

# Catalytic, Asymmetric Mannich-Type Reactions of $\alpha$ -Imino Esters Bearing Readily Removable Substituents on Nitrogen

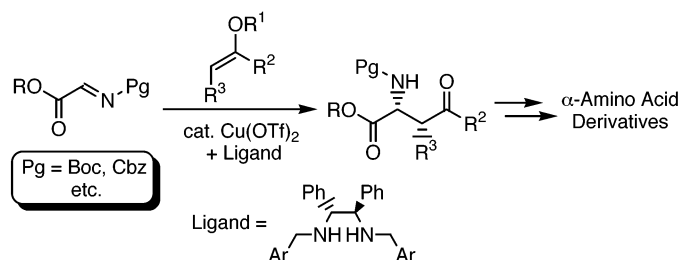
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## ABSTRACT



Catalytic, enantioselective Mannich-type reactions of  $\alpha$ -imino esters bearing readily removable substituents on nitrogen are described. Several N-carbamate-protected  $\alpha$ -imino esters, which are readily prepared from 2-bromoglycine esters using a polymer-supported amine, reacted with silicon enolates to afford the desired adducts in high yields with high enantioselectivity using a copper(II)–diamine complex. Easy deprotection of the product amine and transformation to free  $\alpha$ -amino acid derivatives have also been demonstrated.

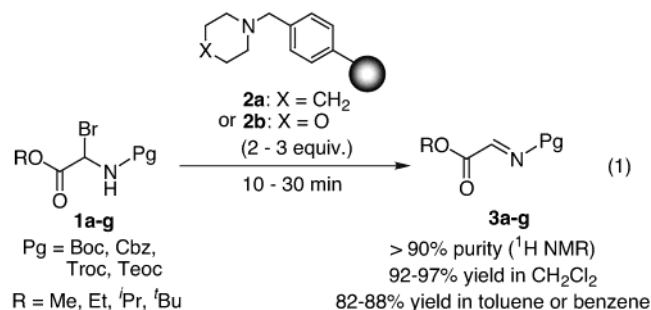
Optically active  $\alpha$ -amino acid derivatives constitute various components important to life such as peptides, proteins, and many other biologically important compounds. Asymmetric Mannich-type reactions of  $\alpha$ -imino esters with enolate components provide one of the most efficient ways for the preparation of optically active  $\alpha$ -amino acid derivatives. While some chiral catalysts for this reaction have been developed,<sup>1</sup> there still remain several problems, including the strong conditions required for deprotection of the product amine.<sup>2,3</sup> In this paper, we describe a highly efficient route to readily removable, N-carbamate-protected  $\alpha$ -amino acid derivatives via the enantioselective addition of silicon enolates to  $\alpha$ -imino esters in the presence of a chiral Cu(II)-catalyst.<sup>1e,f</sup>

First, the preparation of N-carbamate-protected  $\alpha$ -imino esters was examined. N-carbamate-protected  $\alpha$ -imino esters are known to be unstable, and their use in organic synthesis has been rather limited. Conventionally, they have been

prepared by aza-Wittig reaction<sup>4</sup> or dehydrohalogenation of  $\alpha$ -halogenoglycine esters with triethylamine;<sup>5</sup> however, the desired products were contaminated by the starting materials or by-products in both reactions. To overcome this problem, we have developed a method using a polymer-supported amine as a base for the dehydrohalogenation reactions.<sup>6</sup> 2-Bromoglycine esters<sup>4,7</sup> **1a–g** were treated with commercially available piperidinomethylpolystyrene **2a** in di-

(1) For catalytic enantioselective Mannich-type Reactions of  $\alpha$ -imino esters, see: (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drurry, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (d) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (e) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (f) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (g) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1843. (h) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. To the best of our knowledge, there has been no example of catalytic enantioselective Mannich-type reactions of N-carbamate-protected  $\alpha$ -imino esters.

