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Chiral Calcium Complexes as Brønsted Base Catalysts for Asymmetric Addition of α-Amino Acid Derivatives to α,β-Unsaturated Carbonyl Compounds

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The group 2 elements, Mg, Ca, Sr, and Ba, are widely distributed in minerals and in the sea.[1] However, their use in organic synthesis is limited except for organomagnesium compounds (Grignard reagents). As for the area of asymmetric catalysis, while various types of chiral catalysts have been developed during the past decades, there are few reports on the use of the group 2 metals except for magnesium Lewis acids.[2] Since these metals are divalent and have high coordination number and low electronegativity, we have focused on their use as novel Brønsted base catalysts.[3] In this paper, we report chiral calcium-catalyzed asymmetric 1,4-addition reactions and [3+2] cycloaddition reactions of α-amino acid derivatives with α,β-unsaturated carbonyl compounds.

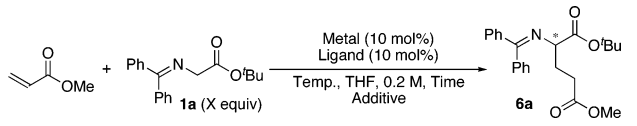
Catalytic asymmetric 1,4-addition reaction of α-amino acid derivatives with α,β-unsaturated carbonyl compounds provides efficient synthetic methods of chiral glutamic acid derivatives.[4] While several systems, mainly chiral phase-transfer catalysts, have been developed for this purpose,[5] the reactions need excess amounts of substrates and additional bases in most cases. Therefore, a versatile reaction system, which affords glutamic acid derivatives with high enantioselectivity only using a catalytic amount of a Brønsted base catalyst would be highly desirable.

We first examined alkaline earth metal alkoxides with chiral ligands as catalysts in the reaction of glycine derivatives **1a** with methyl acrylate (Table 1). Among metal alkoxides tested, Ca(O*i*-Pr)$_2$-ligand **1** gave the desired 1,4-addition (Michael) product with the best enantioselectivity although the yield was moderate (entries 1−4). As for chiral ligands, while *tert*-BuBox **3** gave poor selectivity, PhBox **4** provided the product in better enantioselectivity (entry 7). We further optimized the reaction conditions and finally found that the desired product could be obtained in 88% yield with 94% ee when the reaction was conducted using Ca(O*i*-Pr)$_2$-ligand **4** in THF at −30 °C for 12 h in the presence of MS 4A (entry 13).

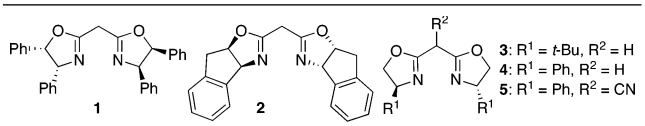
Next we investigated the substrate scope of this 1,4-addition reaction under the optimized conditions, (Table 2). Gratifyingly it was found that acrylate esters reacted with **1a** smoothly to afford the desired Michael products in high yields with high enantioselectivities (entries 3−6). Variation of the ester moiety revealed that methyl esters gave the product in highest enantioselectivity. It is noteworthy that the Weinreb amide[6] of acrylic acid also gave the desired Michael adduct in good yield with high enantioselectivity (entry 6). We further examined the reactions of α-substituted acrylic acid esters. The methyl, ethyl, and even chloro-substituted α,β-unsaturated esters also reacted with **1a** smoothly to afford the Michael adducts in high yields with high enantioselectivities (entries 7−11).

During the examination of the substrate scope, we discovered that when methyl crotonate was allowed to react with **1a** under the standard reaction conditions the reaction also proceeded smoothly; however, the product was not the expected Michael adduct but the corresponding pyrrolidine derivative, obtained in excellent yield and enantioselectivity via a formal [3+2] cycloaddition pathway[7] (Table 3, entry 1). We examined other related substrates and found that in the cases of amides, even acrylic acid amides reacted with **1a** to afford the corresponding [3+2] cycloaddition products exclusively (entries 3−6). Moreover, only a single diastereomer of the pyrrolidine derivative was obtained exclusively and the enantioselectivity was excellent in each case. It should be noted from a synthetic point of view that other glycine and even DL-alanine derivatives reacted with several α,β-unsaturated carbonyl

