equiv of benzyl ester **1** (Table 1, entries 1−5).[18] LiOAr (Ar = 4-MeO-C_6H_4) and $Ba(OAr)_2$ promoted both the Mannich-type α-addition and desired isomerization at 0 °C to afford product (*E*)-**3a** in 51% (entry 1) and 74% (entry 3) yield, respectively. Considering the extension to an asymmetric variant, $Ba(OAr)_2$ was selected for further studies.[19] The use of another alkaline earth metal (entry 2: Ca), and rare earth metals (entries 4 and 5: Sc and La) gave trace, if any, product **3a**. The first Mannich-type reaction was problematic in

(6) For selected recent examples, see: (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359. (b) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (c) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (d) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (e) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (f) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010. (g) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (h) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (i) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043. (j) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. For related reactions with a diketone, see also: (k) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(7) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365.

(8) Racemic reactions: (a) Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3146. Asymmetric reactions: (b) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.*, published online July 14, http://dx.doi.org/10.1021/ja073285p.

(9) Racemic reactions: Saito, S.; Tsubogo, T.; Kobayashi, S. *Chem. Commun.* **2007**, 1236.

(10) β,γ-Unsaturated nitriles and a β,γ-unsaturated ester were utilized in direct catalytic aldol reactions. The isomerization step to afford MBH-type adducts was, however, problematic when using the β,γ-unsaturated ester: Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.

(11) Diastereoselective addition of a dienolate from a β,γ-unsaturated ester to imines with chiral auxiliary afforded α-alkylidene-β-amino esters; however, stoichiometric amounts of LDA were required in the method: Garcia Ruano, J. L.; Fernández, I.; del Prado Catalina, M.; Hermoso, J. A.; Sanz-Aparicio, J.; Martínez-Ripoll, M. *J. Org. Chem.* **1998**, *63*, 7157.

(12) Recently, an elegant organocatalytic enantioselective Mannich-type reaction/isomerization sequence using α,β-unsaturated aldehydes and α-imino esters to produce chiral α-alkylidene-β-amino aldehydes was reported. Excellent enantioselectivity (99% ee) and stereoselectivity were achieved; however, 5 equiv of donor and 1 equiv of imidazole were used in the system to obtain isomerized adducts in good yield: Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 1878.

(13) For recent reviews on MBH reaction and *aza*-MBH reactions, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(14) For selected leading references: (a) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (b) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103. (c) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521. (d) Shi, M.; Xu, Y.-M.; Shi, Y.-L. *Chem. Eur. J.* **2005**, *11*, 1794. (e) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (f) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680 and references cited therein. For other examples, see ref 13 and references cited therein.

(15) Racemic *aza*-MBH reactions with acyclic β-substituted esters. (a) Shi, Y.-L.; Shi, M. *Tetrahedron* **2006**, *62*, 461. For the use of an acyclic β-substituted ester in racemic MBH reactions: (b) Krishna, P. R.; Narsingam, M.; Reddy, P. S.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2005**, *46*, 8885. (c) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692.

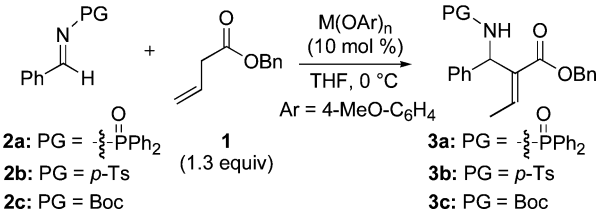
(16) For alternative approaches to α-alkylidene-β-amino esters, nitriles, and ketones, see: Pd-catalyzed allylic aminations: (a) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (b) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801. (c) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927. Phosphine-catalyzed allylic aminations: (d) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337. Vanadium-catalyzed isomerization/addition sequence of propargyl alcohols to imines: (e) Trost, B. M.; Chung, C. K. *J. Am. Chem. Soc.* **2006**, *128*, 10358. For other approaches, see also: (f) Wei, H.-X.; Hook, J. D.; Fitzgerald, K. A.; Li, G. *Tetrahedron*: *Asymmetry* **1999**, *10*, 661. (g) Li, G.; Wei, H. X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061. (h) Reginato, G.; Mordini, A.; Valacchi, M.; Piccardi, R. *Tetrahedron*: *Asymmetry* **2002**, *13*, 595.

