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Alkaline Earth Metal Catalysts for Asymmetric Reactions

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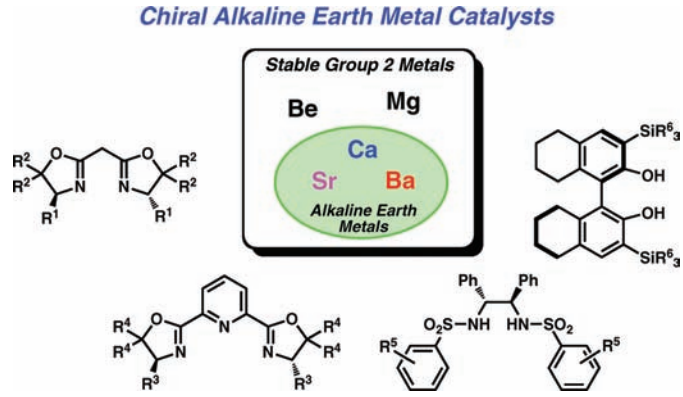

The group 2 alkaline earth metals calcium (Ca), strontium (Sr), and barium (Ba) are among the most common elements on Earth, abundant in both the sea and the Earth's crust. Although they are familiar in our daily lives, their application to organic synthesis has, so far, been limited. Some particularly useful properties of these elements include (i) low electronegativity, (ii) a stable oxidation state of +2, meaning that they can potentially form two covalent bonds with anions, and (iii) the ability to occupy a variety of coordination sites due to their large ionic radius. Furthermore, the alkaline earth metals, found between the group 1 and group 3 elements, show mild but significant Lewis acidity, which can be harnessed to control coordinative molecules via a Lewis acid–base interaction. Taken together, these characteristics make the metals Ca, Sr, and Ba very promising components of highly functionalized acid–base catalysts. In this Account, we describe the development of chiral alkaline earth metal catalysts for asymmetric carbon–carbon bond-forming reactions.

Recently prepared chiral alkaline earth metal complexes have shown high diastereo- and enantioselectivities in fundamental and important chemical transformations. We chose chiral bisoxazoline (Box) derivatives bearing a methylene tether as a ligand for chiral modification. These molecules are very useful because they can covalently coordinate to alkaline earth metals in a bidentate fashion through deprotonation of the tether portion. It was found that chiral calcium–Box complexes could successfully promote catalytic asymmetric 1,4-addition and [3 + 2] cycloaddition reactions with high diastereo- and enantioselectivities. Both the calcium–Box complexes and chiral strontium–bis-sulfonamide and chiral barium–BINOLate complexes could catalyze asymmetric 1,4-addition reactions with high enantioselectivities. Furthermore, we designed a calcium-neutral coordinative ligand complex as a new type of chiral alkaline earth metal catalyst. We found that pyridinebisoxazolines (Pybox) worked well: they served as excellent ligands for calcium compounds in 1,4-addition reactions and Mannich reactions. Moreover, they were successful in 1,4-additions in concert with enantioselective protonation, affording the desired products in good to high enantioselectivities.

Our results demonstrate that alkaline earth metals are very useful and attractive catalysts in organic synthesis. Moreover, their ubiquity in the environment is a distinct advantage over rare metals for large-scale processes, and their minimal toxicity is beneficial in both handling and disposal.

Introduction

The development of environmentally friendly and atom-economical chemical processes is one of the most important research topics in modern synthetic organic chemistry.[1] In particular, the replacement of toxic, harmful metals with less toxic,

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harmless metals is of interest from the viewpoint of safety of chemical processes. Moreover, the use of ubiquitous metals instead of rare metals is desirable because the availability of rare metals is limited, and their exhaustion is also a serious problem. Isotopically stable group 2 alkaline earth metals, calcium, strontium, and barium, are recognized as being among the most abundant elements in the natural world, being found, for example, in the sea and in the Earth's crust.[2] While they are familiar in our daily lives, their application to organic synthesis has been limited.[3]

The characteristics of these elements are as follows: (1) they have low electronegativity, (2) they exhibit a stable oxidation state of +2, which means that they can form two covalent bonds with anions, and (3) they can inhabit various coordination sites due to their large ionic radius. Among these characteristics, their low electronegativity is the most interesting from the viewpoint of synthetic chemistry, because it usually leads to stronger Brønsted basicity of their counteranions, leading to the activation of synthetic intermediates with active hydrogen by deprotonation. The Brønsted basicity of the alkaline earth metal compounds should align with their order in the periodic table, because basicity is correlated with the electronegativity of a metal atom. Therefore, barium compounds should show the strongest Brønsted basicity compared with strontium and calcium compounds. On the other hand, the Lewis acidity of alkaline earth metals is also interesting. The group 2 alkaline earth metals, which lie between group 1 (e.g., Na(I) and K(I)) and group 3 elements (e.g., Sc(III) and Y(III)) can show mild but significant Lewis acidity for controlling coordinative molecules via Lewis acid−base interactions. From the viewpoint of electronegativity, calcium shows the strongest and the most attractive Lewis acidity of the alkaline earth metals. Both the Lewis acidity and the Brønsted basicity are very important for the development of effective metal catalysts.

Asymmetric transformations are an important topic in recent synthetic organic chemistry, and asymmetric catalysis is of great current interest. Highly stereoselective reactions, including asymmetric reactions, are required for efficient routes to highly functionalized molecules, such as biologically active compounds for medicines.[4] In the development of enantioselective metal catalysts, the strict control of the asymmetric environment around a metal by chiral ligands is a very important subject.[5] Alkaline earth metals have a large ionic radius compared with other elements, such as the transition metals that are often employed in asymmetric catalysis. Metals with a larger ionic radius would have a higher number of coordination sites, which usually means that the chiral modification of the metals would be nontrivial, because flexible coordination geometries are possible. However, the formation of an effective environment may be achieved by strict tuning of the chiral ligand structure. Bearing these characteristic features in mind, we decided to develop highly enantioselective chiral catalysts based on alkaline earth metals. When we began this project, only a few chiral calcium and barium catalysts had been reported, and highly enantioselective reactions had not been realized in most cases.[6] Not only the barium bases but also calcium and strontium bases had been assumed to be less attractive for asymmetric catalysis.[7]

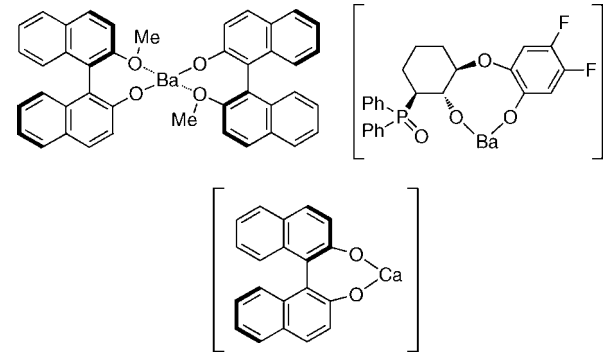


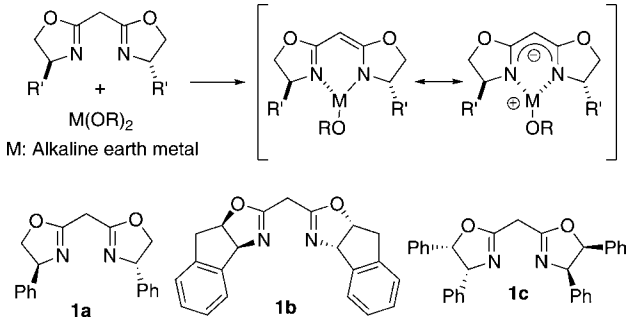
FIGURE 1

Development of Chiral Alkaline Earth Metal Catalysts Prepared from Bisoxazoline Ligands with Acidic Hydrogen

Catalyst Design. Chiral modification of alkaline earth metals has not been investigated in depth due to the difficulty of controlling many coordination sites derived from their large ionic radius. Until now, chiral alcohol or phenol ligands, such as BINOL derivatives, have been employed in catalytic asymmetric direct-type reactions. However, the enantioselectivity has not reached a sufficient level as yet (Figure 1). The reason for these unsatisfactory results may be the steric influence of the atoms that are weakly coordinated to the alkaline earth metal center, so designs of other chiral ligands are required to create a stricter asymmetric environment.