chloromethane to give various N-carbamate-protected  $\alpha$ -imino esters such as *N*-Boc (*N*-*tert*-butoxycarbonyl)-, *N*-Cbz (*N*-benzyloxycarbonyl)-, and *N*-Teoc (*N*-2-trimethylsilylethoxycarbonyl)-protected<sup>8</sup>  $\alpha$ -imino esters, in excellent yields, and with good purity (eq 1). In the case of  $\alpha$ -imino esters



having more electron-withdrawing N-carbamates such as *N*-Troc (2,2,2-trichloroethoxycarbonyl)-protected<sup>9</sup>  $\alpha$ -imino ester **3f**, a substantial amount of decomposition of **3f** occurred during the imine formation using **2a**. In this case, less nucleophilic morpholinomethylpolystyrene **2b** was more effective than **2a** for the reaction to proceed cleanly. As for solvents, toluene or benzene could also be used instead of dichloromethane with a slight decrease in the yield. It is noteworthy that solutions of the  $\alpha$ -imino esters can be directly used for the following asymmetric Mannich-type reactions by simply removing the polymer-supported amines.

We then conducted Mannich-type reaction of *N*-Boc- $\alpha$ -imino ester **3a** with silyl enol ether **4a** as a model substrate using a catalyst prepared from Cu(OTf)<sub>2</sub> and diamine ligand **5a** (Table 1, entry 1).<sup>1e,f</sup> The reaction was found to go to

(2) Only a few successful examples of catalytic enantioselective reactions of imines bearing readily removable N-carbamates have been reported so far. For Friedel-Crafts-type reactions of N-carbamate-protected  $\alpha$ -imino esters, see: (a) Sabby, S.; Bayon, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, 67, 4352. For Mannich-type reactions of *N*-Boc-imines derived from aromatic aldehydes, see: (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, 124, 12964. For aziridinations of *N*-Boc- or *N*-TcBoc-imines derived from aromatic aldehydes, see: (c) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, 40, 1433. See also: (d) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, 6, 2435. In this paper, a Mannich-type adduct was observed as a by-product in 37% ee in catalytic asymmetric aza-Diels-Alder reaction of *N*-ethoxycarbonyl  $\alpha$ -imino ester with Danishefsky's diene.

(3) Lectka et al. have reported chiral Cu(I)-catalyzed Mannich-type reactions using several N-sulfonyl-protected imines and deprotection of the Mannich-type adducts; see: Ferraris, D.; Dudding, T.; Young, B.; Drurry, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, 64, 2168.

(4) (a) Plieninger, H.; von der Bruck, D. *Tetrahedron Lett.* **1968**, 9, 4371. (b) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, 22, 4607. See also ref 2a.

(5) (a) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599. (b) Bretschneider, T.; Miltz, W.; Munster, P.; Steglich, W. *Tetrahedron* **1988**, 44, 5403 and references therein.

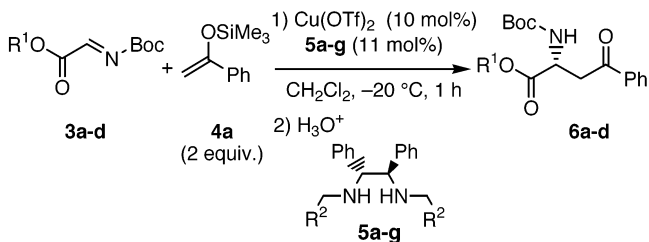
(6) Kobayashi, S.; Kitagawa, H.; Matsubara, R. *J. Comb. Chem.* **2001**, 3, 401.

(7) For the synthesis of *N*-Cbz- $\alpha$ -bromoglycinates, see: Williams, R. M.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1990**, 55, 4657.

(8) *N*-Teoc group can be easily deprotected by a fluoride ion or in mild acidic conditions; see: *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999; p 512 and refs cited therein.

(9) *N*-Troc group can be easily deprotected by reduction with zinc; see: *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999; p 510 and refs cited therein.

