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Calcium-Catalyzed Diastereo- and Enantioselective 1,4-Addition of Glycine Derivatives to α,β-Unsaturated Esters

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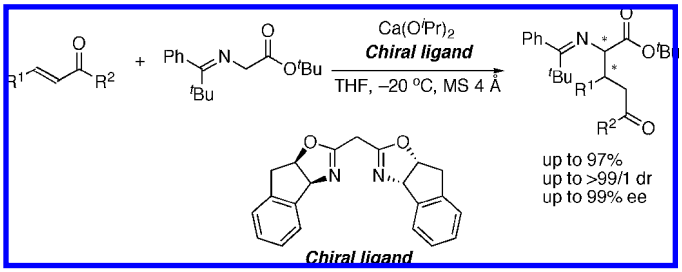
ABSTRACT



The first highly diastereo- and enantioselective catalytic asymmetric 1,4-addition reactions of a glycine Schiff base to β-substituted α,β-unsaturated esters have been developed. The reaction pathway was successfully controlled, and the desired 1,4-addition products were exclusively obtained with high enantioselectivities. The product obtained was converted to a 3-substituted glutamic acid derivative by acid hydrolysis.

Efficient synthesis of optically active α-amino acid derivatives is an important topic in current organic synthesis.[1] In particular, unnatural amino acid units are often valuable in drug design, since mimics of biologically active compounds containing such unnatural amino acids can work as antagonists to receptors in cells.[2] Glutamic acid and its derivatives are biologically important compounds because they work not only as essential components of peptides and proteins but also as signal mediators.[3] One of the most efficient preparation methods of glutamic acid derivatives is 1,4-addition of glycine derivatives to α,β-unsaturated esters or amides. Asymmetric versions of this reaction have been developed.[4,5] However, there are no successful examples of *catalytic*, *diastereo-*, and *enantioselective* 1,4-additions to afford 3-substituted glutamic acid derivatives. Here, we report the first example of such reactions using chiral calcium catalysts.

We have recently reported catalytic asymmetric 1,4-additions and [3 + 2] cycloadditions of a glycine Shiff base to α,β-unsaturated esters or amides using novel chiral calcium complexes (Scheme 1).[6] Interestingly, the product structures greatly depended on the α,β-unsaturated compounds used in these reactions. In the reactions with acrylic

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(4) Stereoselective synthesis of 3-subsutituted glutamic acid derivatives: Soloshonok, V. A. *Curr. Org. Chem.* **2007**, *6*, 341 as a review. Other representative examples: (a) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296. (b) Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747. (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron* **1999**, *55*, 12031. (e) Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1999**, *64*, 6554. (f) Alvarez-Ibarra, C.; Csáky, A. G.; Maroto, M.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 6700. (g) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875. (h) Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301. (i) Achqar, A. El; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (j) Mauger, A. B. *J. Org. Chem.* **1981**, *46*, 1032.

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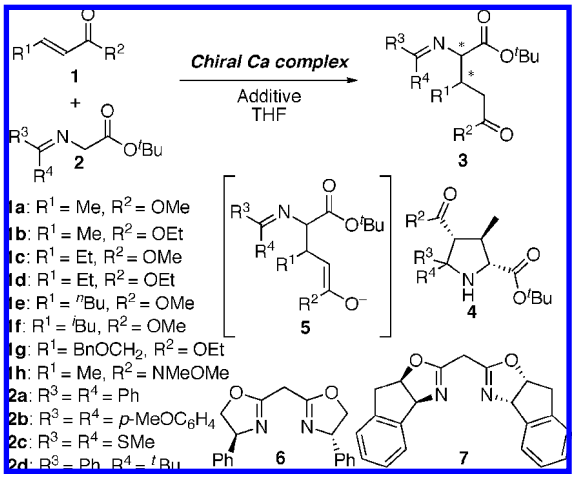
Scheme 1. Catalytic Asymmetric 1,4-Addition of Glycine Schiff Bases (**2**) to α,β-Unsaturated Carbonyl Compounds (**1**)



esters, only 1,4-adducts were obtained, while pyrrolidine derivatives were exclusively produced in the reactions with crotonate derivatives. Careful examination of the reaction mechanism suggested that the reaction might proceed via a stepwise mechanism; that is, 1,4-addition of **2** to **1a** provides enolate **5**, followed by protonation providing **3** or cyclization giving **4**. We envisioned that if enolate **5** prepared from crotonate derivatives and glycine derivatives **2** were protonated, 3-substituted glutamic acids might be obtained. Based on this consideration, we started to investigate diastereo- and enantioselective 1,4-addition of **2** to crotonate derivatives using a calcium catalyst.