We turned our attention to the chiral bisoxazoline framework as a model chiral ligand. Bisoxazoline derivatives are some of the most efficient chiral ligands that are often employed in asymmetric catalysis.[8] When the methylene-tethered bisoxazoline ligand (**1**) is used, an alkaline earth metal base can deprotonate the methylene moiety of the ligand to form a rigid chiral complex, where two nitrogen atoms coordinate to the metal center in a bidentate fashion (Scheme 1).[9] These complexes are readily available because synthesis of the ligands is not complicated and the chirality of the ligands can be easily pooled from natural α-amino acids. Therefore,

SCHEME 1. Alkaline Earth Metal−Chiral Bisoxazoline Complexes



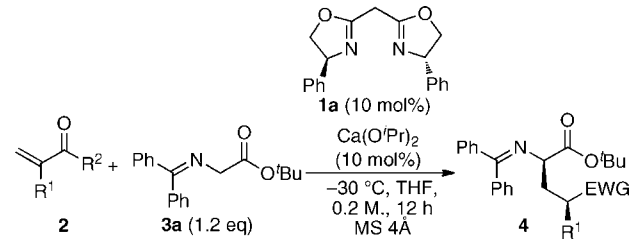
we selected chiral bisoxazoline derivatives as ligands to begin the development of catalytic asymmetric reactions.

Asymmetric 1,4-Addition of Glycine Derivatives Using a Chiral Calcium Catalyst. First, we envisioned the asymmetric 1,4-addition of a Schiff base of glycine esters to α,β-unsaturated carbonyl compounds, which would provide optically active glutamic acid derivatives. These compounds are important molecules as α-amino acid analogues and also as synthetic intermediates for chiral molecules.[10] Although some successful examples have been reported using this methodology, excess base or substrates are required to realize high conversions in most cases. However, we envisaged that a catalytic amount of a Brønsted base should work effectively in this reaction. The 1,4-addition of *N*-diphenylmethylideneglycine ester (**3**) to acrylate derivatives (**2**) in THF using alkaline earth metal alkoxides was examined, and it was revealed that a combination of calcium isopropoxide and ligand **1a** provided an effective asymmetric environment around the metal in this reaction, and the desired 1,4-adducts were obtained in high yields with high enantioselectivities (Table 1). We also carried out the reaction using strontium and barium alkoxides, but no promising result was obtained. When acrylates with substituents at the 2-position were used, moderate to good diastereoselectivities were observed. It was found that the size of the substituent at the 2-position of the acrylates influenced the diastereoselectivity, for example, substrates with larger groups, 2-phenylacrylate and 2-chloroacrylate, showed a higher *syn*/*anti* ratio. In general, the asymmetric 1,4-addition of glycine esters to acrylate derivatives proceeds well with a high enantioselectivity in the presence of a chiral calcium catalyst.[11]

Next, we carried out the asymmetric 1,4-addition of glycine derivatives to crotonates, which is also an important method for synthesizing branched α-amino acid derivatives, although successful examples of this reaction are limited.[12] The direct application of the current calcium catalyst system to a 1,4-addition to crotonates was unsuccessful, because an unexpected [3 + 2] cycloaddition occurred (*vide infra*). From an analysis of the reaction pathway, it was assumed that the desired 1,4-addition to the crotonate may be accomplished using a glycine derivative with a bulkier substituent on the imine part, which could prevent a second cyclization step to afford the 1,4-addition product. The glycine derivative **3b** with *tert*-butyl phenyl methylidene as the protecting group has been synthesized[13] and employed in the reaction with methyl crotonate. It was found that the 1,4-addition product was obtained exclusively as a single diastereomer with a high enantioselectivity using the calcium−**1b** catalyst. As shown in Table 2, not only crotonates but also other β-substituted acrylate derivatives reacted with **3b** in a 1,4-addition manner with good to high enantioselectivities.[14] It should be noted that this is the first example of catalytic, highly stereoselective 1,4-addition of a glycine enolate to β-substituted acrylate derivatives.

The chiral calcium catalyst was also applied to the synthesis of 1,4-addition products containing chiral quaternary carbon centers. α-Alkylcysteines are recognized as important building blocks for biologically active peptide mimics, and the asymmetric synthesis of these compounds is valuable in medicinal chemistry and pharmaceutical science.[15] However, few reports concerning the efficient synthesis of chiral α-alkylcysteines by asymmetric 1,4-addition reactions have appeared. A chiral calcium catalyst has been tested in 1,4-addition reactions, and it was found that a Schiff base derived

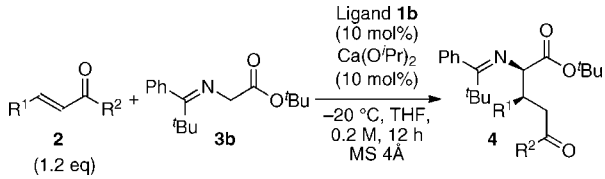
TABLE 1. Asymmetric 1,4-Addition of a Schiff Base of a Glycine Ester with Acrylate Derivatives Using a Chiral Calcium Catalyst



entry	R^1	R^2	yield (%)	2,4-*syn*/*anti*	ee (%)
1	H	OMe	88		94
2[a,c]	H	OEt	56		95
3[a,c]	H	O^{t}Bu	74		92
4[a]	H	NMeOMe	46		87
5[b]	Me	OMe	93		99[d]/94[e]
6	Et	OMe	quant	61/39	86[d]/91[e]
7	^{i}Pr	OMe	81	63/37	92[d]/80[e]
8	^{t}Bu	OMe	quant	55/45	90[d]/86[e]
9[a]	Ph	OMe	quant	67/33	84[d]
10[a]	Cl	OMe	95	91/9	81[d]
11[a,c]	Me	NMeOMe	83	83/17	85[d]

[a] For 24 h. [b] Compound **3a** (1.5 equiv) was used. [c] Compound **2** (1.5 equiv) was used. [d] Value represents the ee of the major product. [e] Value represents the ee of the minor product.

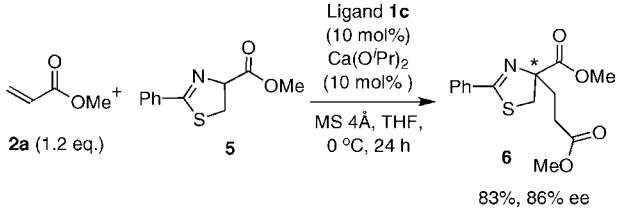
TABLE 2. Asymmetric 1,4-Addition of a Schiff Base of a Glycine Ester with Crotonate Derivatives



entry	R^1	R^2	dr	yield (%)	ee (%)
1	Me	OMe	>99/1	97 (93)[a]	99 (99)[a]
2	Et	OMe	>99/1	96	96
3[b]	^{n}Bu	OMe	>99/1	73	91
4[c]	^{t}Bu	OMe	>99/1	56	82
5	$BnOCH_2$	OEt	82/18	82	96
6	Me	NMeOMe	>99/1	94	98
7[c]	Et	NMeOMe	>99/1	92	96
8[c]	^{t}Bu	NMeOMe	>99/1	89	95

[a] 2 mol % catalyst. [b] At −20 °C for 48 h. [c] For 24 h.

SCHEME 2. Asymmetric 1,4-Addition of a Cysteine Derivative



from cysteine reacted with methyl acrylate to afford the desired product with a high enantioselectivity (Scheme 2).[11b] This result indicated that the current calcium catalyst could also form an effective asymmetric environment around sterically hindered α,α-disubstituted enolates.

A possible mechanism of the calcium-catalyzed asymmetric 1,4-addition is shown in Figure 2.[11b] The chiral calcium complex would deprotonate the α-position of the glycine derivative (**3**) to form a chiral calcium enolate (**1-A**), in which the imine nitrogen atom would also coordinate to the calcium atom. The enolate would then react with an α,β-unsaturated carbonyl compound (**2**) with a high enantioselectivity to form the 1,4-addition product, initially as a calcium enolate (**1-B**). Further, the enolate (**1-B**) would be protonated with the glycine derivative **3** to afford the product **4**, along with the regeneration of the reactive calcium enolate (**1-A**) (pathway 1). Alternatively, the free alcohol (^{i}PrOH) would quench **1-B** to give **4** and the active calcium complex (**1**) (pathway 2).

