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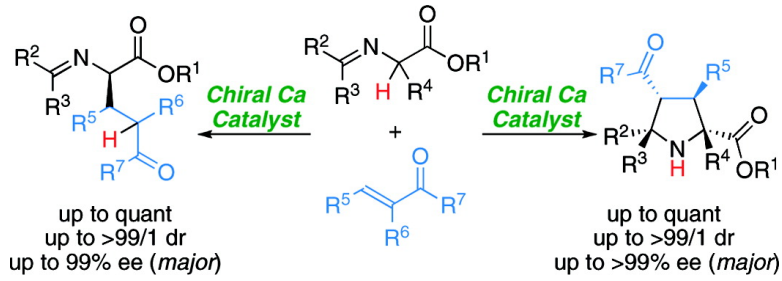

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Development of Catalytic Asymmetric 1,4-Addition and [3 + 2] Cycloaddition Reactions Using Chiral Calcium Complexes

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Abstract: Catalytic asymmetric 1,4-addition and [3 + 2] cycloaddition reactions using chiral calcium species prepared from calcium isopropoxide and chiral bisoxazoline ligands have been developed. Glycine Schiff bases reacted with acrylic esters to afford 1,4-addition products, glutamic acid derivatives, in high yields with high enantioselectivities. During the investigation of the 1,4-addition reactions, we unexpectedly found that a [3 + 2] cycloaddition occurred in the reactions with crotonate derivatives, affording substituted pyrrolidine derivatives in high yields with high enantioselectivities. On the basis of this finding, we investigated asymmetric [3 + 2] cycloadditions, and it was revealed that several kinds of optically active substituted pyrrolidine derivatives containing contiguous stereogenic tertiary and quaternary carbon centers were obtained with high diastereo- and enantioselectivities. In addition, optically active pyrrolidine cores of hepatitis C virus RNA-dependent polymerase inhibitors and potential effective antiviral agents have been synthesized using this [3 + 2] cycloaddition reaction. NMR spectroscopic analysis and observation of nonamplification of enantioselectivity in nonlinear effect experiments suggested that a monomeric calcium species with an anionic ligand was formed as an active catalyst. A stepwise mechanism of the [3 + 2] cycloaddition, consisting of 1,4-addition and successive intramolecular Mannich-type reaction was suggested. Furthermore, modification of the Schiff base structure resulted in a modification of the reaction course from a [3 + 2] cycloaddition to a 1,4-addition, affording 3-substituted glutamic acid derivatives with high diasterero- and enantioselectivities.

Introduction

Group 2 alkaline-earth metals calcium, strontium, and barium are recognized as being among the most abundant elements in the natural world, for example, in the sea or in the earth's crust.[1] While they are familiar to our life, their application to organic synthesis has been limited. Characteristic points of these elements are (1) lower electron negativity, (2) stable oxidation state of 2, which means two covalent bonds with anions are possible, and (3) various coordination sites.[1] Among them, the lower electronegativity is interesting from the viewpoint of synthetic chemistry, because it usually leads to stronger Brønsted basicity of their counteranions. We have recently investigated organic reactions using barium catalysts and found that barium aryl oxides work as excellent catalysts in direct-type aldol and Mannich-type reactions of imides.[2] However, the other alkaline-earth-metal bases, calcium, strontium, and radium, are relatively understudied.[3]

Asymmetric transformations are one of the most important topics in modern organic chemistry,[4] and asymmetric catalysis is of great current interest.[5] In development of highly enantioselective metal catalysts, strict control of the asymmetric environment around the metal bound by chiral ligands is a very important subject. Alkaline-earth metals have a larger ionic radius compared to other elements, such as the transition metals which are often employed in asymmetric catalysis. The metals with larger ionic radius have larger coordination sites, which usually mean that chiral modification of the metals is nontrivial since flexible coordination geometries are possible. Thus, while only very few chiral barium catalysts, including our efforts, have been reported, highly enantioselsctive reactions have not yet been realized. Not only barium bases[6] but also calcium and strontium bases have been less attractive to asymmetric catalysis.[7]

Chiral modification of alkaline-earth-metal catalysts has not been well investigated. In the barium case, previous reports of chiral diol ligands such as BINOL derivatives were used; however, the enantioselectivities have not yet reached sufficient

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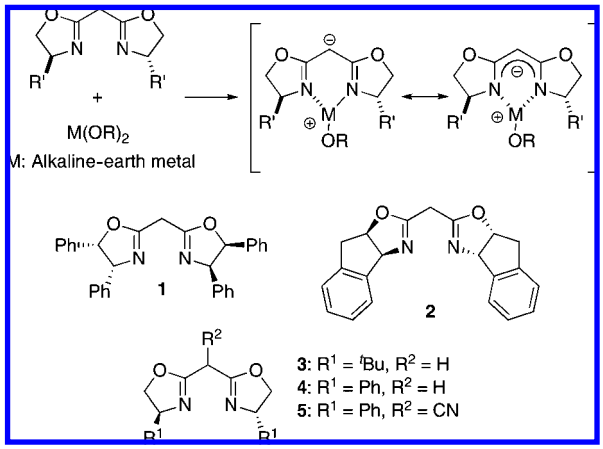
10.1021/ja8032058 CCC: $40.75

Scheme 1. Alkaline-earth-metal complexes prepared from bisoxazolidine ligands.



levels.[6,7] We turned our attention to the chiral bisoxazoline skeleton as a model chiral ligand. Bisoxazoline derivatives are one of the most efficient and often employed chiral ligands in asymmetric catalysis.[8] When the methylene-tethered bisoxazoline ligand (e.g., **1**−**5**) is used, the alkaline-earth-metal base could deprotonate the methylene moiety of the ligand to form a rigid chiral complex where two nitrogen atoms coordinate the metal center in a bidentate fashion (Scheme 1).

Furthermore, the other basic site, the remaining alkoxide, could also deprotonate active protons of substrates to form optically active carbanions. These types of complexes are known in asymmetric carbon−carbon bond forming reactions using stoichiometric amounts of chiral complexes prepared from alkyl zinc or Grignard reagents, although use of these complexes as chiral catalysts has been limited.[9]

Recently, catalytic asymmetric carbon−carbon bond forming reactions using glycine ester derivatives are receiving a lot of attention since they provide efficient synthetic routes to optically pure α-amino acid derivatives.[10] Since the first report on asymmetric alkylation using a chiral phase-transfer catalyst by O'Donnell et al. in 1978,[11] many highly stereoselective reactions have been developed.[10] Among them, asymmetric Michael-type 1,4-addition of Schiff bases of glycine esters to α,β-unsaturated carbonyl compounds provides an efficient route to optically active glutamic acid derivatives.[10] Although some successful examples have been reported in this reaction, excess amounts of bases or substrates are required to realize high conversions in most cases.[12] However, conceptually a catalytic amount of a Brønsted base should work effectively in this reaction. We envisioned that the alkaline-earth metals were suitable for this reaction and started our investigation to develop asymmetric 1,4-addition reactions of glycine derivatives to α,β-unsaturated carbonyl compounds using a chiral-alkaline-earth metal catalyst.[13] In this system, a catalytic amount of a Brønsted base was found to work effectively, which means that this reaction system is highly atom economical. On the other hand, in the course of our research, we found that a [3 + 2] cycloaddition unexpectedly proceeded under similar reaction conditions to afford optically active pyrrolidine derivatives in good to high enentioselectivities. It was revealed that small differences in the substrate structure changed the reaction course dramatically. Here, we describe full details of our investigation into the development of catalytic asymmetric 1,4-additions and catalytic asymmetric [3 + 2] cycloadditions of glycine esters with α,β-unsaturated carbonyl compounds using chiral alkaline-earth-metal−bisoxazoline complexes.

Results and Discussion

We started our examination of the 1,4-addition of *N*-(diphenylmethylidene)glycine *tert*-butyl ester (**7a**) to methyl acrylate (**6a**) in THF using alkaline-earth-metal alkoxides. Except for low activity of the magnesium alkoxide, the calcium, strontium, and barium alkoxides showed good catalytic activity (Table 1). In particular, the strontium and barium alkoxides promoted the reaction smoothly to afford the desired product in high yields. Addition of 5 Å molecular sieves (MS 5Å) was very effective, and the calcium alkoxide catalyst also gave a good yield in a shorter reaction time in the presence of MS 5Å. With those good results in hand, we decided to examine asymmetric 1,4-addition using chiral alkaline-earth-metal catalysts.

In our initial investigation, BINOL derivatives were examined by combining them with calcium isopropoxide; unfortunately,

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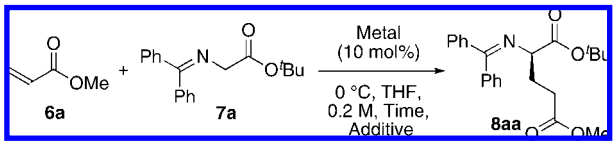
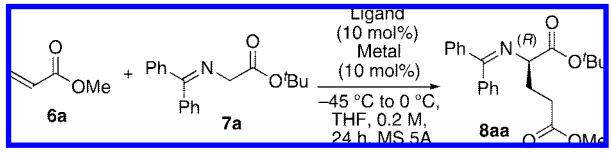
Table 1. Catalytic 1,4-Addition Reaction of Glycine Schiff Base **7a** to Methyl Acrylate (**6a**)



entry	metal	additive[a]	time (h)	yield (%)
1[b]		MS 5Å	24	no reaction
2	$Mg(OPr)_2$		18	trace
3	$Mg(OPr)_2$	MS 5Å	2	no reaction
4	$Ca(O^iPr)_2$		18	16
5	$Ca(O^iPr)_2$	MS 5Å	2	76
6	$Sr(O^iPr)_2$		18	82
7	$Sr(O^iPr)_2$	MS 5Å	2	81
8	$Ba(O^tBu)_2$		18	91
9	$Ba(O^tBu)_2$	MS 5Å	2	95

[a] 100 mg/0.3 mmol. [b] 0 °C (8 h) to room temperature (rt).