First, we examined a proton source to trap the enolate intermediate **5** in the reaction of **1a** with **2a** using a chiral calcium catalyst prepared from $Ca(O^iPr)_2$ and ligand **6**. When 1,1,1,3,3,3-hexafluoroisopropyl alcohol was selected as a proton source, the reaction proceeded in good yield but the 1,4-adduct was racemic (Table 1, entry 2). Phenol derivatives were then tested as proton sources. When phenol or *p*-methoxyphenol were employed, the [3 + 2] cycloaddition proceeded predominantly (entries 3 and 4). However, the 1,4-addition product was obtained preferentially using bulkier phenol derivatives albeit with low selectivities (entries 5−7). Next, we employed glycine derivatives with modified imines to probe supression of the intramolecular cycloaddition by controlling its electrophilicity. When a glycine derivative bearing a bis(*p*-methoxyphenyl)methylene group (**2b**) was

Table 1. Asymmetric 1,4-Addition of **2** to Methyl Crotonate (**1a**) in the Presence of a Chiral Ca Complex[a]

entry	**2**	additive (10 mol %)	yield (%)	**3**/**4**	ee(**3**/**4**) (%)
1[b]	**2a**		quant	<1/>99	−/99
2	**2a**	$(CF_3)_2CHOH$	85	58/42	0/82
3	**2a**	phenol	90	11/89	−/95
4	**2a**	**8a**	46	8/92	−/94
5	**2a**	**8b**	71	44/56	19/77
6	**2a**	**8c**	89	68/32	20/68
7	**2a**	**8d**	78	56/46	23/87
8	**2b**		90	18/82	96/98
9	**2c**		N.P.		
10	**2d**		95	>99/<1	72/−
11[c]	**2d**		97	>99/<1	99/−

[a] All reactions were performed in THF at −30 °C for 12 h by using **1** (0.36 mmol) and **2** (0.30 mmol) in the presence of MS 4Å (100 mg) and a chiral Ca complex prepared from $Ca(O^iPr)_2$ (0.030 mmol) and ligand **6** (0.030 mmol) unless otherwis noted. [b] The reaction time was 3 h. [c] Ligand **7** was used and the reaction temperature was −20 °C. **8a** = *p*-methoxyphenol, **8b** = 2,6-dimethylphenol, **8c** = 2-phenylphenol, **8d** = 2-(2-methoxyphenyl)phenol. N.P. = no desired product.

employed, the 1,4-addition product was obtained with high enantioselectivity (entry 8) but still in low yield. To suppress the intramolecular cyclization further, we conducted the reaction using bis(methylthio)methylene-protected glycine derivative (**2c**). However, the desired reaction did not proceed at all (entry 9). We then planned to control the reaction course by altering the steric properties of the substrates. When a *tert*-butylphenylmethylene glycine derivative (**2d**) was used,[7] the desired 1,4-addition adduct was obtained exclusively with good enantioselectivity (entry 10). Additionally, the use of ligand **7** improved the selectivity, and the desired 1,4-addition adduct was obtained exclusively with excellent enantioselectivity (entry 11). Moreover, to our delight, the product obtained was a single diastereoisomer; notably diastero- and enantioselective 1,4-addition has been attained.

We then investigate the substrate scope of this 1,4-addition reaction, summarized in Table 2. In most cases, the reactions proceeded smoothly to afford the desired glutamic acid derivatives with excellent diastereo- and enantioselectivities. The reaction proceeded even in the presence of 2 mol % catalyst loading (entry 2). Ethyl crotonate (**1b**) also worked well; however, the selectivity was a little lower (entry 3). Methyl or ethyl 2-pentenoate reacted with **2d** smoothly, with excellent yields and enantioselectivities (entries 4 and 5). The reactivity of α,β-unsaturated esters with longer alkyl chains was a little lower, and the reaction of **1e** proceeded slowly, but high selectivity was obtained (entry 6). Branched substrate **1f** also gave the corresponding product in moderate yield with high ee (entry 7). The reaction of **1g**, bearing a benzyloxy group at the terminal position, gave the desired product as a diastereomeric mixture in good yield. The ee