It has been revealed that the calcium−chiral bisoxazoline catalyst system has worked successfully in asymmetric 1,4-addition reactions of glycine derivatives with α,β-unsaturated esters or amides, and the desired glutamic acid derivatives were obtained in high enantioselectivities. It should be noted that a catalytic amount of the calcium complex without the addition of an external base could activate the substrates.

Asymmetric [3 + 2] Cycloaddition Using a Chiral Calcium Catalyst. Asymmetric [3 + 2] cycloaddition reactions of azomethine imines with substituted olefins are some of the most efficient and often used methods to construct highly functionalized pyrrolidine derivatives in an optically active form.[16] While several enantioselective metal catalyst systems have been developed, most of these systems have required additional bases, such as tertiary amines. These facts prompted us to investigate asymmetric [3 + 2] cycloaddition reactions using a chiral calcium catalyst.

As previously mentioned, a chiral calcium-catalyzed [3 + 2] cycloaddition reaction was observed during our investigation into the asymmetric 1,4-addition reactions of crotonates (*vide supra*). When the *N*-diphenylmethylene-protected glycine *tert*-butyl ester (**3a**) was treated with crotonate **2** under the optimized reaction conditions for the 1,4-addition reactions, the reaction proceeded smoothly, but an unexpected [3 + 2] cycloadduct **7** was obtained exclusively with excellent diastereo- and enantioselectivity (Table 3). Therefore, we continued to investigate the catalytic asymmetric [3 + 2] cycloaddition of glycine esters. The reactions had a wide scope; not only β-substituted acrylates but also acrylamides afforded [3 + 2] cycloadducts in high yields with very high enantioselectivities. In addition, it should be noted that single diastereoisomers were obtained in all cases and that this is a rare example of a highly stereoselective [3 + 2] cycloaddition of *N*-diphenylmethylene-protected glycine derivatives.[11b]

The [3 + 2] cycloaddition process was successfully applied to other substrates. It was found that several types of substrate were applicable to this process and that high stereoselectivities were obtained, as shown in Tables 4, 5, and 6.[11b] The reactions of several glycine imines with crotonate (Table 4), other amino acid imines with acrylate (Table 5), and several amino acid imines with β-substituted acrylates (Table 6) proceeded smoothly to afford the desired [3 + 2] cycloadducts in high diastereo- and enantioselectivities. It should be noted that the products containing contiguous chiral tertiary and quaternary carbon centers were obtained with perfect control of the stereoselectivity using a chiral calcium−bisoxazoline catalyst system. This high level of stereocontrol is one of the remarkable features of this chiral calcium catalyst compared with other chiral catalyst systems reported previously in asymmetric [3 + 2] cycloadditions.

A possible mechanism of the calcium-catalyzed asymmetric [3 + 2] cycloaddition is shown in Figure 3.[11b] The enolate intermediate (**1-B**) generated by the initial 1,4-addition would take place via an intramolecular Mannich-type reaction to

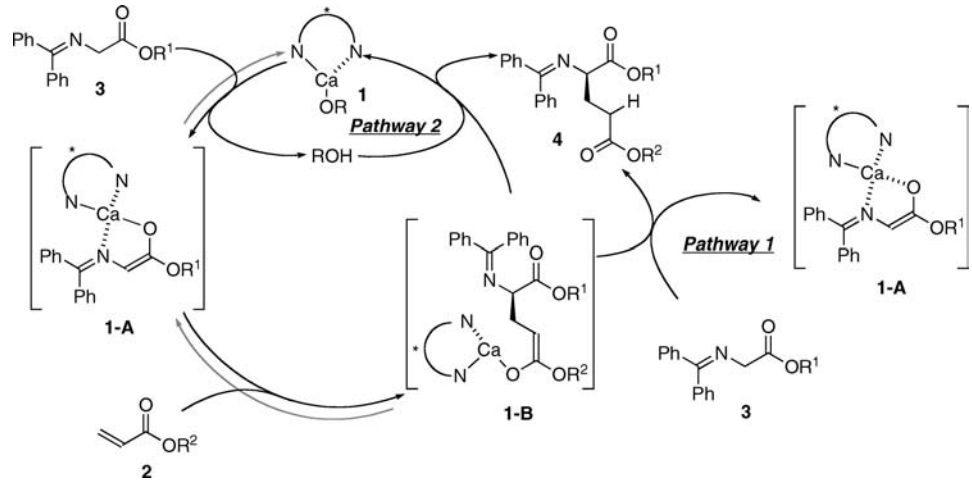
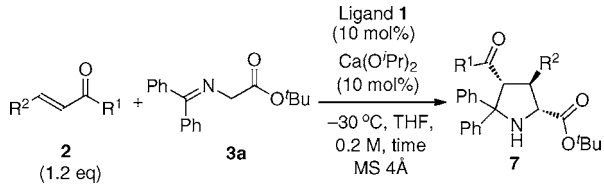


FIGURE 2. Assumed catalytic cycle of the asymmetric 1,4-addition of a Schiff base of a glycine ester.

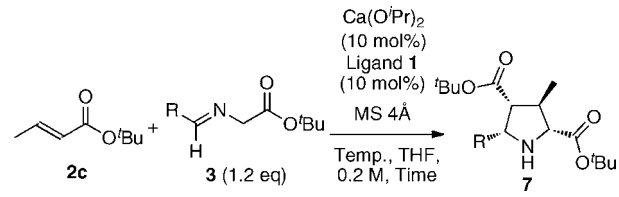
TABLE 3. Asymmetric [3 + 2] Cycloaddition of a Schiff Base of a Glycine Ester with α,β-Unsaturated Carbonyl Compounds



Entry	R^1	R^2	Ligand	Time (h)	Yield (%)	Ee (%)
1	OMe	Me	**1a**	3	quant	>99
2[a]	OMe	Me	**1b**	72	quant	93
3	OMe	Et	**1b**	24	quant	95
4	OMe	^{i}Bu	**1b**	24	quant	99
5	OMe	Heptyl	**1b**	48	97	>99
6	NMe_2	H	**1a**	12	83	95
7	 X = O	H	**1a**	24	76	98
8	X = CH_2	H	**1a**	24	84	97
9	NCy_2	H	**1a**	24	93	91

[a] 0.1 mol % catalyst at 20 °C. The 1,4 -adduct was observed in the isolated product (3%).

TABLE 4. Asymmetric [3 + 2] Cycloaddition of a Schiff Base of Glycine Esters with *tert*-Butyl Crotonate



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

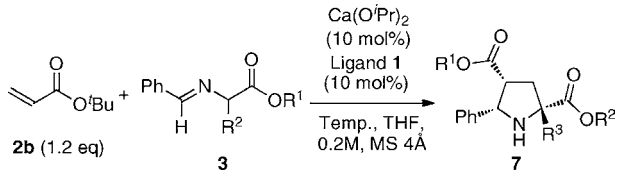
[a] 1.1 equiv. of the glycine ester. [b] The absolute configuration of the product was reversed.

form a pyrrolidine derivative with a high stereoselectivity. As is also shown in Figure 2, the first chiral induction would occur in the 1,4-addition step (from **1-A** to **1-B**). Because the successive Mannich-type reaction proceeded stereoselectively, the three stereogenic centers of **1-C** and **7** were highly stereocontrolled.