Table 2. Asymmetric 1,4-Addition Reaction of **7a** with **6a** Using Chiral Alkaline-Earth-Metal Complexes



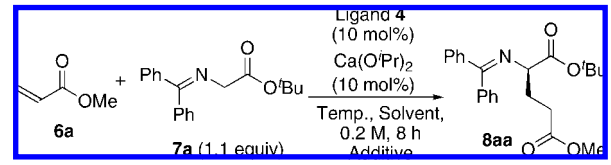
entry	metal	ligand	yield (%)	ee (%)
1	$Mg(OEt)_2$	**1**	no reaction	
2	$Ca(O^iPr)_2$	**1**	39	73[a]
3	$Sr(O^iPr)_2$	**1**	76	29[a]
4	$Ba(O^tBu)_2$	**1**	79	17[a]
5	$Ca(O^iPr)_2$	**2**	24	71
6	$Ca(O^iPr)_2$	**3**	19	6[a]
7	$Ca(O^iPr)_2$	**4**	54	82
8	$Ca(O^iPr)_2$	**5**	31	44

[a] The (*S*)-enantiomer was obtained.

no significant chiral induction was observed. We then conducted the reaction using bisoxazoline (Box) ligand **1** (Table 2). To our delight, the reaction proceeded in moderate to good yields in the presence of the catalysts prepared from alkaline-earth-metal alkoxides and ligand **1**, and a good enantioselectivity was observed in the reaction using calcium isopropoxide (entry 2). While strontium and barium alkoxides showed higher reactivities, enantioselectivities were insufficient (entries 3 and 4). Those results indicated that the metal with smaller ionic radius, calcium, formed a better chiral environment for asymmetric induction in the reaction. Next, other Box ligands were investigated. The Box ligand **2** synthesized from 2-amino-1-indanol showed a little lower selectivity. Among the Box ligands tested, ligand **4** gave the best result (82% ee).

Optimization of the reaction conditions using calcium isopropoxide and ligand **4** was conducted, and the results are summarized in Table 3. The Ca catalyst was prepared by mixing $Ca(O^iPr)_2$ and ligand **4** in THF at room temperature for 15 h in the presence of molecular sieves, and then all volatile materials (THF and ^{i}PrOH) were removed under reduced pressure before the reaction was conducted. First, the effect of the reaction temperature was examined. In the presence of MS 5Å, the yield and selectivity were improved at lower temperature, and high enantioselectivities were obtained at −20 and −30 °C (87% ee, entries 3 and 4). However, the reactivity and selectivity decreased at lower temperature (entries 5 and 6). Molecular sieves were necessary for this reaction; the reaction proceeded

Table 3. Optimization of Reaction Conditions in the 1,4-Addition Reaction[a]



entry	temp (°C)	additive	solvent	yield (%)	ee (%)
1	0	MS 5Å	THF	48	82
2	−10	MS 5Å	THF	56	85
3	−20	MS 5Å	THF	56	87
4	−30	MS 5Å	THF	63	87
5	−45	MS 5Å	THF	46	82
6	−78	MS 5Å	THF	36	80
7	−30	none	THF	6	2
8	−30	MS 3Å	THF	77	83
9	−30	MS 4Å	THF	71	90
10	−30	MS 13X	THF	15	3
11[b]	−30	MS 4Å	THF	70	92
12[b]	−30	MS 4Å	Et_2O	23	14
13[b]	−30	MS 4Å	TBME	20	11
14[b]	−30	MS 4Å	toluene	34	28
15[b]	−30	MS 4Å	CH_2Cl_2	44	23
16[b]	−30	MS 4Å	DME	15	<1
17[b]	−30	MS 4Å	CH_3CN	4	28
18[b,c]	−30	MS 4Å	THF	85	92
19[b−d]	−30	MS 4Å	THF	88	94

[a] The catalyst was prepared at rt for 15 h. [b] The catalyst was prepared at rt for 2 h. [c] The reaction time was 12 h, and 1.2 equiv of the glycine derivative was used. [d] Without removal of ^{i}PrOH in the catalyst preparation step.

sluggishly in their absence (entry 7). MS 3Å to 5Å were generally effective; 90% ee was obtained in the reaction with MS 4Å (entry 9), but MS 13X was not effective (entry 10). The conditions for the catalyst preparation were also examined, and finally it was found that a shorter preparation time gave a slight improvement in selectivity (entry 11). The solvent effect was then studied, and THF was revealed to be the best solvent for this reaction. Surprisingly, almost all other solvents investigated gave disappointing results (entries 12−17). For further improvement of the yield, use of a slightly excess amount of the glycine derivative over a longer reaction time gave a higher yield (entry 18). Moreover, removal of THF and ^{i}PrOH from the catalyst system was found not to be necessary at the catalyst preparation stage, and finally the enantiomeric excess reached 94% under optimized reaction conditions (entry 19).

Next, we investigated the substrate scope of this asymmetric 1,4-addition reaction (Table 4). The effect of the ester parts of the Schiff bases was examined in the reaction with methyl acrylate (**6a**). While the methyl and ethyl (**7b**) esters showed higher reactivity, enantioselectivity was lower than the reaction using the *tert*-butyl ester (entries 1 and 2). The ester part of the acrylate was also examined. Ethyl acrylate (**6b**) and *tert*-butyl acrylate (**6c**) reacted with the Schiff base to afford the desired products in moderate to good yields with high selectivities (entries 3 and 4). The acrylamide **6d** with a methoxy group on the N atom (Weinreb amide)[14] also reacted with good enantioselectivity (entry 5). Next, the effect of substituents at the 2-position of the acrylates was investigated.[15] The reaction of 2-methylacrylate **6e** with the glycine ester proceeded smoothly

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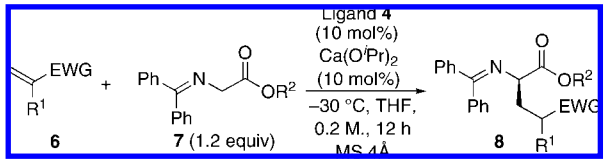
(15) Stereoselective synthesis of 4-substituted glutamic acid derivatives: Belokon, Y. N.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 12860.

Table 4. Substrate Scope of the 1,4-Addition Reactions



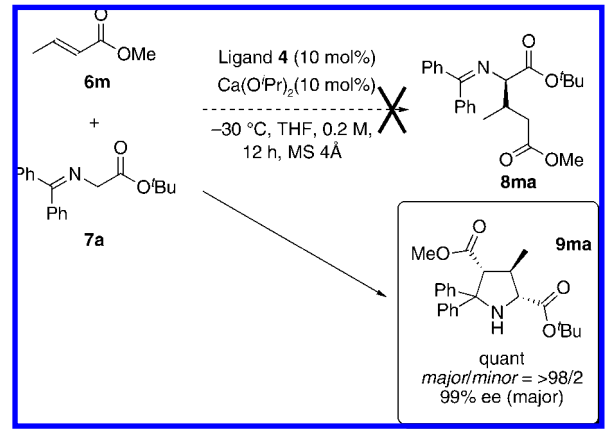
entry	R^1	EWG	R^2	product	yield (%)	2,4-*syn*/*anti*	ee (%)
1	H	CO_2Me	^{t}Bu	**8aa**	88		94
2	H	CO_2Me	Me	**8ac**	quant		83
3[a,c]	H	CO_2Et	^{t}Bu	**8ba**	56		95
4[a,c]	H	$CO_2{}^t$Bu	^{t}Bu	**8ca**	74		92
5[a]	H	CONMeOMe	^{t}Bu	**8da**	46		87
6[b]	Me	CO_2Me	^{t}Bu	**8ea**	93	61/39	99[d]/94[e]
7	Et	CO_2Me	^{t}Bu	**8fa**	quant	63/37	86[d]/91[e]
8	^{i}Pr	CO_2Me	^{t}Bu	**8ga**	81	55/45	92[d]/80[e]
9	^{t}Bu	CO_2Me	^{t}Bu	**8ha**	quant	67/33	90[d]/86[e]
10[a]	Ph	CO_2Me	^{t}Bu	**8ia**	quant	91/9	84[d]
11[a]	Cl	CO_2Me	^{t}Bu	**8ja**	95	83/17	81[d]
12[a,c]	Me	CONMeOMe	^{t}Bu	**8ka**	83	91/9	85[d]
13	H	SO_2Ph	^{t}Bu	**8la**	43		52

[a] 24 h. [b] **7a** (1.5 equiv) was used. [c] **6k** (1.5 equiv) was used. [d] ee of the major product. [e] ee of the minor product.

to afford two diastereomers in high yield with moderate diastereoselectivity and excellent enantioselectivities (entry 6). 2-Ethylacrylate **6f**, 2-isopropylacrylate **6g**, and 2-isobutylacrylate **6h** reacted smoothly with high enantioselectivities (entries 7−9). It was found that the size of the substituents at the 2-position of the acrylates affected the diastereoselectivity; substrates with larger groups, 2-phenylacrylate **6i** and 2-chloroacrylate **6j**, showed higher *syn*/*anti* ratios (entries 10 and 11). 2-Methylacrylamide **6k** with an *N*-methoxy group reacted with the glycine Schiff base **7a** to afford the 1,4-addition product in high yield with high diastero- and enantioselectivity (entry 12). Phenyl vinyl sulfone (**6l**) also worked as an acceptor to afford the desired 1,4-adduct in moderate yield and selectivity (entry 13). In general, it was revealed that asymmetric 1,4-addition of glycine esters to acrylate derivatives proceeded well with high enantioselectivities.