(17) A review on the utility of *N*-Dpp-imines: (a) Weinreb, A. M.; Orr, R. K. *Synthesis* **2005**, 1205. For the use of *N*-Dpp-imines in direct Mannich-type reactions, see: (b) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (c) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339. See also ref 4a.

(18) Benzyl ester **1** was selected in this study because benzyl ester is easily detected on TLC and is less volatile than methyl ester.

(19) For chiral Ba-aryloxide catalysts: (a) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (b) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704. For the utility of Ba-aryloxides in racemic direct catalytic Mannich-type reactions, see ref 9.

Table 1. Optimization of Reaction Conditions



entry	imine	$M(OAr)_n$	time (h)	yield (%)	α/γ^a
1	**2a**	LiOAr	21	51	>15:1
2	**2a**	$Ca(OAr)_2$	21	trace	ND[b]
3	**2a**	$Ba(OAr)_2$	17	74	>15:1
4	**2a**	$Sc(OAr)_3$	21	0	ND[b]
5	**2a**	$La(OAr)_3$	21	trace	ND[b]
6	**2b**	$Ba(OAr)_2$	21	trace[c]	ND[b]
7	**2c**	$Ba(OAr)_2$	21	39[d]	>15:1

[a] Ratio of **3**/γ-adduct determined by ^{1}H NMR analysis. [b] Not determined. [c] Trace amount of unisomerized α-adduct was obtained. [d] Mixture of α-adduct and isomerized adduct **3c**.

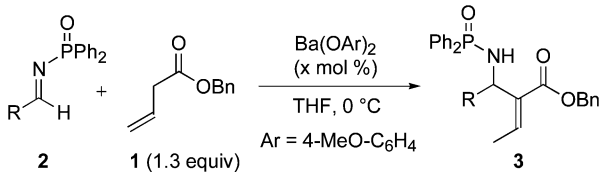
entries 2, 4, and 5. Imines with other protective groups were not suitable (entries 6 and 7). *N*-Ts-imine **2b** gave trace of unisomerized Mannich-adduct (entry 6). *N*-Boc-imine **2c** gave a mixture of the desired *aza*-MBH-type adduct and unisomerized Mannich-adduct in low yield (entry 7, 39%).

$Ba(OAr)_2$ was applicable to various aryl, heteroaryl, and alkyl *N*-Dpp-imines to afford (*E*)-products (Table 2).[20] No (*Z*)-adduct was observed in all entries. Aryl imines **2d**−**f** with an electron-donating group at either the 4- or the 2-position afforded the desired (*E*)-products in 81−84% yield and high α/γ selectivity (entries 2−4, α/γ >15/1). Catalyst loading was successfully reduced to 5 and 0.5 mol % while maintaining high α/γ selectivity (entries 5 and 6). The turnover number of the catalyst reached as high as 150 (entry 6; 75% yield). Imine **2g** with an electron-withdrawing group gave a less satisfactory yield and α/γ selectivity under standard conditions (entry 7, 55% yield, α/γ 7/1). The moderate yield of the desired product was partially due to a sequential α-addition/γ-addition reaction, giving a side-product containing one ester and two imine units. Slow addition of both imine **2g** and ester **1** over 2 h improved α/γ selectivity as well as yield to some extent (entry 8, 64%, α/γ 13/1). Heteroaryl imines **2h**,**i** were also applicable (entries 9 and 10). Slow addition was required for imine **2h** (entry 10). Not only nonisomerizable alkyl imine **2j**, but also isomerizable alkyl imines **2k** and **2*l*** with an α-proton were applicable,[21] giving **3k** and **3*l*** in 75% and 61% yield, respectively (entries 12 and 13). The results implied that the Ba-catalyst chemoselectively deprotonated the α-proton from ester **1** over alkyl imines **2k** and **2*l***. In the case of linear alkyl imine **2m**, however, the desired product **3m** was obtained in only 27% yield (entry 14), possibly because

(20) For determination of stereochemistry of products, see the Supporting Information.