Catalyst Structure. The formation of the chiral calcium catalyst was confirmed by ^1H and ^{13}C NMR analysis of the catalyst.[11b] When ligand **1b** was mixed with Ca(O^{i}Pr)$_2$ or Ca(N(SiMe$_3$)$_2$)$_2$ in THF-d_8, two peaks appeared in the spectra shown in Charts 1 and 2, and the chemical shift of the peaks was reasonable compared with the data from previously reported anion metal species. When Ca(HMDS)$_2$ was used as the calcium source, the chart was clear, and almost no free ligand was observed. These results confirm that the active calcium catalyst was formed as expected (Scheme 3). The Ca(HMDS)$_2$−**1b** complex also showed a high enantioselectivity in the [3 + 2] cycloaddition reaction, similar to the Ca(O^{i}Pr)$_2$−**1b** catalyst (Scheme 4).[17]

An aggregation state of the active calcium species was also investigated. It is known that calcium−diimine complexes easily form dimeric structures in solution. The relationship between the product ee and the optical purity of the ligand was examined (Figure 4). As a result, no nonlinear effects were observed, and the same reactivity was obtained when low-ee ligands were used. These results suggest that the calcium cat-

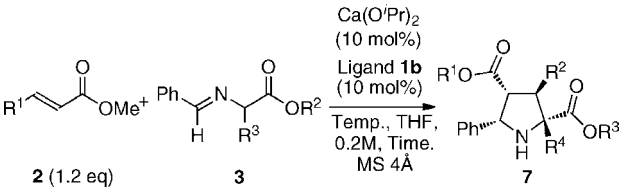
TABLE 5. Asymmetric [3 + 2] Cycloaddition of a Schiff Base of α-amino Esters with *tert*-Butyl Acrylate



entry	R^1	R^2	ligand	conditions	yield (%)	ee (%)
1	Me	Me	**1a**	10 °C, 12 h	quant	90
2	Et	Me	**1a**	10 °C, 3 h	quant	91
3	Bn	Me	**1a**	10 °C, 3 h	93	90
4	Me	Et	**1b**	−30 °C, 12 h	82	96
5	^{t}Bu	Bn	**1b**	−30 °C, 12 h	90	92
6	Me	^{n}Bu	**1b**	−20 °C, 12 h	94	94
7	Me	^{i}Bu	**1b**	−30 °C, 12 h	98	87
8	Me	^{i}Pr	**1a**	10 °C, 3 h	32	59
9	Me	CH_2CH_2SMe	**1b**	−20 °C, 12 h	81	81
10[a]	^{t}Bu	CH_2O^tBu	**1b**	−20 °C, 12 h	80	93

[a] L-Amino acid was used.

TABLE 6. Asymmetric [3 + 2] Cycloaddition of a Schiff Base of α-Amino Esters with α,β-Unsaturated Carbonyl Compounds



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

[a] 20 mol % of the catalyst was used. [b] The L-amino acid derivative was used.

alyst worked as a monomeric species without any significant aggregation to afford the desired product in a high enantioselectivity.

As described above, we successfully demonstrated the ability of calcium alkoxide−chiral bisoxazoline complexes to act as new chiral Brønsted base catalysts. The anionic ligands coordinated to the calcium cation in a stable bidentate fashion to form a rigid asymmetric environment. In our investigation, calcium gave the best results among the alkaline earth metals. This could be ascribed to the sufficient Brønsted basicity and a significant Lewis acidity. The smaller ionic radius of the calcium ion compared with strontium and barium ions in the chiral complexes may be another key. These results present new possibilities for calcium complexes as effective Lewis acid and Brønsted base catalysts.

Development of a Chiral Strontium Catalyst. Strontium appears below calcium in the periodic table, and it commonly occurs in nature in the form of the sulfate mineral celestite ($SrSO_4$) and the carbonate strontianite ($SrCO_3$). However, there have been few reports of its use as a catalyst in organic transformations.[18] The stable oxidation state of strontium is also +2, the same as other alkaline earth metals, which means it is possible to use chiral anionic ligands with strontium to form stable metal complexes. We investigated suitable ligands for strontium and found that the Sr−chiral bissulfonamide **8** formed an effective asymmetric environment around the strontium center, and excellent enantioselection was attained in 1,4-additions of malonates **9** to chalcone derivatives **10**.[19] The system tolerated both electron-withdrawing and electron-donating groups or both substituents in phenyl groups on a chalcone framework with little effect on either the yield or the selectivity. A high selectivity was also obtained in the reactions with heteroaromatic substituents (Table 7).

Further investigations into strontium species were conducted, and strontium bis(hexamethyldisilazide) ($Sr(HMDS)_2$), which is a stronger Brønsted base compared with $Sr(O^iPr)_2$ used in the initial study, was found to be a new and effective strontium source to form a highly stereoselective catalyst. The chiral strontium catalyst prepared from $Sr(HMDS)_2$ and the chiral bis-sulfonamide ligand **8** showed a higher reactivity compared with the catalyst prepared from $Sr(O^iPr)_2$, and this successfully catalyzed asymmetric 1,4-addition reactions to chalcones with a high enantioselectivity (Table 8). 2-Benzylidene-1-tetralone (**12**) was also employed as a 1,4-acceptor, and a high enantioselectivity was obtained (Scheme 5).[20]

The catalyst structure was analyzed using NMR. $Sr(O^iPr)_2$ was treated with 1 equiv of bissulfonamide ligand **8** in THF-d_8 for 2 h, and the ^1H and ^{13}C NMR spectra were recorded. The spectra indicated that the bissulfonamide ligand was covalently coordinated to the strontium atom, releasing 2 equiv of ^{i}PrOH (Scheme 6). At room temperature, the peaks corresponding to the strontium bissulfonamide complex **14** were considerably broadened, indicating a possible conformational equilibrium, whereas the peaks of the free ^{i}PrOH were sharp.[19]

Development of a Chiral Barium Catalyst. Barium is located below strontium in the periodic table, and it has the largest size among the three isotopically stable alkaline earth metal ions. In addition, the strong Brønsted basicity of its counteranions due to its low electronegativity is one of the most characteristic and interesting features. Until now, although much work has been carried out to develop a chiral barium Brønsted base catalyst, successful examples are

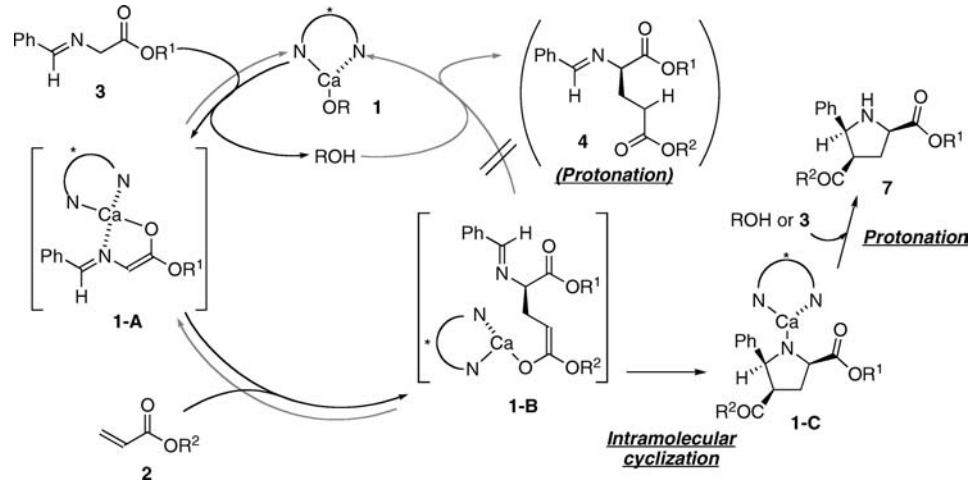


FIGURE 3. Assumed catalytic cycle of the asymmetric [3 + 2] cycloaddition.