Next we planned the asymmetric 1,4-addition reactions of crotonates using the chiral calcium catalyst. Successful diastereo- and enantioselective 1,4-addition of glycine enolates to crotonates has not yet been reported.[16] When the glycine *tert*-butyl ester **7a** was treated with methyl crotonate (**6m**) under the optimized reaction conditions, the reaction proceeded and the starting material was consumed rapidly; however, the desired 1,4-addition product **8ma** was not obtained, but a substituted pyrrolidine derivative (**9ma**) as a single diastereomer unexpectedly resulted. The structure was unambiguously determined by X-ray crystallographic analysis.[13] Moreover, the enantioselectivity of the product was extremely high. The structure of the

Scheme 2. Unexpected Highly Stereoselective [3 + 2] Cycloaddition Reaction



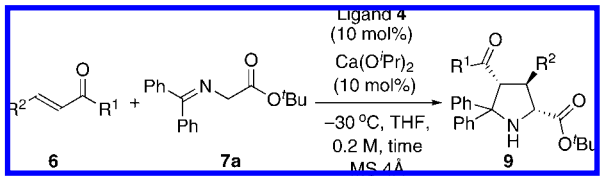
product indicated that [3 + 2] cycloaddition proceeded with high diastereo- and enantioselectivity (Scheme 2). This result is remarkable since only one small structural difference, hydrogen or methyl, on the terminal position of the acrylate determined the reaction course decisively.

This interesting finding prompted us to investigate catalytic asymmetric [3 + 2] cycloaddition of glycine esters using the chiral calcium catalyst.[17] At the outset, the ester part of the crotonates was examined. It was found that substrates with larger ester groups also reacted to afford the products, but the yields and selectivities decreased (Table 5, entries 1−3). Notably, the chiral calcium catalyst worked well at only 0.1 mol % loading (entry 1). Other β-substituted acrylates reacted in high enantioselectivities (entries 4−6). Not only crotonates and their derivatives but also acrylamides afforded [3 + 2] cycloadducts **9** in good yields with very high enantioselectivities (entries 7−9). Substrates with bulkier amide substituents showed slightly lower selectivities (entry 10). It is noted that single diastereoisomers were obtained in all cases and that this is a rare example

(16) (a) Stereoselective synthesis of 3-substituted glutamic acid derivatives: Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341. Other representative examples: (b) Mauger, A. B. *J. Org. Chem.* **1981**, *46*, 1032. (c) Achqar, A. E.; Boumzebra, M.; Roumestant, M, L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (d) Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301. (e) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875. (f) Alvarez-Ibarra, C.; Csákÿ, A. G.; Maroto, M.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 6700. (g) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron* **1999**, *55*, 12031. (h) Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1999**, *64*, 6554. (i) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747. (j) Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217. (k) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296.

(17) For some recent reviews and examples on catalytic asymmetric [3 + 2] cycloaddion reactions see: (a) Padwa, A.; Pearson, W. H. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; John Wiley & Sons: New York, 2002. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (d) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (e) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (f) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043. (g) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569. (h) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241. (i) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047. (j) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. (k) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. Syntheses of quaternary carbon centers in asymmetric [3 + 2] cycloaddition reactions: (l) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (m) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (n) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (o) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587. (p) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025. (q) Fukuzawa, S.-i.; Oki, H. *Org. Lett.* **2008**, *10*, 1747. Intramolecular symmetric [3 + 2] cycloadditon reaction: (r) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. Organocatalytic asymmetric [3 + 2] cycloaddition reactions: (s) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (t) Xue, M.-X.; Zang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691.

Table 5. Asymmetric [3 + 2] Cycloaddition of **7a** to Crotonates and Acrylamides



Entry	R^1	R^2	Time (h)	Product	Yield (%)	Ee (%)
1	OMe	Me	3	**9ma**	quant (quant)[a]	>99 (93)[a]
2	OEt	Me	3	**9na**	98	98
3	O^{t}Bu	Me	3	**9oa**	77	87
4[b]	OMe	Et	24	**9pa**	quant	95
5[b]	OMe	^{t}Bu	24	**9qa**	quant	99
6[b]	OMe	Heptyl	48	**9ra**	97	>99
7	NMe_2	H	12	**9sa**	83	95
8	 X = O	H	24	**9ta**	76	98
9	X = CH_2	H	24	**9ua**	84	97
10	NCy_2	H	24	**9va**	93	91

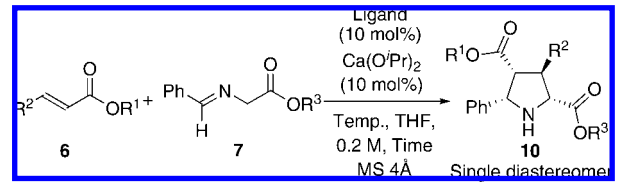
[a] 0.1 mol % catalyst. The reaction was carried out at 20 °C for 72 h. Ligand **2** was used. The 1,4-adduct was observed in the isolated product (3%). The detailed experimental procedure is given in the Supporting Information. [b] Ligand **2** was used.

of highly stereoselective [3 + 2] cycloaddition of *N*-diphenylmethylene-protected glycine derivatives.[18]

We then conducted the reactions of the aldimines of glycine esters **7** with α,β-unsaturated carbonyl compounds **6**. When the benzaldehyde imine **7d** derived from glycine *tert*-butyl ester was treated with methyl acrylate in the presence of the calcium catalyst prepared from Ca(O^{i}Pr)$_2$ and ligand **4**, the reaction proceeded at −30 °C to afford the cycloadduct **10ad** in good yield but with moderate ee (entry 1, Table 6), and no 1,4-addition product was obtained. Bulkier ester parts of the substrates showed higher enantioselectivies (entries 2 and 3). Interestingly, almost the same selectivity was obtained in the reactions at −30 and 0 °C (entry 4). Next, the effect of the ligand structure was investigated. While the Box ligand **3** with a *tert*-butyl group gave no chiral induction (entry 5), ligand **2** showed almost the same yield with a slightly lower enaniose-lectivity (entry 6). The yield was improved at 10 °C with almost the same selectivity (entry 7). We then examined the reactions of crotonate derivatives. It was found that bulkier substrates were also effective to get higher selectivity and that the enantioselectivity reached 86% ee when *tert*-butyl esters were employed (entry 11). Ethyl cinnamate was also employed; however, the ee was moderate (entry 12). It is noted again that single diastereomers were obtained in all these cases.

Next, the substrate scope of the imine part of the glycine ester **7** was examined (Table 7). In this reaction, ligand **4** as well as ligands **1** and **2** worked well. Halogen-substituted aromatic imines reacted smoothly to afford the cycloadducts in good selectivites (entries 2 and 3). In addition, the effect of the substitution positions was examined, and among the tolyl substrates, the *meta*-substituted one gave the highest enantiose-

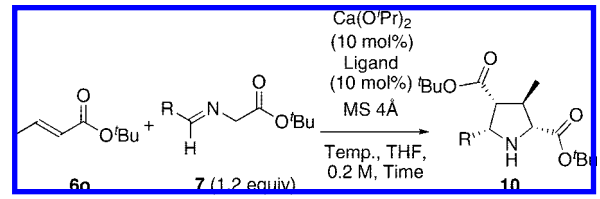
Table 6. Asymmetric [3 + 2] Cycloaddition of Glycine Schiff Bases **7** with α,β-Unsaturated Esters **6**



entry	R^1	R^2	R^3	ligand	conditions	product	yield (%)	ee (%)
1	Me	H	Me	**4**	−30 °C, 3 h	**10ad**	73	46[a]
2	^{t}Bu	H	Me	**4**	−30 °C, 3 h	**10cd**	78	66[a]
3	^{t}Bu	H	^{t}Bu	**4**	−30 °C, 3 h	**10ce**	92	76
4	^{t}Bu	H	^{t}Bu	**4**	0 °C, 3 h	**10ce**	92	76
5	^{t}Bu	H	^{t}Bu	**3**	0 °C, 12 h	**10ce**	32	1
6	^{t}Bu	H	^{t}Bu	**2**	0 °C, 12 h	**10ce**	78	66
7	^{t}Bu	H	^{t}Bu	**4**	10 °C, 3 h	**10ce**	98	76
8	Me	Me	Me	**4**	10 °C, 3 h	**10md**	67	39
9	^{t}Bu	Me	Me	**4**	10 °C, 3 h	**10od**	86	70
10	Me	Me	^{t}Bu	**4**	10 °C, 3 h	**10me**	89	84
11	^{t}Bu	Me	^{t}Bu	**4**	10 °C, 3 h	**10oe**	86	86
12	Et	Ph	^{t}Bu	**4**	10 °C, 3 h	**10we**	91	61

[a] The absolute configuration is (2*R*,4*R*,5*S*).