(21) For synthesis of isomerizable alkyl *N*-Dpp-imines, see ref 4a. See also: Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985.

Table 2. Substrate Scopes and Limitations of Mannich-Type Reaction/Isomerization Sequence



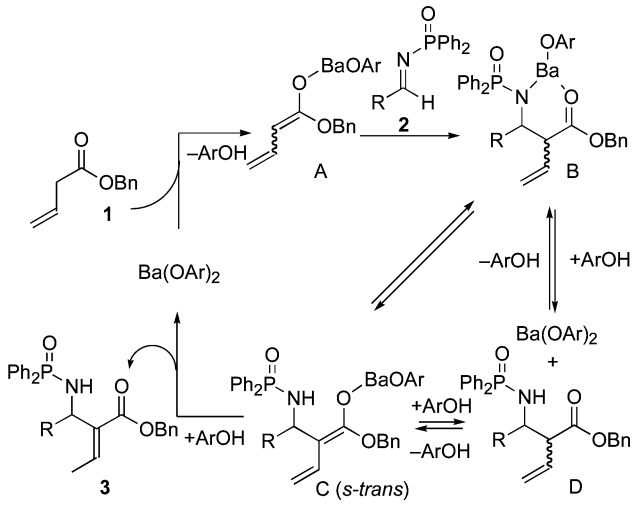
entry	imine **2**: R =	imine **2**	cat. (mol %)	time (h)	yield (%)	α/γ^a
1	Ph	**2a**	10	17	74	>15:1
2	4-Me-C_6H_4	**2d**	10	17	82	>15:1
3	2-Me-C_6H_4	**2e**	10	17	81	>15:1
4	4-MeO-C_6H_4	**2f**	10	17	84	>15:1
5	4-MeO-C_6H_4	**2f**	5	19	81	>15:1
6	4-MeO-C_6H_4	**2f**	0.5	24	75	>15:1
7	4-Cl-C_6H_4	**2g**	10	21	55	7:1
8[b]	4-Cl-C_6H_4	**2g**	10	17	64	13:1
9[b]	2-furyl	**2h**	10	19	61	>15:1
10	2-thienyl	**2i**	10	17	76	11:1
11	cyclopropyl	**2j**	10	19	88	>15:1
12[b]	cyclohexyl	**2k**	10	17	75	>15:1
13[b]	$(CH_3)_2CHCH_2$-	**2*l***	10	17	61	>15:1
14[b]	*n*-butyl	**2m**	10	17	27	>15:1
15[b,c]	*n*-butyl	**2m**	10	19	53	>15:1

[a] Ratio of **3**/γ-adduct determined by crude ^{1}H NMR analysis. [b] Imine **2** and ester **1** were added slowly over 2 h. [c] 3 equiv of ester **1** was used.

undesired isomerization of the imine to enamide was competitive with the desired reaction pathway. By using excess ester **1** (3 equiv), **3m** was obtained in 53% yield (entry 15).

The postulated catalytic cycle is shown in Scheme 2. A Brønsted basic Ba-OAr moiety deprotonates the α-proton in β,γ-unsaturated ester **1** to form dienolate A. The dienolate reacts with *N*-Dpp-imine **2** selectively at the α-position to give intermediate B. Dienolate C would be derived from intramolecular proton transfer from B and/or deprotonation

Scheme 2. Postulated Catalytic Cycle



of Mannich adduct D by the Ba-catalyst. Protonation of C at the γ-position gives the desired product **3** and regenerates the Ba-catalyst. We assume that the high *E*-selectivity shown in Table 2 would be due to the preference of an *s-trans* conformation of intermediate **C** over an *s-cis* conformation. Further studies to clarify the precise reaction mechanism as well as the origin of high stereoselectivity are ongoing.