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

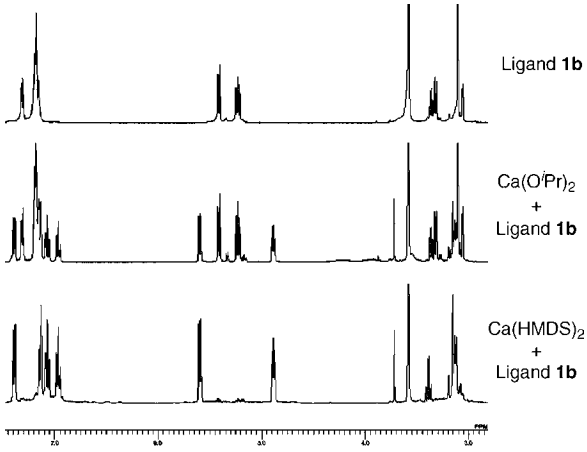
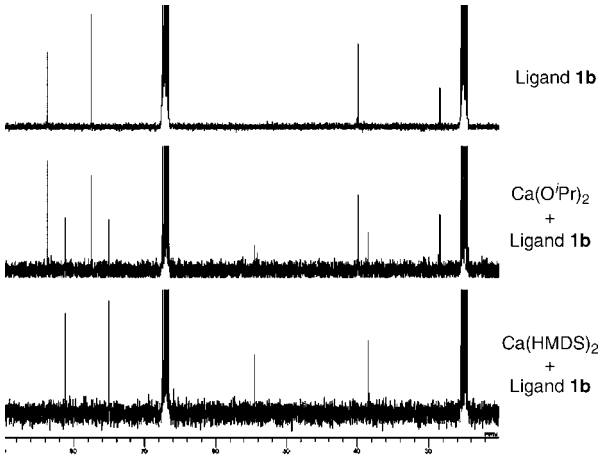


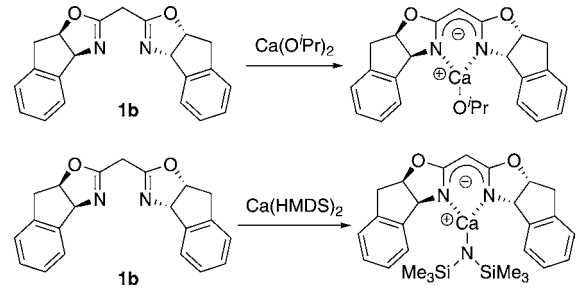
CHART 2. ^{13}C NMR Data of a Calcium Complex Prepared from Ligand **1b**



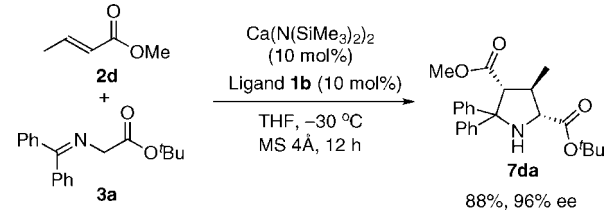
limited.[6,7] In the course of our research to develop chiral alkaline earth metal catalysts, we also focused on developing a chiral barium catalyst. In a Friedel–Crafts-type reaction of indole with chalcone, we surveyed several ligands for modification of barium, and a BINOL framework was finally found to be the most promising.[21] In particular, the BINOL derivative **17** with large steric bulkiness at the 3,3′ positions of the ring system showed a higher enantioselectivity, and excellent enantioselectivities >90% were obtained under optimum reaction conditions (Table 9).[22] In our investigation, barium bis(hexamethyldisilazide) ($Ba(HMDS)_2$) was an important barium source, and showed better results than other barium alkoxides.

A possible catalytic cycle is shown in Figure 5. First, the barium phenoxide deprotonates the nitrogen proton of an indole derivative to afford a chiral barium indole complex **15-A**. The complex then reacts with a chalcone derivative **10** enantioselectively to afford an initial Friedel–Crafts adduct **15-B**. The barium moiety then moves from the oxygen to the nitrogen

SCHEME 3. Formation of the Chiral Calcium Complexes



SCHEME 4. The Asymmetric [3 + 2] Cycloaddition Using a Calcium Catalyst Prepared from Calcium Bis(hexamethyldisilazide)



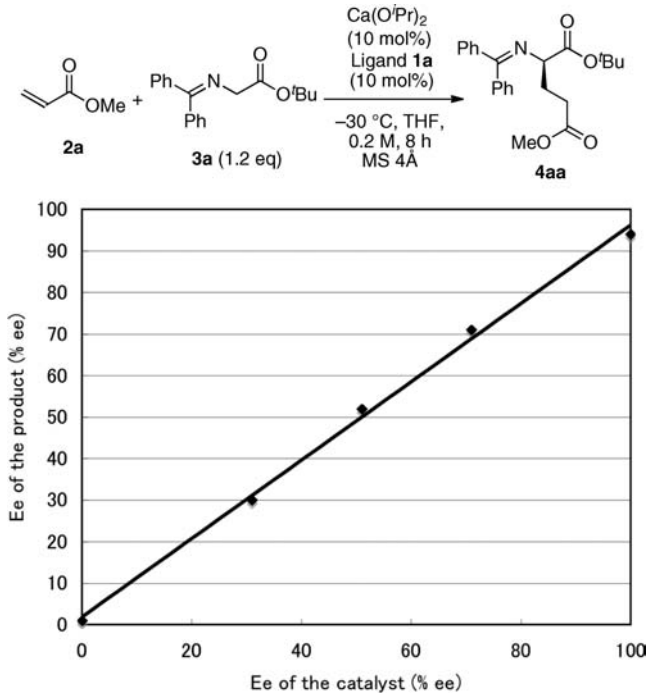
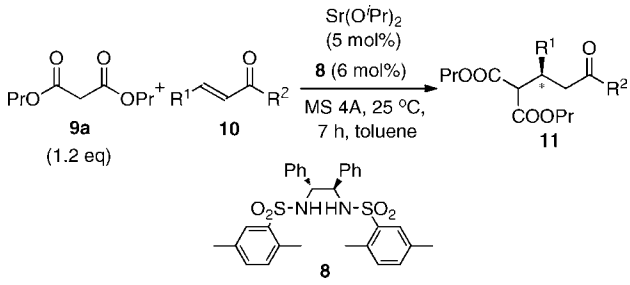


FIGURE 4. The relationship between the optical purity of the ligand and the ee of the product.

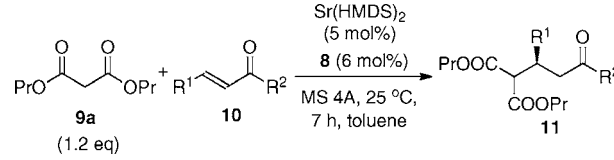
TABLE 7. Asymmetric 1,4-Addition of a Malonate with Chalcone Derivatives Using a Chiral Strontium Catalyst



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Ph	92	99
2	2-ClC_6H_4	Ph	76	92
3	4-ClC_6H_4	Ph	93	97
4	4-FC_6H_4	Ph	92	98
5	4-$MeOC_6H_4$	Ph	80	>99
6	4-$NO_2C_6H_4$	Ph	98	96
7	3-$NO_2C_6H_4$	Ph	94	94
8	4-FC_6H_4	4-FC_6H_4	91	96
9	4-$MeOC_6H_4$	4-FC_6H_4	81	>99
10	3,4-(MeO)2C_6H_3	4-FC_6H_4	61	96
11	4-ClC_6H_4	4-FC_6H_4	97	97
12	2-ClC_6H_4	4-FC_6H_4	80	93
13	4-FC_6H_4	4-MeC_6H_4	90	98
14	Ph	4-ClC_6H_4	98	99
15	Ph	4-FC_6H_4	92	99
16	Ph	4-$MeOC_6H_4$	85	99
17	2-thienyl	2-thienyl	73	97
18[a]	5-methylfuran-2-yl	Ph	71	96
19[b]	Ph	1-pyrrolyl	93	99
20[c]	Ph	PhCH=CH	97	86
21[c]	PhCH=CH	Ph	62	97

[a] For 48 h. [b] For 24 h. [c] 2.2 equiv of the malonate was used.