**Table 1.** Effect of Structure of Diamine Ligands



entry	$\alpha$ -imino ester R <sup>1</sup> =	ligand R <sup>2</sup> =	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	Me ( <b>3a</b> )	1-naphthyl ( <b>5a</b> )	97	84
2	Et ( <b>3b</b> )	1-naphthyl ( <b>5a</b> )	96	87
3	<sup>i</sup> Pr ( <b>3c</b> )	1-naphthyl ( <b>5a</b> )	85 <sup>c</sup>	81
4	<sup>t</sup> Bu ( <b>3d</b> )	1-naphthyl ( <b>5a</b> )	74 <sup>c</sup>	53
5	Et ( <b>3b</b> )	Ph ( <b>5b</b> )	92	85
6	Et ( <b>3b</b> )	<i>m,m</i> -Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>5c</b> )	92	86
7	Et ( <b>3b</b> )	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>5d</b> )	89	85
8	Et ( <b>3b</b> )	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>5e</b> )	87	86
9	Et ( <b>3b</b> )	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>5f</b> )	92	91
10	Et ( <b>3b</b> )	<sup>t</sup> Bu ( <b>5g</b> )	96	22

<sup>a</sup> Isolated yield from  $\alpha$ -imino ester. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Isolated yield from the corresponding 2-bromoglycine ester.

completion within 1 h at  $-20^\circ\text{C}$  to give the Mannich-type adduct **6a** in 97% yield with 84% ee. While the use of ethyl  $\alpha$ -imino ester **3b** slightly improved the enantioselectivity (entry 2), bulkier ester substituents resulted in lower enantioselectivity (entries 3, 4). To improve the enantioselectivity, several chiral diamine ligands were screened, and it was revealed that most of the diamine ligands bearing substituted benzyl groups on nitrogens such as **5b–e** showed almost the same enantioselectivity as **5a** (entries 5–8). Interestingly, *N,N'*-bis(*o*-methoxybenzyl)diamine ligand **5f** was effective, exhibiting higher enantioselectivity (91% ee, entry 9). Since sterically similar ligand **5d** (*o*-Me-substituted) or electronically similar ligand **5e** (*p*-MeO-substituted) showed no enhancement of the selectivity, we assume that coordination of the *o*-methoxy oxygens of **5f** to the copper may function to control the enantioselective additions in the transition states.<sup>10</sup> On the other hand, *N*-*tert*-butyl-substituted diamine **5g** showed only low selectivity (22% ee, entry 10).<sup>11</sup>

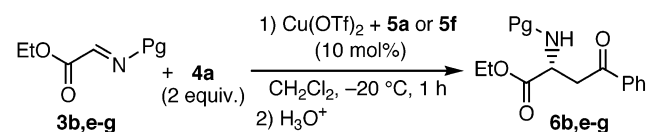
To extend the applicability of the reaction,  $\alpha$ -imino esters bearing other readily removable carbamates such as *N*-Cbz- (**3e**), *N*-Troc- (**3f**), or *N*-Teoc- $\alpha$ -imino esters (**3g**) were then investigated (Table 2).  $\alpha$ -Imino esters **3e–g** also reacted with **4a** smoothly to give the Mannich-type adducts in high yields with good enantioselectivity using the Cu(OTf)<sub>2</sub>-diamine **5f** complex. In all cases examined, the ligand **5f** exhibited higher enantioselectivity than **5a** did.

As for nucleophiles, silyl enol ethers **4a–f** derived from aromatic ketones also reacted with **3b** to afford the desired

(10) Buono et al. have reported the synthesis of a chiral phosphonium compound bearing a *N,N'*-bis(*o*-methoxybenzyl)cyclohexane-1,2-diamine moiety. They mentioned that coordination of the methoxy groups to the cationic phosphorus atom played a key role on the stability of this species; see: Brunel, J.-M.; Villard, R.; Buono, G. *Tetrahedron Lett.* **1999**, 40, 4669.

(11) For the mechanism of this reaction, see ref 1f.