Table 7. Asymmetric [3 + 2] Cycloaddition of Various Glycines



entry	R	ligand	conditions	product	yield (%)	ee (%)
1[a]	Ph	**4**	10 °C, 3 h	**10oe**	86	86
2	*p*-ClC_6H_4	**2**	−20 °C, 8 h	**10of**	92	82
3	*p*-BrC_6H_4	**4**	10 °C, 3 h	**10og**	95	86
4	*p*-MeC_6H_4	**1**	−30 °C, 12 h	**10oh**	92	87[b]
5	*m*-MeC_6H_4	**2**	−20 °C, 12 h	**10oi**	quant	91
6	*o*-MeC_6H_4	**4**	10 °C, 3 h	**10oj**	86	78
7	3,5-$(Me)_2C_6H_3$	**4**	10 °C, 12 h	**10ok**	quant	94
8	2-naphthyl	**4**	10 °C, 3 h	**10ol**	97	92
9	*p*-$MeOC_6H_4$	**4**	10 °C, 12 h	**10om**	76	86
10	2-furyl	**1**	−30 °C, 12 h	**10on**	97	90[b]
11	^{t}Bu	**2**	−20 °C, 12 h	**10oo**	80	38
12	Cy	**2**	−20 °C, 12 h	**10op**	97	29

[a] A 1.1 equiv sample of glycine ester was used. [b] The absolute configuration of the product was reversed.

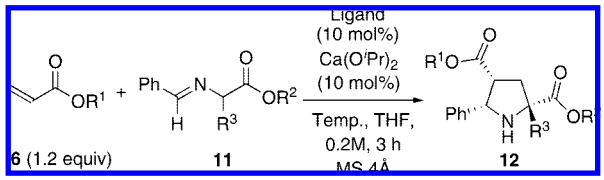
lectivities (entries 4−6). Bulkier imines showed higher selectivities, and the enantiomeric excess reached 94% when an imine prepared from the 3,5-xylene derivative was used (entry 7). An electron-rich imine also gave good enantioselectivity using ligand **4** (entry 9), while a 2-furaldehyde-derived imine also gave high ee using ligand **1** (entry 10). On the other hand, cyclohexanecarboxyaldehyde- and pivaldehyde-derived imines showed lower selectivities (entries 11 and 12). It should be noted that these reactions are the first successful examples of the asymmetric [3 + 2] cycloaddition of crotonates.[19]

The fact that the aldimines reacted with *tert*-butyl crotonate (**6o**) in a [3 + 2] cycloaddition manner in high yields with perfect diastereoselectivities and high enantioselectivities encouraged us to investigate the synthesis of pyrrolidine derivatives with chiral quaternary carbon centers.[17l−q] On the basis of our

(18) For an example of a [3 + 2] cycloadditon reaction using *N*-diphenylmethylene-protected glycine, see ref 17m, o.

(19) For an example of a [3 + 2] cycloaddition reaction using crotonate, see ref 17l.

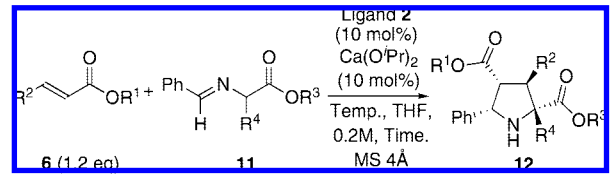
Table 8. Asymmetric [3 + 2] Cycloaddition of Schiff Bases Derived from α-Amino Acids



entry	R^1	R^2	R^3	ligand	temp (°C)	product	yield (%)	ee (%)
1	Me	Me	Me	**4**	10	**12aa**	95	70
2[a]	^{t}Bu	Me	Me	**4**	10	**12ca**	quant	90
3	^{t}Bu	Et	Me	**4**	10	**12cb**	quant	91
4	^{t}Bu	Bn	Me	**4**	10	**12cc**	93	90
5[a]	^{t}Bu	Me	Et	**2**	−30	**12cd**	82	96
6[a]	^{t}Bu	^{t}Bu	Bn	**2**	−30	**12ce**	90	92
7[a]	^{t}Bu	Me	^{n}Bu	**2**	−20	**12cf**	94	94
8[a]	^{t}Bu	Me	^{i}Bu	**2**	−30	**12cg**	98	87
9	^{t}Bu	Me	^{i}Pr	**4**	10	**12ch**	32	59
10[a]	^{t}Bu	Me	CH_2CH_2SMe	**2**	−20	**12ci**	81	81
11[a,b]	^{t}Bu	^{t}Bu	CH_2O^tBu	**2**	−20	**12cj**	80	93

[a] 12 h. [b] The L-amino acid was used.

Table 9. Asymmetric Synthesis of Contiguous Tertiary and Quaternary Carbon Centers



entry	R^1	R^2	R^3	R^4	conditions	product	yield (%)	ee (%)
1	Me	Me	Me	Me	0 °C, 12 h	**12ma**	79	96
2	Et	Me	Me	Me	10 °C, 24 h	**12na**	55	93
3	Me	Et	Me	Me	0 °C, 12 h	**12pa**	64	96
4[a]	Me	^{n}Bu	Me	Me	0 °C, 18 h	**12ya**	81	98
5	Me	Me	Me	Et	−20 °C, 24 h	**12md**	41	89
6[a]	Me	Me	Me	^{n}Bu	−30 °C, 72 h	**12nf**	50	93
7[a]	Me	Me	^{t}Bu	Bn	−30 °C, 72 h	**12me**	98	85
8[b]	Me	Me	^{t}Bu	CH_2O^tBu	10 °C, 24 h	**12mj**	80	97
9[a,b]	Me	^{i}Bu	^{t}Bu	CH_2O^tBu	0 °C, 24 h	**12qj**	87	95

[a] Catalyst (20 mol %) was used. [b] The L-amino acid derivative was used.

working model, a calcium enolate formed in the reaction of the glycine ester with calcium isopropoxide, where the nitrogen atom of the enolate could coordinate to the calcium atom, resulting in bidentate coordination. Therefore, it was assumed that the substituent at the α-position of the enolate would not significantly affect the asymmetric environment. In addition, since the bulkiness of the imine part improved the enantioselectivity in the earlier system, we envisioned that introduction of appropriate steric bulk at the α-position of the enolate might improve the enantioselectivity.

First, we investigated the reactions of alanine derivatives with α,β-unsaturated carbonyl compounds. The benzilidene-protected alanine methyl ester reacted with methyl acrylate to afford the desired [3 + 2] adduct **12aa** in good enantioselectivity (Table 8, entry 1). In this reaction, bulkier ester parts also gave better effects, and the highest enantioselectivity was obtained using *tert*-butyl acrylate (entry 2). In contrast, the selectivity did not depend on the structure of the alanine ester part (entries 2−4). Amino acid esters with simple alkyl substituents on their α-positions were also investigated (entries 5−9). 2-Ethylglycine, phenylalanine, norleucine, and leucine derivatives also gave good to high selectivities, although the valine derivative did not work well presumably due to a steric factor (entry 9). We also investigated the reactions of the amino acid derivatives with α-substituents containing heteroatoms. Methionine and *O*-*tert*-butylserine derivatives also worked well, and good to high enantioselectivities were obtained (entries 10 and 11). In all cases, single diastereomers were obtained exclusively. It is noted that this method is superior to other previous chiral pyrrolidine syntheses[17] via asymmetric [3 + 2] cycloaddition in terms of yields and diastereo- and enantioselectivities and that chiral quaternary carbon centers have been constructed efficiently.

As a more challenging trial, we further investigated asymmetric synthesis of pyrrolidine derivatives containing contiguous chiral tertiary and quaternary carbon centers. This kind of complex molecule is usually difficult to synthesize, especially in an enantiomerically pure form, since steric bulk around the reaction site often prevents strict enantioselection.[20] First, the reaction of an alanine derivative with crotonates was examined. Remarkably, the desired reaction proceeded smoothly to afford the desired pyrrolidine derivatives as single diastereomers in moderate to good yields with excellent enantioselectivity (Table 9, entries 1 and 2). Longer chain α,β-unsaturated esters methyl 2-pentenoate and methyl 2-heptenoate also reacted with the alanine derivative, and excellent enantioselectivities were obtained (entries 3 and 4). Next we studied the reactions of α-substituted α-amino acid esters. In the reaction of 2-ethylglycine derivative **11d**, a moderate yield with high enantioselectivity was observed (entry 5). On the other hand, the reactions of amino esters with larger substituents proceeded slowly, and high enantioselectivities were also obtained (entries 6 and 7). Interestingly, an amino ester derived from a bulky serine derivative reacted with α,β-unsaturated esters to afford the desired products in good yields with excellent enantioselectivities (entries 8 and 9). These results clearly showed that the chiral calcium catalysts can construct highly sterically hindered and complicated carbon centers directly with high stereoselectivities. This is one of the remarkable features of this chiral calcium catalyst compared to other chiral catalyst systems reported previously in asymmetric [3 + 2] cycloaddition.[17]

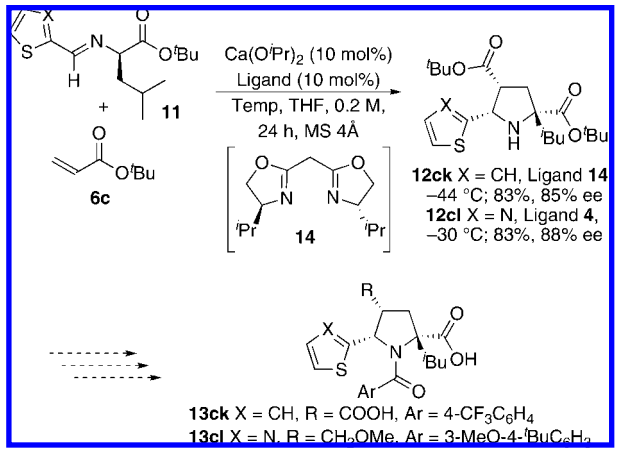
As discussed, the present catalytic asymmetric [3 + 2] cycloaddition reactions have a wide substrate scope with high diastereo- and enantioselectivities. We then decided to synthesize optically active pyrrolidine cores of biologically active compounds using this [3 + 2] cycloaddition reaction. Compounds **13ck** and **13cl** are hepatitis C virus RNA-dependent polymerase inhibitors and potential effective antiviral agents,[21] and quite recently, two groups have reported asymmetric total syntheses of these compounds.[22] However, their methods were not necessarily satisfactory in terms of efficiency, especially a stoichiometric use of a chiral source or moderate enantioselectivity. We conducted the [3 + 2] cycloaddition reaction of **11k**

(20) Syntheses of contiguous chiral tertiary and quaternary carbon ceters using β-substituted acrylates were not reported, but those using maleimides were reported; see ref 17m,o,p.