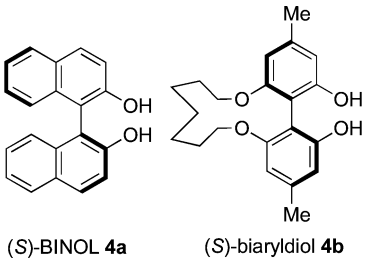
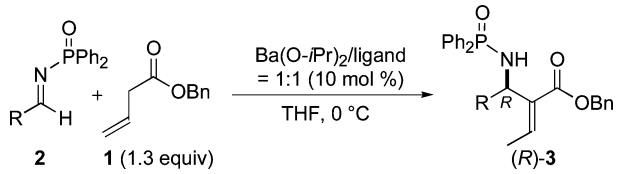


Figure 1. Structures of (*S*)-BINOL **4a** and (*S*)-biaryldiol **4b**.

Preliminary results of catalytic enantioselective reactions with chiral ligands **4** (Figure 1) are summarized in Table 3.

Table 3. Catalytic Enantioselective Mannich-Type Reaction/Isomerization Sequence with (*S*)-Ligands **4a** and **4b**



entry	ligand	imine **2**	time (h)	yield (%)	α/γ^a	ee[b] (%)
1	(*S*)-BINOL **4a**	**2a**	19	58	>15:1	14
2	(*S*)-biaryldiol **4b**	**2a**	17	69	9:1	77
3	(*S*)-biaryldiol **4b**	**2d**	19	78	>15:1	80
4	(*S*)-biaryldiol **4b**	**2i**	17	73	>15:1	78

[a] Ratio of **3**/γ-adduct determined by crude ^{1}H NMR analysis. [b] Determined by chiral HPLC analysis.

An initial trial with the Ba(O-*i*Pr)$_2$/(*S*)-BINOL **4a** = 1/1 complex resulted in 14% ee (entry 1). After screening of chiral ligands, the Ba(O-*i*Pr)$_2$/(*S*)-biaryldiol **4b**[22] = 1/1 complex showed good selectivity. The biaryldiol complex promoted the Mannich-type reaction/isomerization sequence of imines **2a**, **2d**, and **2i**, giving the desired adducts in 69−78% yield, 9:1 to >15:1 α/γ-selectivity, and 77−80% ee (entries 2−4).[20]

In summary, we have developed a Ba-catalyzed direct Mannich-type reaction/isomerization sequence of a β,γ-unsaturated ester to give β-methyl *aza*-MBH-type products in moderate to good yield. Preliminary trials on asymmetric variants with use of a Ba(O-*i*Pr)$_2$/biaryldiol **4b** complex afforded products in up to 80% ee. Further investigations to improve enantioselectivity and ester generality[23] are ongoing.

Acknowledgment. This work was supported by Grant-in-Aid for Specially Promoted Research, Grant-in-Aid for Encouragements for Young Scientists (B), and the Sumitomo Foundation. A.Y. thanks the JSPS Fellowship for Young Scientists. We thank Dr. H. Kakei at the University of Tokyo for his kind help with chiral ligand synthesis.

Supporting Information Available: Experimental procedures, spectral data of products, determination of stereochemistry of products, and synthesis of biaryldiol **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071380X

(22) Synthesis and use of chiral biaryldiols in asymmetric catalysis: (a) Harada, T.; Tuyet, T. M. T.; Oku, A. *Org. Lett.* **2000**, *2*, 1319. (b) Tosaki, S.-y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (c) Kakei, H.; Tsuji, R.; Ohshima, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 257 and references cited therein.

(23) At present, only γ-unsubstituted ester **1** gave satisfactory results in the Ba-catalyzed α-addition/isomerization sequence. For example, the Ba-catalyst promoted Mannich-type reaction (α-addition) of γ-substituted ester **5**; however, the second isomerization step to produce an *aza*-MBH-type adduct did not proceed in the case of ester **5**.