Table 1. Effect of Metal Sources and Chiral Ligands

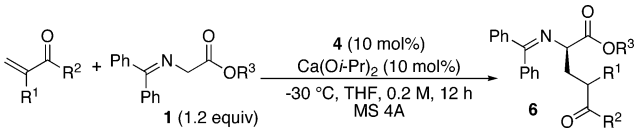


entry	metal	ligand	X (equiv)	additive	temp (°C)	time (h)	yield (%)	ee (%)
1	Mg(OEt)$_2$	**1**	1.2	MS 5A	−45 to 0	24	N.R.[a]	
2	Ca(O*i*-Pr)$_2$	**1**	1.2	MS 5A	−45 to 0	24	39	73 (*S*)
3	Sr(O*i*-Pr)$_2$	**1**	1.2	MS 5A	−45 to 0	24	76	29 (*S*)
4	Ba(O*t*-Bu)$_2$	**1**	1.2	MS 5A	−45 to 0	24	79	17 (*S*)
5	Ca(O*i*-Pr)$_2$	**2**	1.2	MS 5A	−45 to 0	24	24	71 (*R*)
6	Ca(O*i*-Pr)$_2$	**3**	1.2	MS 5A	−45 to 0	24	19	6 (*S*)
7	Ca(O*i*-Pr)$_2$	**4**	1.2	MS 5A	−45 to 0	24	54	82 (*R*)
8	Ca(O*i*-Pr)$_2$	**5**	1.2	MS 5A	−45 to rt	24	31	44 (*R*)
9	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 5A	0	8	48	82 (*R*)
10	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 5A	−20	8	56	87 (*R*)
11	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 5A	−30	8	63	87 (*R*)
12	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 4A	−30	8	71	90 (*R*)
13[b]	Ca(O*i*-Pr)$_2$	**4**	1.2	MS 4A	−30	12	88	94 (*R*)
14	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 5A	−45	8	46	82 (*R*)
15	Ca(O*i*-Pr)$_2$	**4**	1.1	MS 5A	−78	8	36	80 (*R*)



[a] No reaction. [b] The catalyst preparation was conducted at room temperature (rt) for 2 h and then the substrates were added without removal of volatile components.

Table 2. Catalytic Asymmetric 1,4-Addition Reactions of Glycine Derivatives



entry	R^1	R^2	R^3	product	yield (%)	2,4-*syn*/*anti*	ee (%)
1	H	OMe	Me	**6b**	quant		83
2	H	OMe	Et	**6c**	quant		78
3	H	OMe	*t*-Bu	**6a**	88		94
4[a,d]	H	OEt	*t*-Bu	**6d**	56		95
5[a,d]	H	O*t*-Bu	*t*-Bu	**6e**	74		92
6[a]	H	NMeOMe	*t*-Bu	**6f**	46		87
7[b]	Me	OMe	*t*-Bu	**6g**	93	61/39	99[c]
8	Et	OMe	*t*-Bu	**6h**	quant	63/37	86[c]
9[a]	Cl	OMe	*t*-Bu	**6i**	95	83/17	81[c]
10[a]	Ph	OMe	*t*-Bu	**6j**	quant	91/9	84[c]
11[a,d]	Me	NMeOMe	*t*-Bu	**6k**	83	91/9	85[c]

[a] 24 h. [b] Glycine derivative (1.5 equiv) was used. [c] Value represents ee of the major product. [d] α,β-Unsaturated ester (1.5 equiv) was used.

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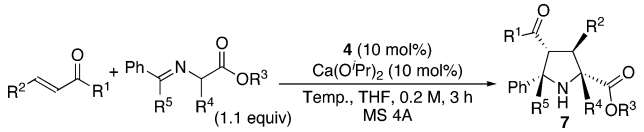
Table 3. Catalytic Asymmetric [3+2] Cycloaddition-Type Reactions of α-Amino Acid Derivatives