(21) (a) Slater, M. J.; et al. *J. Med. Chem.* **2007**, *50*, 897. (b) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenan, R. M.; Dhanak, D. *Bioorg, Med. Chem. Lett.* **2005**, *15*, 1553. (c) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Hofmann, G. A.; Slater, M. J.; Haigh, D.; Dhanak, D.; Johnson, V. K.; Parry, N. R.; Thommes, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930.

(22) (a) Nájera, C.; de Gracia Retamosa, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2007**, 5038. (b) Agbodjan, A. A.; et al. *J. Org. Chem.* **2008**, *73*, 3094.

Scheme 3. Syntheses of Pyrrolidine Derivatives Containing a Heteroaromatic Ring

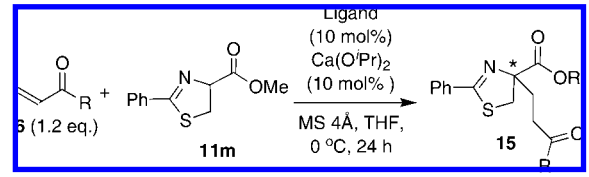


or **11l**, which contained heteroaromatic moieties, in the presence of the chiral calcium catalyst. It was found that under optimized reaction conditions the desired products were obtained in high yields with perfect diastereoselectivities and high enantioselectivities (Scheme 3). It was shown that our method was a powerful tool for construction of these kinds of pyrrolidine compounds in optically active form.

We also applied the calcium catalyst system to the synthesis of 1,4-addition products containing a chiral quaternary carbon center. α-Alkylcysteines are recognized as important building blocks for biologically active peptide mimics, and asymmetric synthesis of these compounds is valuable in medicinal chemistry and pharmaceutical sciences.[23] However, few reports concerning efficient synthesis of chiral α-alkylcysteines by asymmetric 1,4-addition reactions have appeared.[24] We tested the chiral calcium system in the 1,4-addition reaction. A Schiff base (**11m**) derived from cysteine was employed as a substrate, and the reaction with methyl acrylate (**6a**) proceeded smoothly to afford the desired product **15am** with high enantioselectivity in the presence of a 10 mol % concentration of the calcium catalyst prepared from ligand **1** or **4** (Table 10, entries 1 and 2). Other acrylic esters and acrylamides also reacted in good to high yields with high enantioselectivities (entries 3 and 4).

Reaction Mechanism. 1. Catalyst Structure. We assume that the calcium metal is coordinated by the chiral ligand in a covalent fashion via deprotonation of the tethering methylene moiety in the resulting calcium complexes.[25] This complex should be completely different from a *gem*-dimethyl-tethered Box complex. To confirm this assumption, we conducted the reaction of **6a** with **7a** in the presence of $Ca(O^iPr)_2$ and Box ligands **16** with dialkyl groups (no tethered methylene moiety). It was found that the reactions proceeded sluggishly, and very low enantioselectivities were obtained (Scheme 4). These results clearly showed that the active catalyst required the nonsubstituted methylene moiety and could support the assumption that the ligand coordinated to the calcium in an anionic manner via deprotonation.

Table 10. Asymmetric 1,4-Addition Reactions of Cysteine Derivative **11m**



entry	R	ligand	product	yield (%)	ee (%)
1	OMe	**1**	**15am**	83	86
2	OMe	**4**	**15am**	77	86[a]
3	O^{t}Bu	**1**	**15cm**	66	83
4	NMeOMe	**1**	**15dm**	71	80

[a] The absolute configuration of the product was reversed compared to that of the other entries.

Scheme 4. Asymmetric 1,4-Addition Reaction Using Calcium Bisoxazolidine **16**

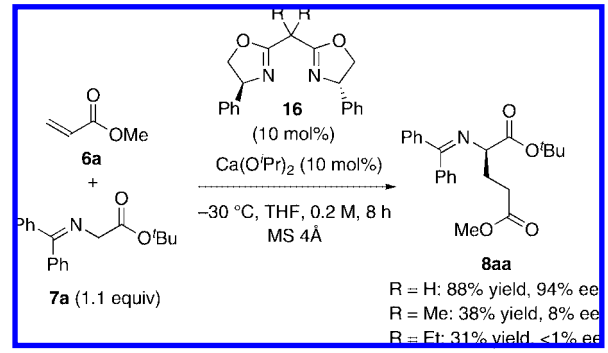
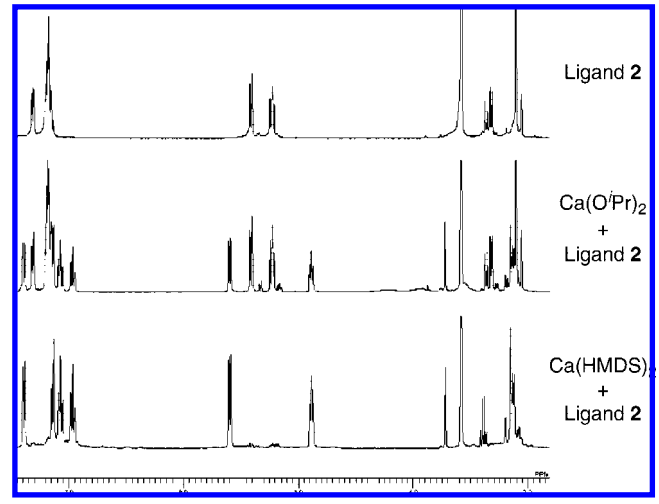


Chart 1. ^{1}H NMR Analysis of a Calcium Complex Prepared from Ligand **2**

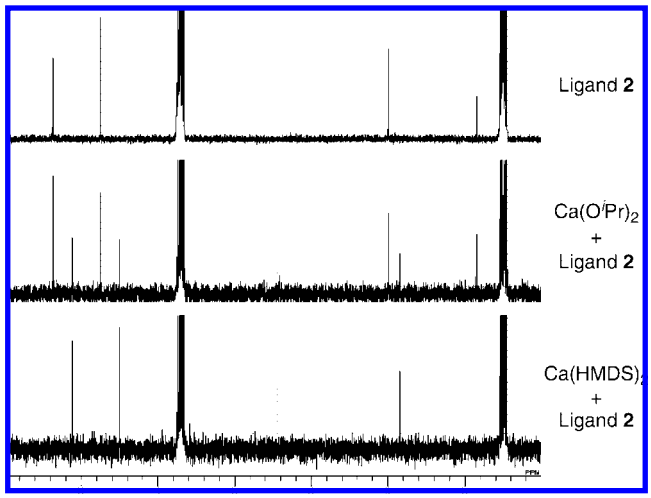


To obtain further information on the catalyst structure, we conducted NMR spectroscopic experiments on this calcium complex. At first, a catalyst solution prepared from $Ca(O^iPr)_2$ and ligand **2** in THF-d_8 was analyzed by ^{1}H and ^{13}C NMR. Expectedly, a pair of peaks appeared in the spectra shown in Charts 1 and 2, and the chemical shifts of the peaks were reasonable compared to the data of reported anionic metal species.[9i] The peaks observed were the same as to those

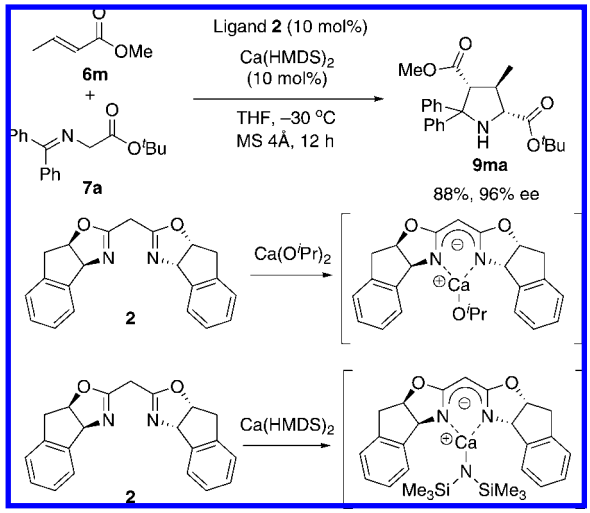
(23) Goodman, M.; Ro, S. In *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1995; Vol. 1, Chapter 20, pp 803−861.

(24) Asymmetric alkylation of a cysteine Schiff base has been reported: (a) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *J. Org. Chem.* **2006**, *71*, 8276. Other related works: (b) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382. (c) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *Org. Lett.* **2005**, *7*, 3207. (d) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557.

Chart 2. ^{13}C NMR of a Calcium Complex Prepared from Ligand **7**



Scheme 5. Asymmetric [3 + 2] Cycloaddition Using a Chiral Ca−HMDS Complex



observed in NMR analysis of a complex prepared from calcium bis(trimethylsilyl)amide ($Ca(HMDS)_2$)[25b,c] and ligand **2**.