**Table 2.** Mannich-Type Reactions of Several N-Protected Imino Esters



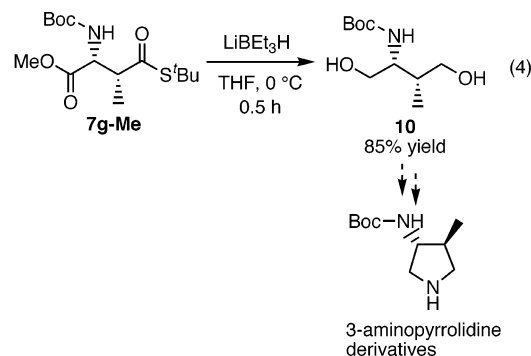
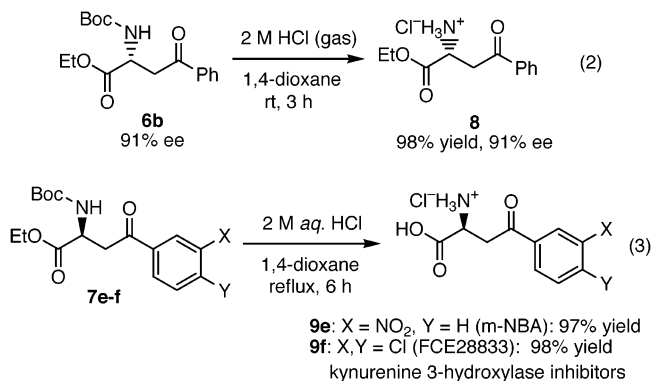
entry	Pg	ligand	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	Boc <sup>c</sup> ( <b>3b</b> )	<b>5a</b>	96	87
2	Boc <sup>c</sup> ( <b>3b</b> )	<b>5f</b>	92	91
3	Cbz <sup>d</sup> ( <b>3e</b> )	<b>5a</b>	92	75
4	Cbz <sup>d</sup> ( <b>3e</b> )	<b>5f</b>	90	85
5	Troc <sup>e</sup> ( <b>3f</b> )	<b>5a</b>	80	36
6	Troc <sup>e</sup> ( <b>3f</b> )	<b>5f</b>	83	85
7	Teoc <sup>f</sup> ( <b>3g</b> )	<b>5a</b>	94	69
8	Teoc <sup>f</sup> ( <b>3g</b> )	<b>5f</b>	95	74

<sup>a</sup> Isolated yield from  $\alpha$ -imino ester. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> Boc: *t*-butoxycarbonyl. <sup>d</sup> Cbz: benzyloxycarbonyl. <sup>e</sup> Troc: 2,2,2-trichloroethoxycarbonyl. <sup>f</sup> Teoc: 2-trimethylsilylethoxycarbonyl.

products in high yields with high enantioselectivity (86–91% ee, Table 3, entries 1–6). On the other hand, while silicon enolate **4g** derived from a thioester gave slightly lower enantioselectivity (entry 7), the selectivity was improved when the reaction was performed using methyl  $\alpha$ -imino ester **3a** in toluene (entry 8). It is noted that alkyl vinyl ethers **4h** and **4i** also reacted with **3b** to give the desired adduct **6b** in good enantioselectivity (entries 9, 10).

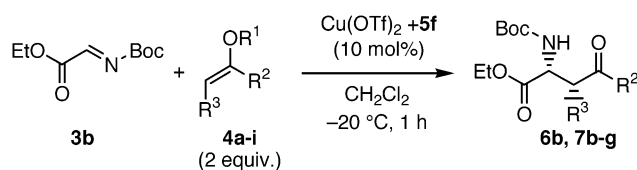
Deprotection of the *N*-Boc Mannich-type adduct **6b** was easily performed under standard conditions to give the hydrochloride salt of the free amine **8** quantitatively without racemization (eq 2).<sup>12</sup> Mannich-type adducts **7e** and **7f** were also successfully transformed to *m*-NBA<sup>13</sup> (**9e**) and FCE28833<sup>14</sup> (**9f**), respectively, in excellent yields (eq 3). A single recrystallization of **9e** and **9f** increased the enantio-

meric purity to 98 and 95% ee, respectively. These compounds are known to be selective kynurenine 3-hydroxylase inhibitors, which are promising drugs for neurological diseases.<sup>15</sup> Furthermore, Mannich-type adduct **7g**-Me was reduced to optically active diol **10**. Diol **10** is reported to be an intermediate of 3-aminopyrrolidine derivatives,<sup>16</sup> which are useful building blocks for several biologically active compounds (eq 4).