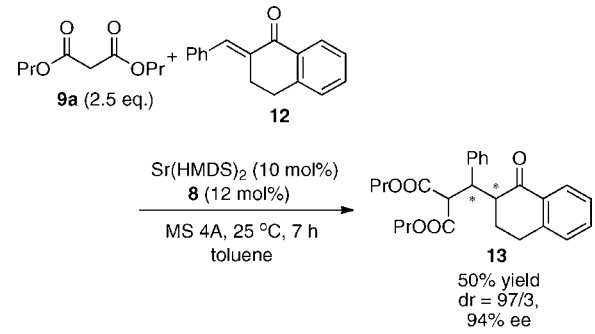
TABLE 8. Asymmetric 1,4-Addition of a Malonate with Chalcone Derivatives Using a Chiral Strontium Catalyst Prepared from Strontium Bis(hexamethyldisilazide)



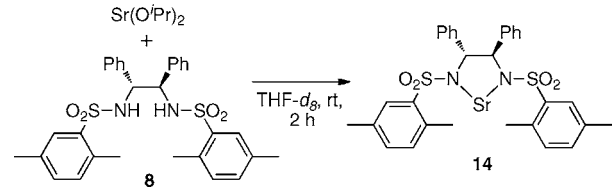
entry	R^1	R^2	yield (%)	ee (%)
1[a]	Ph	Ph	92	99
2	Ph	Ph	97	99
3[b]	Ph	Ph	96	92
4	2-ClC_6H_4	Ph	82	95
5	4-ClC_6H_4	Ph	93	97
6	3-$NO_2C_6H_4$	Ph	86	96
7	4-$NO_2C_6H_4$	Ph	81	97
8	2-ClC_6H_4	4-FC_6H_4	92	93
9	4-FC_6H_4	4-FC_6H_4	94	98
10	Ph	PhCH=CH	95	90

[a] $Sr(O^iPr)_2$ was used. [b] The reaction was conducted for 12 h using 2 mol % catalyst.

SCHEME 5. Asymmetric 1,4-Addition of a Malonate with an Alkylidene-1-tetralone



SCHEME 6. Formation of a Chiral Strontium Complex

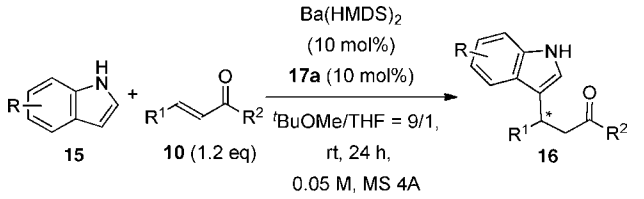


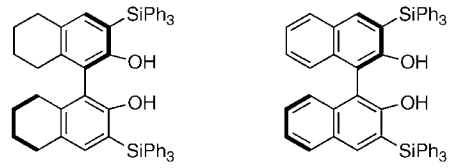
of the adduct to form a barium amide **15-C** again. Finally, this species deprotonates indole to afford the product **16**, along with regeneration of the chiral indole **15-A**.

Development of Chiral Alkaline Earth Metal Catalysts Prepared from Pyridinebisoxazoline Ligands

New Catalyst Design Using a Neutral Coordinative Ligand. The use of several types of ligand frameworks is desirable for the development of more versatile chiral alkaline earth metal catalysts. However, there has been a restriction on the design of chiral alkaline earth metal catalysts in

TABLE 9. Asymmetric 1,4-Addition Reaction of Indole Derivatives with Chalcone Derivatives Using a Chiral Barium Catalyst





(*R*)-3,3'-$(Ph_3Si)_2$-H_8-BINOL (**17a**) (*R*)-3,3'-$(Ph_3Si)_2$BINOL (**17b**)

entry	R	R^1	R^2	yield (%)	ee (%)
1	H	Ph	Ph	86	95
2[a]	H	*p*-ClC_6H_4	Ph	quant	93
3	H	*o*-ClC_6H_4	Ph	97	91
4	H	Ph	*p*-ClC_6H_4	92	93
5	H	*p*-FC_6H_4	Ph	89	96
6	H	*p*-$MeOC_6H_4$	Ph	68 (80)[b]	95 (92)[b]
7[a]	H	Ph	*p*-$MeOC_6H_4$	80	95
8	H	*p*-MeC_6H_4	Ph	87	95
9	H	*m*-MeC_6H_4	Ph	81	85
10	H	*o*-MeC_6H_4	Ph	78	89
11[a]	H	*p*-$MeOC_6H_4$	*p*-FC_6H_4	92	94
12	5-Cl	Ph	Ph	90	85
13	5-MeO	Ph	Ph	96	93
14	4-MeO	Ph	Ph	67	96
15[a]	5-Me	Ph	Ph	88	95
1[a,c]	2-Me	Ph	Ph	84	70

[a] 60 h. [b] ^{t}BuOMe/THF = 2/1. [c] (*R*)-3,3′-$(Ph_3Si)_2$BINOL (**17b**) was used.

previous investigations, in that the formation of a stable salt to connect the metal with a chiral ligand is required. This restriction affects not only the ligand design but also the catalyst activity. In these systems, the Brønsted basicity of the catalyst is sometimes decreased due to the acidic nature of chiral ligands. In the course of our investigations to develop more efficient catalysts, we envisioned that a complex of an alkaline earth metal compound and a chiral-neutral coordinative ligand may act as a more active chiral Brønsted base species.[23] The key point for modification of the metal compounds using a neutral coordinative ligand is the Lewis acidity of the metal. As mentioned above, alkaline earth metals should have significant Lewis acidity due to their electronegativity and stable oxidation state of +2. These facts encouraged us to develop a new chiral calcium catalyst with a neutral coordinative ligand.

The pyridinebisoxazoline (Pybox) framework is often used as an effective coordinative ligand of a Lewis acid. It has three nitrogen atoms in its structure and can coordinate to one metal atom via three coordinative bonds. Therefore, Pybox was expected to form a more stable complex with a metal cation than the bidentate bisoxazoline structure. We screened several neutral coordinative ligands and found that the pyridinebisoxazoline framework was a promising candidate for modification of alkaline earth metal compounds, especially calcium alkoxides (Scheme 7).[24]

Asymmetric 1,4-Addition Reaction of Malonates to Nitroolefins. We investigated asymmetric 1,4-addition reactions of malonate **9b** to nitroalkenes **20** using the calcium alkoxide−Pybox complex **18a** (Table 10).[25] Asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds to nitroalkenes are some of the most important methods for the preparation of chiral γ-nitro carbonyl compounds, which can be converted into various chiral amines by reduction. It was found that the addition of *p*-methoxyphenol as an additive to form a calcium aryloxide was the key for achieving a high enantioselectivity, and nitroalkenes **20** with substituted phenyl groups reacted smoothly to afford the desired 1,4-adducts **21** in high yields with a high enantioselectivity. A nitroalkene bearing a heterocycle and an aliphatic nitroalkene also worked well. The important role of the phenol derivative was assumed to be from its steric bulkiness, as well as it being a more acidic proton source than alkyl alcohol to accelerate the catalyst turnover.

The assumed catalytic cycle of this reaction is shown in Figure 6. The calcium−Pybox complex **19** prepared from calcium alkoxide, ligand **18**, and *p*-methoxyphenol deprotonates the α-position of malonate **9b** to give the chiral calcium enolate **19-A** *in situ*. The enolate that is formed reacts with β-nitroalkene **20** to afford the initial 1,4-addition intermediate **19-B**, and the subsequent protonation by the phenol derivative affords the 1,4-adduct **21** and regenerates the catalyst.

Asymmetric Mannich Reaction. Our chiral calcium−neutral coordinative ligand system is applicable to Mannich reactions of malonates with imines. The Mannich reaction of malonates with imines represents one of the most attractive ways to provide β-aminocarbonyl compounds, which are interesting building blocks in synthetic organic and medicinal chemistry. We found that the use of $Ca(O^iPr)_2$ and Pybox **18b** was the best system for the Mannich reaction of dibenzyl malonate **9c** with the *N*-Boc imine **22** and that the desired reactions occurred within 2 h in most cases, with moderate to good enantioselectivities (Table 11).[26] The interaction between the benzyl part of the malonate and the aromatic group of the ligand may be important in forming an effective asymmetric environment. To the best of our knowledge, this is the first reported use of a chiral calcium−Pybox complex in the Mannich reaction of malonates with imines.