We also investigated the asymmetric [3 + 2] cycloaddition reaction using the chiral Ca−HMDS complex (Scheme 5). The reaction proceeded well and provided the desired adduct in high yield with high enantioselectivity. This result also supports the assumption that ligand **2** coordinated to the calcium in an anionic manner, and we assured the structures of the active calcium catalysts are those shown in Scheme 5.[25h]

Next we investigated an aggregation state of the active calcium species. It is known that calcium−diimine complexes form dimeric structures easily in solution.[25] While measurements of the molecular

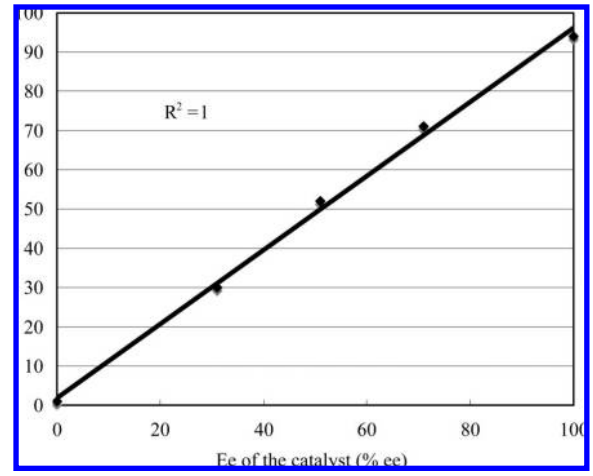
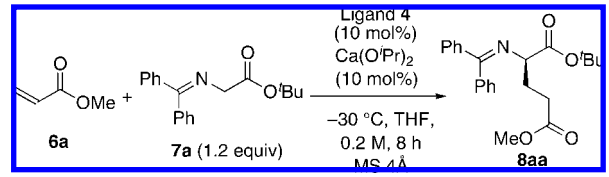


Figure 1. Relationship between the optical purity of the ligand and the ee of the product.

Table 11. Relationship between the Optical Purity of the Ligand and the ee of the Product



entry	ligand ee (%)	yield (%)	ee (%)
1	>99	88	94
2	71	84	71
3	51	91	52
4	31	80	30
5	0	85	1

weight of the calcium complexes using **1**, **2**, and **4** were not successful, we examined the relationship between the product ee and the optical purity of the ligand.[26] The results are shown in Table 11 and Figure 1. No nonlinear effect was observed, and the same reactivity was obtained when a racemic ligand was used. These results might suggest that the calcium catalyst worked as a monomeric species without significant aggregation to afford the desired product in high enantioselectivity.

2. Reaction Course and Catalytic Cycle. A possible mechanism of the calcium-catalyzed asymmetric 1,4-addition is shown in Figure 2. The chiral calcium complex deprotonated the α-position of the glycine derivative **7** to form a chiral calcium enolate (**1B**), in which the imine nitrogen also coordinated to the calcium atom. The enolate then reacted with an α,β-unsaturated carbonyl compound (**6**) with high enantioselection to form the 1,4-addition product initially as a calcium enolate (**1C**). Further, the enolate **1C** was protonated with glycine derivative **7** to afford the product **8** along with regeneration of the reactive calcium enolate **1B** (pathway 1). Alternatively, the free alcohol ^{i}PrOH quenched **1C** to give **8** and the active calcium complex **1A** (pathway 2).

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(26) Girard, V.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.

(27) (a) Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudziński, J. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2525. (b) Neumann, F.; Lambert, C.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1998**, *120*, 3357. (c) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (d) Zubia, A.; Mendoza, L.; Vivanco, S.; Aladaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vana-clocha, F.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2903.

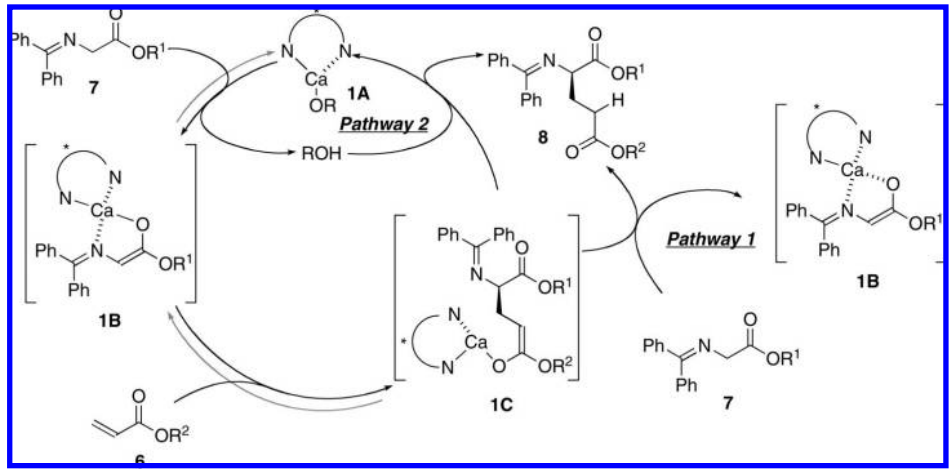
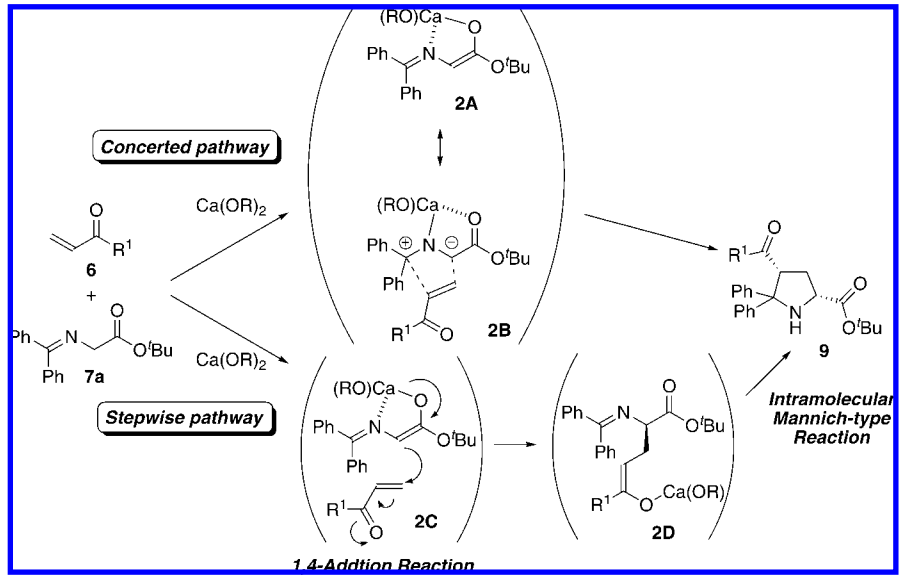


Figure 2. Catalytic cycle of the 1,4-addition reaction.

Scheme 6. Two Possible Reaction Mechanisms of the [3 + 2] Cycloaddition Reaction

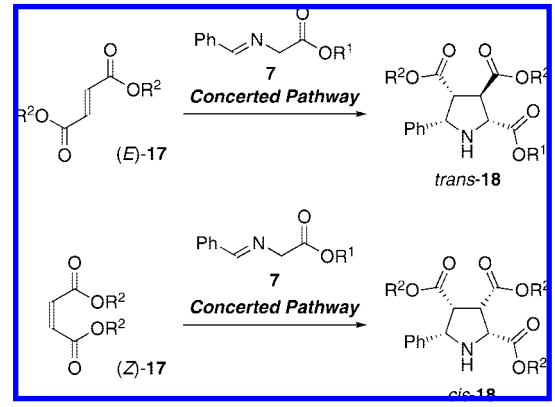


On the other hand, two reaction mechanisms are possible for the [3 + 2] cycloaddition reaction; either a concerted or a stepwise pathway is plausible (Scheme 6). Until now, few mechanistic studies of the reaction have been reported; for example, Kanemasa et al. reported that the [3 + 2] cycloaddition of a lithium enolate of a glycine derivative to α,β-unsaturated carbonyl compounds proceeded in a stepwise mechanism on the basis of their computational study.[27a] Other groups have also described that reactions of glycine enolates with electron-deficient olefins proceeded in a stepwise mechanism.[27b−d]

First, we compared the absolute configuration of the 1,4-adduct **8aa** and the [3 + 2] cycloadduct **9ma**. It was found that the absolute configurations of the stereogenic carbons at the 2-positions of both products were the same, which indicated that the activated olefin approached the calcium enolate from the same face. Next we investigated the reactions of fumaric diester (*E*)-**17** and maleic diester (*Z*)-**17** in the [3 + 2] cycloaddition. If the reaction were to proceed via the concerted mechanism, only two diastereomers would be formed; namely, (*E*)-**17** would give a *trans* product, while (*Z*)-**17** would give a *cis* product (Scheme 7).