(5) Catalytic asymmetric 1,4-addition reactions: (a) Arai, S.; Takahashi, F.; Tsuji, R.; Nishida, A. *Heterocycles* **2006**, *67*, 495. (b) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (d) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743. (e) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734. (f) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (g) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535. (h) O'Donnell, M. J.; Delgado, F. *Tetrahedron* **2001**, *57*, 6641. (i) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (j) Zhang, F.-Y., Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (k) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.

(6) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364.

(7) (a) Duhamel, L.; Duhamel, P.; Fouquay, S.; Eddine, J. J.; Peschard, O.; Plaquevent, J.-C.; Ravard, A.; Solliard, R.; Valonot, J.-Y.; Vincens, H. *Tetrahedron* **1988**, *44*, 5495. (b) Duhamel, P.; Eddine, J. J.; Valonot, J.-Y. *Tetrahedron Lett.* **1984**, *25*, 2355.

Table 2. Asymmetric 1,4-Addition of **2d** to **1** in the Presence of a Chiral Ca Comlplex Prepared Using Ligand **7**[a]

entry	1	product	yield (%)	dr	ee of **3** (%)
1	**1a**	**3ad**	97	>99:1	99
2[b]	**1a**	**3ad**	93	>99:1	99
3	**1b**	**3bd**	95	>99:1	93
4	**1c**	**3cd**	96	>99:1	96
5	**1d**	**3dd**	97	>99:1	94
6[c]	**1e**	**3ed**	73	>99:1	91
7[d]	**1f**	**3fd**	56	>99:1	82
8	**1g**	**3gd**	82	82/18	96[e]
9	**1h**	**3hd**	94	>99:1	98

[a] All reactions were performed in THF at −20 °C for 12 h by using **1** (0.36 mmol) and **2d** (0.30 mmol) in the presence of MS 4Å (100 mg) and a chiral Ca complex prepared from $Ca(O^iPr)_2$ (0.030 mmol) and ligand **7** (0.030 mmol) unless otherwise noted. [b] 2 mol % of catalyst was used. [c] For 48 h. [d] For 24 h. [e] ee of the major product.

of the major product was excellent. Furthermore, when a crotonamide with *N*-methoxy and *N*-methyl groups (Weinreb amide) was employed, the reaction proceeded smoothly and the desired product was obtained in high yield with excellent diastereo- and enantioselectivity (entry 9).

Transformation of the product **3ad** was conducted as follows (Scheme 2). The imine of **3ad** was easily cleaved by acidic hydrolysis to afford the corresponding amino ester **9** in quantitative yield.[8] Cyclization occurred under neat conditions to afford the lactam **10** in 98% yield. The physical data for product **10** correspond to those previously reported for the 2*R*,3*R* stereochemical relationship.[9] NOE experiments revealed that the protons appended to the stereogenic carbons are *cis* to one another. Further acid treatment of the lactam

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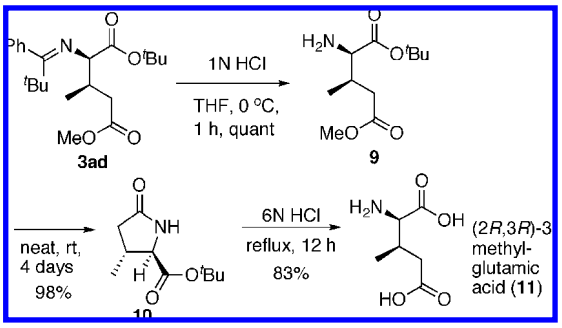
Scheme 2. Transformation to 3-Methylglutamic Acid (**11**)



gave 3-methyl glutamic acid **11** in high yield (physical data corresponds to the reported values).[9]

In summary, we have developed the first diastereo- and enantioselective 1,4-addition of glycine derivatives to α,β-unsaturated esters. A chiral calcium catalyst displayed excellent results for the synthesis of enantiomerically enriched 3-substituted glutamic acids in good ee. The product could be converted to the free glutamic acid derivatives in good yields. Further studies of the catalyst system and its application to other reactions are in progress.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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