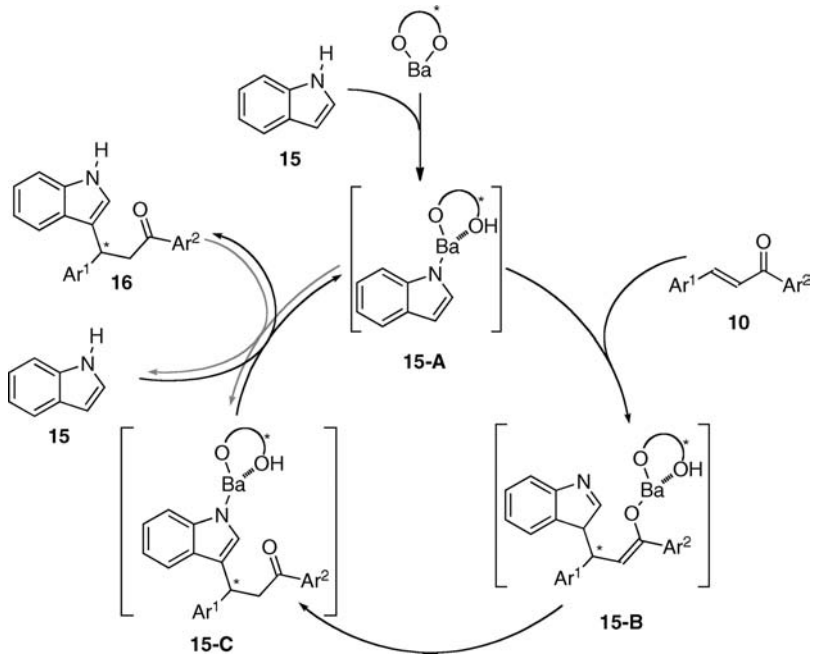
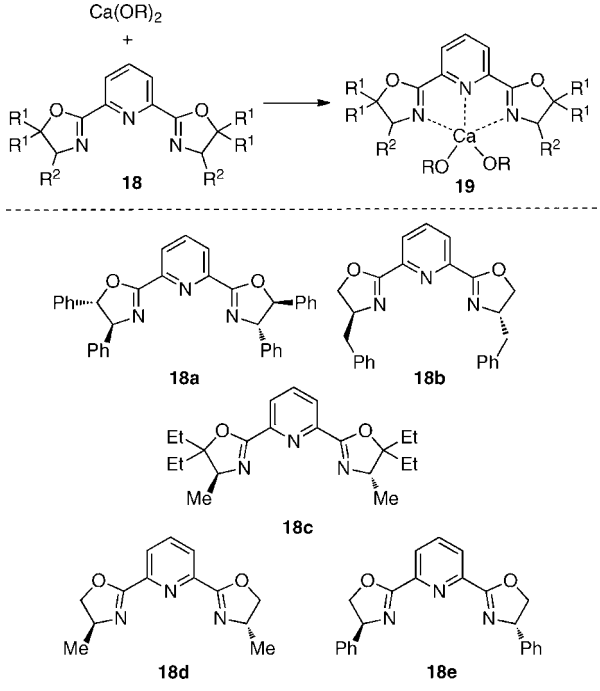


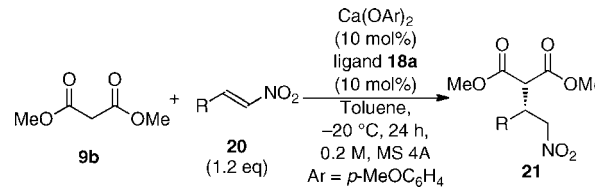
FIGURE 5. Assumed catalytic cycle of the asymmetric Friedel–Crafts-type reaction of indole.

SCHEME 7. Calcium Alkoxide–Chiral Pyridinebisoxazoline Complexes



Asymmetric 1,4-Addition of Azlactones. Furthermore, the catalytic asymmetric 1,4-addition of α-amino acid derivatives to α,β-unsaturated esters was investigated using the calcium alkoxide–Pybox **18** system for synthesis of chiral α-substituted glutamic acid derivatives. α,α-Disubstituted amino acids are recognized as interesting components in bioorganic chemistry because these unnatural amino acids can modify structures of peptides or proteins in an unusual manner. For this purpose, azlactones **24** are attractive enolate equivalents of α-amino acids due to their active α-protons having a high acidity. We investigated the asymmetric 1,4-addition of azlactone **24** to acrylate **2a** and found that calcium isopropoxide–Pybox complexes **18c** or **18d** were effective. The desired 1,4-adduct **25** was obtained with moderate to good enantioselectivity (Table 12).[27] To the best of our knowledge, this is the first reported example of catalytic asymmetric 1,4-addition reactions of azlactones to acrylic esters.

TABLE 10. Asymmetric 1,4-Addition of a Malonate with Nitroalkenes Using a Calcium–Chiral Pybox Complex



entry	R	yield (%)	ee (%)
1	Ph	80 (quant)[a]	96 (94)[a]
2[b]	*p*-$MeOC_6H_4$	95	93
3[b]	*p*-MeC_6H_4	92	94
4[b]	*m*-MeC_6H_4	quant	94
5[b]	*o*-MeC_6H_4	97	65
6	*p*-BrC_6H_4	93	93
7	2-furyl	96	94
8[c]	$^cC_6H_{11}$	73	87

[a] 1.0 mol % catalyst in 0.6 M for 18 d. [b] For 48 h. [c] For 72 h.

Catalytic 1,4-Addition and Enantioselective Protonation. Asymmetric protonation is an attractive method to build tertiary chiral carbon centers.[28] However, control of the proton transfer is usually difficult, because the proton is the smallest

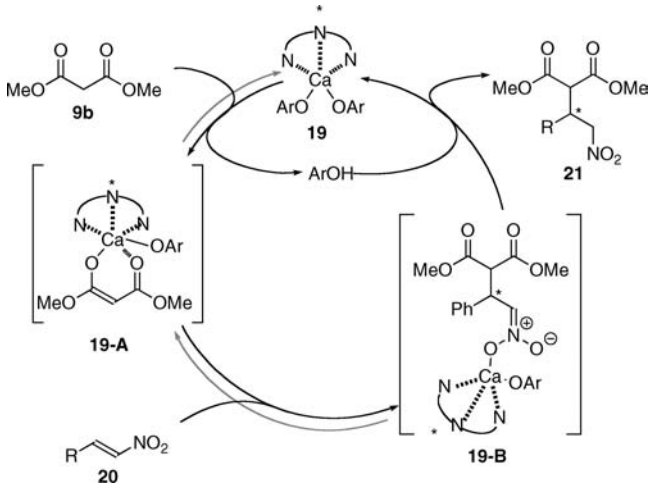
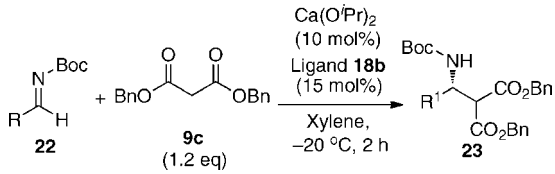


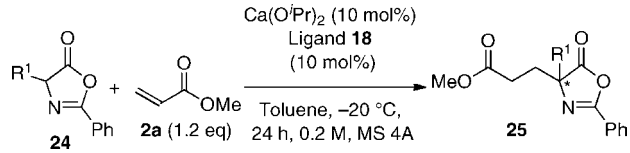
FIGURE 6. Assumed catalytic cycle of the asymmetric 1,4-addition with the nitroolefins.