When (*E*)-**17a** was treated with **7e** in the presence of $Ca(O^iPr)_2$ (10 mol %) and ligand **4** (10 mol %), the reaction

Scheme 7. [3 + 2] Cycloaddition with Fumaric or Maleic Esters



proceeded to afford only *trans* diastereomers (*trans*-**18ae**), and the enantioselectivity of the major product was moderate. On the other hand, the reaction with (*Z*)-**17a** gave the products as a *cis* and *trans* mixture with moderate enantioselectivities (Scheme 8). In the reaction system, isomerization of (*Z*)-**17a** to (*E*)-**17a** was not observed by TLC analysis. These results support the assumption that the reactions proceeded via a

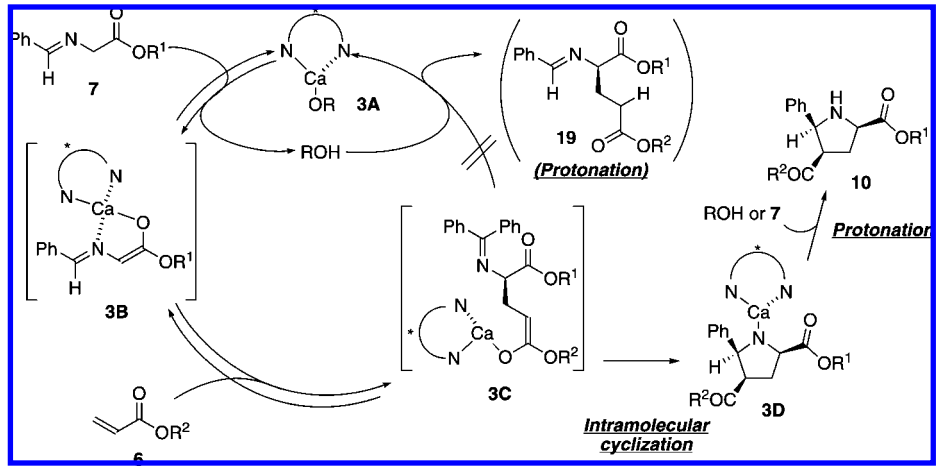


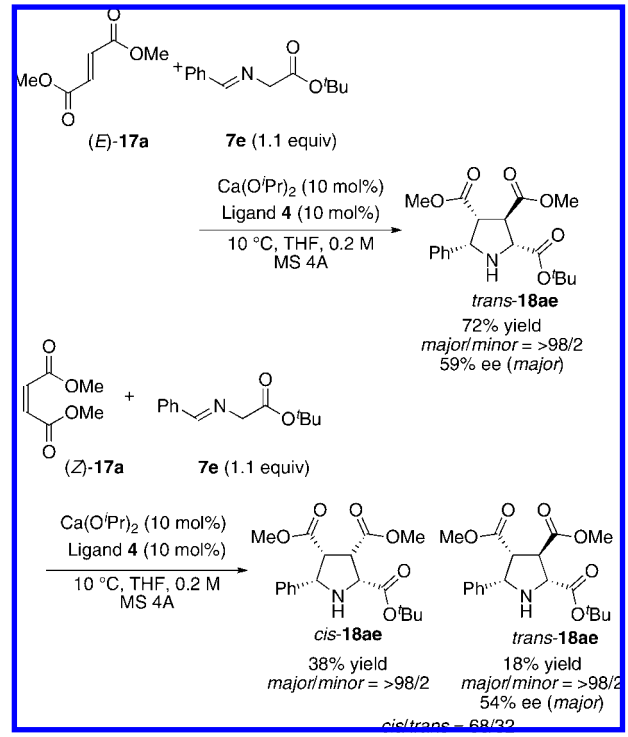
Figure 3. Proposed catalytic cycle of the [3 + 2] cycloaddition reaction.

stepwise mechanism, and a proposed catalytic cycle is shown in Figure 3. The enolate intermediate **3C** generated by the initial 1,4-addition would attack the imine part of the same molecule to form a pyrrolidine derivative with high stereoselectivity.

On the basis of this mechanism, we can reasonably explain these interesting results. As we have already described, acrylates gave 1,4-adducts exclusively with high enantioselectivity (Table 4), while acrylamides gave [3 + 2] cycloadducts exclusively (Table 5). The major difference between these reactions is only the structure of the ester or amide part. Also the reactions of aldehyde-protected glycine derivatives **7d**−**p** gave only [3 + 2] cycloadducts (Tables 6 and 7). We could explain these results by assuming a stepwise mechanism mainly based on the reactivity of the enolate intermediate in the second cyclization step. In the reactions of benzophenone derivatives of glycine **7a**−**c**, the nucleophilicity of the generated enolate intermediates toward the ketimine part is an important factor. The amide enolates formed by the reactions of acrylamides are more reactive than the ester enolates formed by the reactions of acrylates to afford the cyclic adducts. The ester enolates are less reactive and are protonated by the substrates or the free alcohol in the reaction system to afford the 1,4-addition products. In the cases of the aldehyde-protected glycine derivatives **7**, the reactivity of the aldimine part is higher than that of the ketimine part, and therefore, the less reactive acrylate-derived enolates could attack the imine to give the [3 + 2] cycloaddition products **10**.

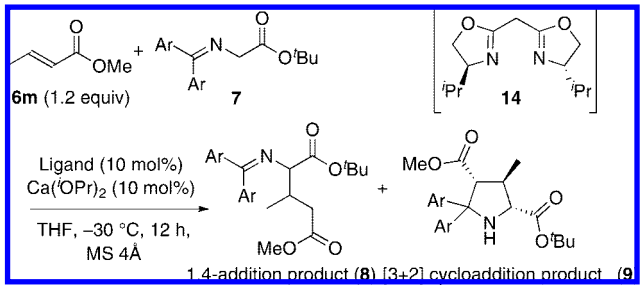
A special case is the [3 + 2] cycloaddition of crotonates, where the reactions proceeded faster and only [3 + 2] cycloadducts were obtained. To further elucidate the reaction mechanism, we investigated the [3 + 2] cycloaddtion reaction of methyl crotonate (**6m**) with **7** using bisoxazoline ligands (Table 12). When the reaction was conducted in the absence of ligand, the product was obtained as a mixture of the 1,4-addition adduct and the [3 + 2] cycloaddition product (entry 1), while only the [3 + 2] cycloaddition product was obtained in the reaction using ligand **2** or **4** (entries 2 and 3). These results suggested that steric factors of the ligand could affect the reaction course. Therefore, we performed the reaction using less sterically demanding ligand **14** bearing isopropyl groups. As predicted, the product was obtained as a mixture of the 1,4-addition product and the [3 + 2] cycloadduct with high enantioselesctivities (entry 4). This fact showed that the steric bulk of the chiral ligand affected the reaction course significantly and that the reactions of crotonates also proceeded in a stepwise fashion, through 1,4-addition and cyclization pathways. As further evidence, the reaction of the glycine derivative bearing a bis(*p*-methoxyphenyl)methylene group (**7r**) with methyl crotonate (**6m**) proceeded smoothly to afford a mixture of the 1,4-addition product and the [3 + 2] cycloadduct in high yields with similar excellent enantioselectivities (entry 5). This result also suggested a stepwise mechanism because the imine part of the glycine derivative was less electrophilic and less prone to be attacked in an intramolecular fashion due to the electron-donating effect of the methoxy groups. On the basis of these experimental findings, we concluded that the [3 + 2] reaction of α,β-unsaturated carbonyl compounds with glycine Schiff bases proceeds in a stepwise manner.

Scheme 8. Asymmetric [3 + 2] Cycloadditions with Fumaric or Maleic Ester



As mentioned above, the *N*-diphenylmethylidene-protected glycine derivatives reacted with crotonates or acrylamides to afford [3 + 2] cycloadducts. This is remarkable because only 1,4-addition reaction occurred in combination with these

Table 12. Effect of Ligands on the Reaction Courses



entry	Ar	ligand	yield (%)	8/9[a]	ee (%)
1	Ph	none	34	62/38	
2	Ph	**2**	95	**9mc** only	99
3	Ph	**4**	99	**9mc** only	>99
4	Ph	**14**	quant[b]	18/82	98[c]
5	*p*-MeOC$_6$H$_4$	**4**	90	18/82	96/98

[a] Determined by NMR spectroscopic analysis. **8** was obtained as a single diastereomer in all cases. [b] Determined by NMR spectroscopic analysis using 1,1,2,2,-tetrachloroethane as an internal standard. [c] ee of the [3 + 2] cycloaddition product.

substrates in previously reported cases due to lower reactivity of the bulky ketimine group as an electrophile; this could be explained by the reactivity difference of the metal enolates of the intermediates. Compared to other metal enolates (Co, Ag, etc.), alkaline-earth-metal enolates show higher reactivity. Presumably interaction between oxygen anions and alkaline-earth-metal cations is not strong; that is, the corresponding enolates would be more reactive than other metal enolates. Therefore, it is reasonable to assume that the highly reactive intermediates alkaline-earth-metal enolates can attack the ketimine parts efficiently to afford the [3 + 2] cycloadducts.

We also observed a significant difference of the reaction rate between the 1,4-addition to acrylates and [3 + 2] cycloaddition to crotonates. The [3 + 2] cycloaddition to crotonates proceeded faster than the 1,4-addition, which seemed counterintuitive since the sterically hindered crotonate reacted faster than the less hindered acrylate. In our hypothesis, the chiral calcium-catalyzed reactions proceed via 1,4-addition and successive intramolecular cyclization; therefore, the observed reaction rate does not correspond to that expected in the proposed mechanism. One possible explanation of this phenomenon is offered by considering the rate difference of the second steps in the mechanisms (protonation step or cyclization/protonation steps in Figure 3). If the rate of the second step, protonation, in the reaction with the acrylate is slower than the rate of the cyclization/protonation steps in the reaction with the crotonate, that observation could be made. To clarify this point, we conducted the reactions of the acrylate and the crotonate in the presence of a stoichiometric amount of the chiral calcium catalyst over a shorter reaction time. As a result, the reaction of the acrylate proceeded faster than that of the crotonate with a significant rate difference, which supports our hypothesis that the observed rate difference in the catalytic reactions is caused by efficiency of the second steps (Schemes 8 and 9). The rate difference of the second steps, protonation and cyclization/protonation steps, could be ascribed to the basicity of the intermediates calcium enolate and calcium amide.