In summary, catalytic enantioselective Mannich-type reactions of  $\alpha$ -imino esters bearing readily removable substituents

**Table 3.** Mannich-Type Reactions of Several Nucleophiles



entry	nucleophile	product	% yield <sup>a</sup>	% ee <sup>b</sup>
1	<b>4a</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = Ph, R <sup>3</sup> = H	<b>6b</b>	92	91
2	<b>4b</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = <i>p</i> -MeOPh, R <sup>3</sup> = H	<b>7b</b>	97	86
3	<b>4c</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = <i>p</i> -ClPh, R <sup>3</sup> = H	<b>7c</b>	97	87
4	<b>4d</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = 2-naphthyl, R <sup>3</sup> = H	<b>7d</b>	93	86
5 <sup>c</sup>	<b>4e</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = <i>m</i> -NO <sub>2</sub> Ph, R <sup>3</sup> = H	<b>7e</b>	87	86 <sup>d</sup>
6 <sup>c</sup>	<b>4f</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = <i>m,p</i> -Cl <sub>2</sub> Ph, R <sup>3</sup> = H	<b>7f</b>	90	91 <sup>d</sup>
7	<b>4g</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = S <sup>t</sup> Bu, R <sup>3</sup> = CH <sub>3</sub>	<b>7g</b>	93	78 <sup>e,f</sup>
8 <sup>g,h</sup>	<b>4g</b> : R <sup>1</sup> = SiMe <sub>3</sub> , R <sup>2</sup> = S <sup>t</sup> Bu, R <sup>3</sup> = CH <sub>3</sub>	<b>7g</b> -Me	82	86 <sup>e,i</sup>
9 <sup>j</sup>	<b>4h</b> : R <sup>1</sup> = Me, R <sup>2</sup> = Ph, R <sup>3</sup> = H	<b>6b</b>	69	87
10 <sup>k</sup>	<b>4i</b> : R <sup>1</sup> = Et, R <sup>2</sup> = Ph, R <sup>3</sup> = H	<b>6b</b>	77	87

<sup>a</sup> Isolated yield from  $\alpha$ -imino ester. <sup>b</sup> Determined by chiral HPLC analysis. <sup>c</sup> (S,S)-**5f** was used as a ligand. <sup>d</sup> (S)-Configuration. <sup>e</sup> Ee of the *syn*-isomer. <sup>f</sup> *Syn/anti* = 65/35. <sup>g</sup> In toluene. <sup>h</sup> Methyl  $\alpha$ -imino ester **3a** was used as a substrate. <sup>i</sup> *Syn/anti* = 73/27. <sup>j</sup> Temperature = −78 °C. <sup>k</sup> Temperature = −40 °C.

on nitrogen have been achieved using a chiral copper(II)–diamine complex. Several carbamates such as *N*-Boc- and *N*-Cbz- $\alpha$ -imino ester, etc., were applicable to this reaction. The new diamine ligand **5f**, having *o*-methoxybenzyl groups on nitrogen, gave high enantioselectivity. Easy deprotection of the product amine and transformation to biologically active compounds have been achieved under mild conditions. This

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(12) Mannich-type adducts **6e–g** were also deprotected without racemization under relatively mild conditions. See Supporting Information.

(13) (a) Pellicciari, R.; Natalini, B.; Costantino, G.; Mahmoud, M. R.; Mattoli, L.; Sadeghpour, B. M.; Moroni, F.; Chiarugi, A.; Carpenedo, R. *J. Med. Chem.* **1994**, *37*, 647. (b) Natalini, B.; Mattoli, L.; Pellicciari, R.; Carpenedo, R.; Chiarugi, A.; Moroni, F. *BioMed. Chem. Lett.* **1995**, *5*, 1451. Enantioselective synthesis of *m*-NBA using asymmetric Mannich-type reaction has already been reported, but the yield was moderate; see ref 1c.

(14) Giordani, A.; Corti, L.; Cini, M.; Bormetti, R.; Marconi, M.; Veneroni, O.; Speciale, C.; Varasi, M. *Adv. Exp. Med. Biol.* **1996**, *398*, 531.

(15) Botting, N. P. *Chem. Soc. Rev.* **1995**, 401.

(16) Yoshida, T.; Takeshita, M.; Orita, H.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1128.

reaction system provides an efficient method for the preparation of various free non-natural  $\alpha$ -amino acids.

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**Supporting Information Available:** Experimental details and characterization of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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