TABLE 11. Asymmetric Mannich Reactions of a Malonate



entry	R	yield (%)	ee (%)
1	Ph	90	73
3	*o*-MeC_6H_4	90	77
4	*m*-MeC_6H_4	93	71
5	*p*-$MeOC_6H_4$	75	66
6	*o*-$MeOC_6H_4$	92	56
7	*p*-FC_6H_4	91	72
8	*p*-ClC_6H_4	82	61
9	3,4-$(OCH_2O)C_6H_3$	92	67
10	1-naphthyl	73	66
11	2-furyl	95	76
12	2-thienyl	89	54

TABLE 12. Asymmetric 1,4-Addition of Azlactones with Methyl Acrylate

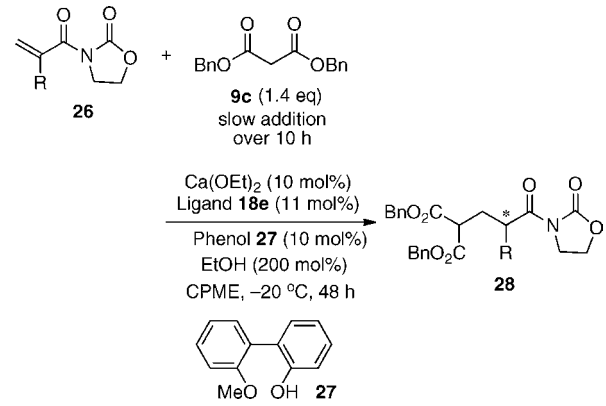


entry	R^1	Pybox	yield (%)	ee (%)
1	Me	**18c**	78	81
2	Et	**18c**	77	71
3	^{n}Pr	**18d**	92	76
4[a]	Bn	**18d**	75	64
5	^{i}Bu	**18d**	78	84

[a] In 0.1 M.

positive species in the periodic table. Strict control of the asymmetric environment around active olefins is required to realize a high enantioselectivity. We designed the asymmetric protonation of an enolate formed after 1,4-addition of malonate **9c** to the α,β-unsaturated carbonyl compound **26** bearing oxazolidinone as a directing group, which can provide a chiral 2-substituted-1,5-pentanedicarboxylic acid derivative in a short-step transformation. The chiral calcium−Pybox **18e** catalyst system was successfully applied to this reaction sequence and excellent enantioselectivities were obtained (Table 13).[29] It was found that cyclopentyl methyl ether (CPME) was the best solvent and that the phenol derivative **27** played a key role in the deprotonation and enantioselective protonation steps to achieve a high enantioselectivity. For this process, the use of an excess of EtOH as well as the slow addition of the malonate were very important to obtain the desired products in high yields. This may be because it is critical to suppress the aggregation of the active complex consisting of the calcium−Pybox and the malonate. These results indicate that the current chiral calcium catalyst system has a good potential to act as a chiral Brønsted base catalyst.

TABLE 13. Catalytic 1,4-Addition and Asymmetric Protonation Sequense Using a Chiral Calcium Complex



entry	R	yield (%)	ee (%)
1	Me	90 (88)[f]	95 (92)[f]
3	CH_2=$CHCH_2$	86	96
4[a,b]	Me_2C=$CHCH_2$	85	93
5	*cis*-ClCH=$CHCH_2$	96	95
6[b,c]	PhCH=$CHCH_2$	85	94
7[d]	$PhCCCH_2$	88	94
8	$BnOCH_2CCCH_2$	77	93
9	$BuCCCH_2$	91	94
10[e]	Ph	72	48

[a] At 0.06 M. [b] For 72 h. [c] In a mixed solvent (CPME/THF = 2/1). [d] In a mixed solvent (CPME/toluene = 4/1). [e] In a mixed solvent (toluene/DCM = 4/1) at 0.06 M for 24 h. [f] 5 mol % of the catalyst.

The assumed catalytic cycle of the 1,4-addition and enantioselective protonation sequence is shown in Figure 7. At first, a chiral calcium complex **29** bearing ethoxide and aryloxide was formed by mixing calcium ethoxide, Pybox **18e**, and phenol derivative **27**. The complex deprotonated malonate **9c** to form calcium enolate **29-A**, releasing **27**. The enolate then attacked the α,β-unsaturated carbonyl compound **26** to form

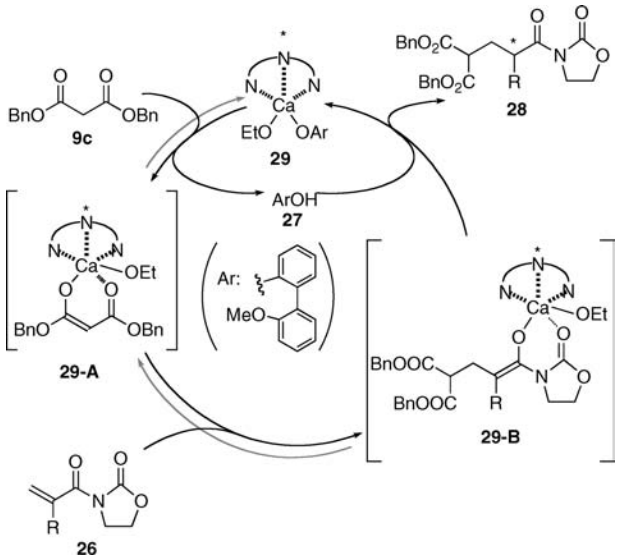


FIGURE 7. Assumed catalytic cycle of the 1,4-addition and asymmetric protonation sequence.

calcium enolate **29-B**, which was protonated by **27** to afford the desired product **28**, along with regeneration of the calcium catalyst **29**. This mechanism was supported by evidence from deuterium-labeling experiments using C_2D_5OD or malonate-d_2.

As described above, neutral coordinative ligands, Pybox derivatives, successfully modified calcium Brønsted base compounds in an asymmetric manner to realize highly enantioselective asymmetric reactions. Thus, a new possibility of using alkaline earth metal compounds in asymmetric catalysis has been shown. Further investigations into effective chiral coordinative ligands for alkaline earth metals are proving promising.

Conclusions

Over the past decade, many types of highly stereoselective metal catalysts have been actively developed. While some metals are in the center of the spotlight, other metals have been left on the edge of the stage, attracting little interest. However, those metals still have the potential and the ability to act as new catalysts or activators that may be hidden. Here, we have developed new chiral alkaline earth metal (calcium, strontium, and barium) catalysts for highly enantioselective carbon−carbon bond-forming reactions. Alkaline earth metals are very attractive because they are abundant and ubiquitous elements in nature and form safe compounds compared with other heavy transition metals. However, their positive use as catalysts in asymmetric synthesis is still limited. Their strong Brønsted basicity and mild Lewis acidity can influence their catalytic activity, as well as chiral modification of a complex in a positive manner.

For the chiral modification of alkaline earth metals, chiral bisoxazoline (Box) derivatives bearing methylene tether parts were first chosen as ligands, and it was found that highly enantioselective chiral Brønsted bases were formed by combining these ligands with calcium alkoxide to promote catalytic asymmetric 1,4-addition and [3 + 2] cycloaddition reactions with high diastereo- and enantioselectivities. Mechanistic studies indicated that the methylene part of the Box ligand was deprotonated by the calcium alkoxide to form an active calcium complex. Not only calcium−Box complexes but also chiral strontium−bissulfonamide and chiral barium−BINOLate complexes could catalyze asymmetric 1,4-addition reactions with high enantioselectivities. We also designed a calcium−neutral coordinative ligand complex as a new type of chiral alkaline earth metal catalyst, and it was revealed that pyridinebisoxazolines (Pybox) could work as promising ligands for calcium compounds in 1,4-addition reactions, Mannich reactions, and 1,4-additions, accompanying enantioselective protonation. It should be noted that the Box or Pybox ligands employed here were prepared from natural α-amino acids or their derivatives. These catalysts can be used as useful and abundant chiral Brønsted base catalysts.

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BIOGRAPHICAL INFORMATION

Shū Kobayashi studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer then associate professor at the Science University of Tokyo. In 1998, he moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as full professor. In April 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, within the Faculty of Science of The University of Tokyo. Professor Kobayashi is also director of the ERATO project of the Japan Science Agency (JST, 2003−2009), and director of the NEDO project of the Ministry of Economy, Trade and Industry, Japan (2009 to the present).

Yasuhiro Yamashita was born in Gifu, Japan, in 1973. He studied chemistry in Graduate School of Pharmaceutical Sciences, The University of Tokyo, and received a Ms.D. in 1998 (supervisor, the late Professor Kenji Koga) and a Ph.D. in 2001 (supervisor, Shū Kobayashi). He started his academic career as an assistant professor in 2001 at Graduate School of Pharmaceutical Sciences, the University of Tokyo. He then joined Professor John F. Hartwig's group at Yale University as a postdoctoral fellow (2005−2006). He returned to The University of Tokyo and was

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FOOTNOTES

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