3. Diastereoselective and Enantioselective 1,4-Addition. If the reaction of crotonates proceeds via a stepwise pathway, we still have a chance to obtain 1,4-adducts exclusively by optimizing the reaction conditions. Asymmetric 1,4-addition of glycine derivatives to crotonates is also an important method for synthesizing branched

Scheme 9. Comparison of the Reaction Rate Using a Stoichiometric Amount of the Catalyst

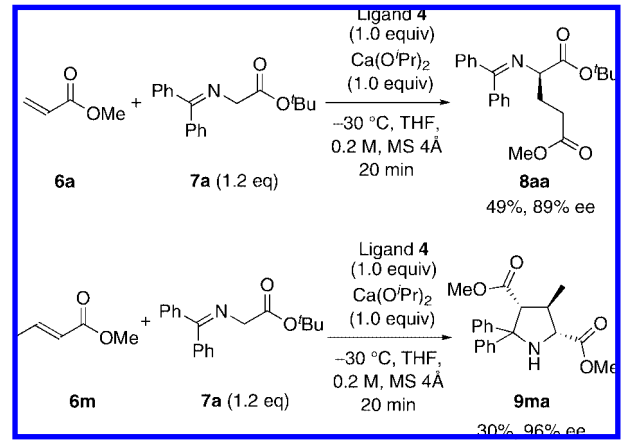
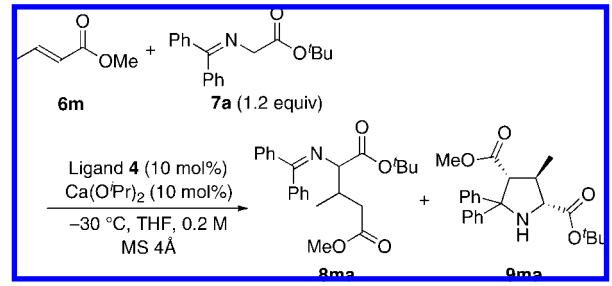


Table 13. Effect of Protic Additives



entry	additive (mol%)	yield (%)	8ma[a]/9ma	ee of **8ma**/ee of **9ma** (%)
1		quant	**9ma** only	–/99
2	$(CF_3)_2CHOH$ (10)	85	58/42	0/82
3	PhOH (10)	90	11/89	–/95
4	*p*-MeOC$_6$H$_4$OH (10)	46	8/92	–/94
5	2,6-Me$_2$C$_6$H$_3$OH (10)	71	44/56	19/77
6	2-phenylphenol (10)	89	68/32	20/68
7	2-(2-methoxyphenyl)phenol (10)	78	56/46	23/87

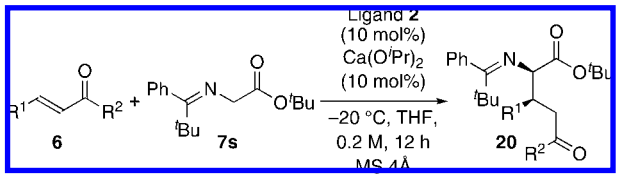
[a] **8ma** was obtaind as a single diastereomer in all cases.

α-amino acid derivatives; however, successful examples are very limited.[16] We started an investigation to realize the 1,4-addition reaction of a ketimine-protected glycine derivative with methyl crotonate (**6m**). First, we tried to trap the corresponding intermediate in the reaction system. Addition of proton sources was investigated for trapping the 1,4-adduct intermediate (Table 13). Acidic alcohols and phenol derivatives were examined in the reaction system; however, in most cases, the [3 + 2] cycloadduct was obtained preferentially. When 2-substituted phenol derivatives were employed, the 1,4-adduct was obtained predominantly, but the enantioselectivities were insufficient.

Next we carried out the reaction of a glycine derivative with a bulkier substituent at the imine part, which could prevent the second cyclization step to afford the 1,4-addition product. We synthesized and employed the glycine derivative **7s** with *tert*-butylphenylmethylidene[28] as a protecting group in the reaction with methyl crotonate (**6m**). Expectedly, the 1,4-addition products were obtained exclusively as a single diastereomer with high enantioselectivity by using calcium-**2** catalyst (Table 14, entry 1).[13,29]

By using glycine derivative **7s**, we could control the reactions with crotonate derivatives in favor of the 1,4-addition reaction. As shown in Table 14, not only crotonates but also 2-pentenoate, 2-heptenoate, and 5-methyl-2-hexenoate reacted with the glycine

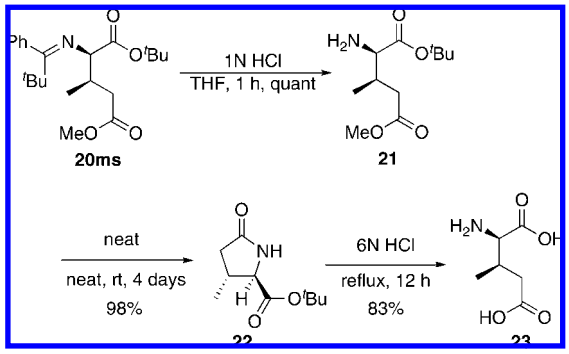
Table 14. Asymmetric 1,4-Addition Reactions with β-Substituted α,β-Unsaturated Carbonyl Compounds



entry	R^1	R^2	product	dr	yield (%)	ee (%)
1	Me	OMe	**20ms**	>99/1	97 (93)[c]	99 (99)[a]
2	Me	OEt	**20ns**	>99/1	95	93
3	Et	OMe	**20ps**	>99/1	96	96
4	Et	OEt	**20xs**	>99/1	97	94
5[b]	^{n}Bu	OMe	**20ys**	>99/1	73	91
6[c]	^{i}Bu	OMe	**20qs**	>99/1	56	82
7	$BnOCH_2$	OEt	**20zs**	82/18	82	96
8	Me	NMeOMe	**20α**s	>99/1	94	98
9[c]	Et	NMeOMe	**20*β*s**	>99/1	92	96
10[c]	^{i}Bu	NMeOMe	**20*γ*s**	>99/1	89	95
11[d]	H	NMe_2	**20ss**		22	82
12[e]	Me	NMe_2	**20*δ*s**	88/12	2	51

[a] 2 mol %. [b] −20 °C, 48 h. [c] 24 h. [d] 0 °C. [e] 40 h.

Scheme 10. Transformation of 1,4-Adduct **20 ms**



derivative in a 1,4-addition manner with good to high enantioselectivities (entries 2−6). A crotonate derivative substituted by a benzyloxy group at the terminal methyl moiety (**6z**) also gave high selectivity (entry 7). On the other hand, reactions with crotonamides showed a different tendency; for crotonamides with an *N*-methoxy group (**6α**) and β-substituted acrylamides with an *N*-methoxy group (**6*β*** and **6*γ***) a high yield and high selectivity were obtained (entries 8−10). However, the reactions using *N*,*N*-dimethylacrylamide (**6s**) and *N*,*N*-dimethylcrotonamide (**6*δ***) showed lower conversions (entries 11 and 12). It should be noted that this is the first example of catalytic highly stereoselective 1,4-addition of a glycine enolate to crotonates.

Deprotection of this *tert*-butylphenylmethylidene group on the nitrogen atom of the product was also studied.[30] Simple acid hydrolysis was found to be effective for removal of this group, and the corresponding primary amine product **21** was obtained in high yield (Scheme 10). This result demonstrates that the *tert*-butylphenylmethylidene group is a useful hindered protecting group for amino acid derivatives. Intramolecular cyclization of **21** occurred easily (standing neat at room temperature) to afford 5-prolinone derivative **22** in high yield. Further hydrolysis of **22** afforded free 3-methylglutamic acid (**23**) in good yield. The absolute configuration of **23** was determined by comparing the optical rotation of **23** to that previously reported.[31] It is noted that this 1,4-addition reaction provides a facile preparation of optically active 3-methylglutamic acid derivatives and proline derivatives.

Conclusion

We have investigated catalytic asymmetric 1,4-addition reactions of glycine derivatives using chiral alkaline-earth-metal complexes as catalysts. It was found that chiral anionic calcium−Box complexes were effective for the reaction, and high yields and high enantioselectivities have been achieved. Compared to previously reported reaction systems, this catalyst system is simpler since only a catalytic amount of Brønsted base is employed. Furthermore, in the reactions of crotonates, [3 + 2] cycloaddition reactions proceeded by using the same reaction system to afford the chiral pyrrolidines in high yields with high diastereo- and enantioselectivities. It is remarkable that small differences in substrate structure affected the reaction course and changed the product structure dramatically. Not only aldehyde-protected glycine derivatives but also ketimine-protected glycine derivatives reacted with active olefins to afford substituted pyrrolidines. Moreover, the first successful asymmetric 1,4-addition reactions of crotonates have been realized by modifying the protecting groups of the amine parts. Remarkably, the calcium catalyst could construct contiguous chiral tertiary and quaternary carbon stereocenters with high stereoselectivities in the [3 + 2] cycloaddition reactions of α-substituted α-amino acid derivatives and 3-substituted acrylates. It is noted that the current chiral calcium catalyst expanded possibilities of the asymmetric 1,4-addition and [3 + 2] cycloaddition reactions of α-amino acid derivatives. The reaction mechanism of the [3 + 2] cycloaddition was also investigated, and a stepwise mechanism, 1,4-addition and successive intramolecular cyclization, was proposed. High reactivity of the second alkaline-earth-metal enolates made the intramolecular cyclization step smooth, thus affording highly substituted chiral pyrrolidine derivatives.

Calcium is one of the most abundant elements in the natural world and an easily available metal. Also Box-type ligands are quite effective for preparing asymmetric environments around metal centers, and most of them can be prepared from natural chiral amino acids readily available. The use of these cheap and naturally abundant metals in fine organic synthesis is quite important from both economical and environmental points of view. Further investigations using alkaline-earth metals as effective Brønsted base catalysts in organic chemistry are in progress.

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Supporting Information Available: Experimental procedures, product characterization, and complete refs 15, 21a, and 22b. This material is available free of charge via the Internet at http://pubs.acs.org.

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