entry	R1	R2	R3	R4	R5	temp (°C)	product	yield (%)	ee (%)
1[a]	OMe	Me	*t*-Bu	H	Ph	−30	**7a**	quant (99)[d]	>99 (99)[d]
2[a]	OEt	Me	*t*-Bu	H	Ph	−30	**7b**	98	98
3[a,c]	NMe_2	H	*t*-Bu	H	Ph	−30	**7c**	83	95
4[b,c]	X = O	H	*t*-Bu	H	Ph	−30	**7d**	76	98
5[b,c]	X = CH_2	H	*t*-Bu	H	Ph	−30	**7e**	84	97
6[b]	NCy_2	H	*t*-Bu	H	Ph	−30	**7f**	93	91
7	O*t*-Bu	H	*t*-Bu	H	H	10	**7g**	98	76
8	OMe	Me	*t*-Bu	H	H	10	**7h**	89	84
9	O*t*-Bu	Me	*t*-Bu	H	H	10	**7i**	86	86
10	O*t*-Bu	H	Me	Me	H	10	**7j**	quant	90
11	O*t*-Bu	H	Et	Me	H	10	**7k**	quant	91
12	O*t*-Bu	H	Bn	Me	H	10	**7l**	93	90

[a] Reaction run in 12 h. [b] Reaction run in 24 h; Cy, cyclohexyl. [c] α,β-Unsaturated amide (1.5 equiv) was used. [d] Reaction run using 5 mol % of the catalyst.

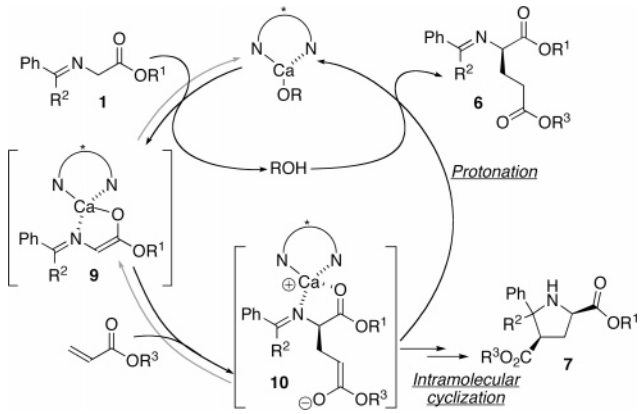
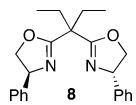


Figure 1. Assumed Catalytic Cycle

compounds to afford the corresponding substituted pyrrolodine derivatives in high yields with excellent diastereo- and enantioselectivities (entries 7−12). In the reactions with dl-alanine derivatives, quaternary asymmetric carbons were constructed efficiently.

As for the structure of the chiral calcium catalyst, we assume that ligand **4** does not work as a neutral ligand but an anionic ligand.[8−10] Indeed, the structurally related ligand **8** which would be expected to form a neutral catalyst complex, gave almost no selectivity when used with $Ca(O\textit{i}\text{-}Pr)_2$ (10 mol %) in the reaction of methyl acrylate with **1a**, the corresponding Michael adduct being produced in only 31% yield in racemic form.[11]



A plausible catalytic cycle of this reaction is shown in Figure 1. In this sequence, a monomeric calcium−Box complex removes the α-proton of the glycine derivative **1** to give chiral calcium enolate **9** in situ. This chiral calcium enolate formed then reacts with an α,β-unsaturated carbonyl compound to afford the initial 1,4-addition adduct **10**. While subsequent protonation of the 1,4-addition adduct with either the proton of the alcohol or the α-proton of the glycine derivative affords the Michael adduct **6**, intramolecular cyclization of **10** gives pyrrolidine derivative **7**. In the reactions of amides, reactivity of the enolate **10** is high and the intermolecular cyclization occurs to afford the pyrrolidine derivative exclusively. The present mechanism cannot rule out a possibility of a concerted [3+2] cycloaddition pathway, especially in the reactions of crotonates.

In summary, we have developed novel Ca−Box catalysts prepared from calcium alkoxides and methylene bridged Box ligands. These catalysts effectively promoted two types of catalytic asymmetric additions of α-amino acid derivatives with α,β-unsaturated carbonyl compounds; 1,4-addition reactions and [3+2] cycloaddition recations. This reaction system does not need excess amounts of electrophiles or the external addition of bases in contrast with usual methods such as these using phase-transfer catalysts. Further investigations to clarify the precise mechanism of this reaction and exact catalyst structure as well as to expand still further the substrate scope are now in progress.

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

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(11) The correlation between the ee of the product and the ee of ligand **4** was shown to be linear, suggesting a monomeric structure of $Ca(O\textit{i}\text{-}Pr)_2$-**4**.

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