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Alkaline-Earth Metal-Based Chiral Lewis Acids

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1.1 Introduction

Catalysis based on transition metal compounds has received considerable attention over the years. In this field, asymmetric catalysis based on chiral Lewis acids is broadly recognized as a significant tool for the preparation of optically active compounds. However, from the perspective of green sustainable chemistry, it is highly preferred to find environmentally friendly processes and catalysts. In contrast to most transition and noble metal complexes, chiral alkaline-earth metal-based catalysts offer high efficiency and stereoselectivity but also less toxicity and less potential for harm. That is why the studies of asymmetric transformations with the use of these novel catalytic systems are attracting ever-growing interest.

1.2 General Properties of Alkaline Earth Metal Compounds

In alkaline-earth metal-catalyzed reactions, the amphoteric acid/base character of the complexes is of extreme importance. The strong Brønsted basicity allows for the abstraction of acidic protons, such as the α-protons of carbonyl compounds. On the other hand, the significant Lewis acidity is used for stereocontrol of the reaction [1–5]. These unique properties of alkaline earth metal complexes are due to the chemical properties of Group II metals. Both the Brønsted basicity and the Lewis acidity are directly connected to the electronegativity of the metals [1, 2, 5]. For this reason, the calcium compounds are weaker Brønsted bases and stronger Lewis acids than barium and strontium complexes when coupled with similar counterions [1, 2, 5]. However, the smaller ionic radius and smaller coordination number of calcium makes it more amenable to chiral modifications than strontium or barium [1, 4, 6]. Moreover, the character of the ligand exerts an influence not only on the asymmetric environment construction but also on the amphoteric acid/base character of the alkaline earth metal compounds.

Chiral Lewis Acids in Organic Synthesis, First Edition. Edited by Jacek Mlynarski.

Taking into account the character of ligands and the type of bonds between the metal and the ligand, chiral alkaline earth metal complexes have been classified into three types (Figure 1.1) [1, 2, 5].

In the first type of complexes, the metal is tightly connected to the anionic chiral ligands through covalent bonds. Since these ligands act as Brønsted bases, it is difficult to control the basicity of the catalyst. However, when anionic chiral ligands are bonded to the metal by a combination of one covalent and further coordinative bonds (type II), the Brønsted basicity can be controlled by changing the remaining free counterion [1, 2, 5]. Thanks to the presence of a covalent bond in both type I and type II complexes, there is a possibility for strict control of the asymmetric environment [1, 2, 5].

On the other hand, the construction of chiral alkaline earth metal complexes by attaching a ligand through only coordinative bonds (type III) is also possible [1, 2, 5]. The metal center interacts efficiently with Lewis bases, such as neutral coordinative ligands, owing to its significant Lewis acidity [1, 2, 5]. In such complexes, the two remaining anionic ligands act as effective Brønsted bases. Moreover, the Brønsted basicity of the whole compound should be enhanced by electron donation of the ligands to the metal center [1, 2, 5].

1.3 Applications in Asymmetric Synthesis

Scientists all around the world still carry out research into highly stereoselective reactions including asymmetric transformations which target optically active compounds [1]. One of the most popular approaches in this regard is organocatalysis based on heavy transition metal compounds. However, there is a necessity to find environmentally friendly catalytic systems from the viewpoint of green sustainable chemistry [1, 2, 5, 7]. An alternative path is the use of the chiral alkaline earth metal catalysts [1, 2, 5]. This approach also allows for enantiomeric or diastereomeric enrichment, which is crucial for asymmetric synthesis, but is less environmentally damaging [1–5]. Moreover, the unique chemical properties of Group II metals, such as amphoteric acid/base character, divalent stable oxidation state, and the high coordination numbers to the metal center allow to obtain three types of chiral alkaline earth metal complexes, which collectively find applications in a number of organic reactions [1, 2, 5]. We review many of these applications below.

1.3.1 Cycloaddition Reactions

Some of the fundamental processes in organic chemistry that have been developed over the years are cycloaddition reactions. This type of pericyclic process

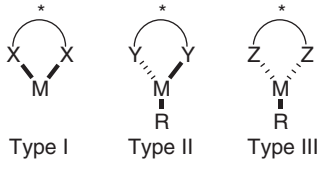


Figure 1.1 Types of alkaline earth metal complexes.

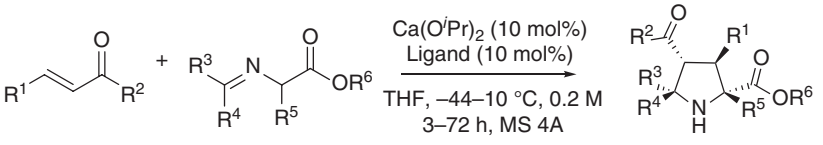
can be used to obtain cyclic adducts and asymmetric versions of such transformations are extremely useful methods to construct highly functionalized derivatives in an optically active form. For instance, asymmetric 1,3-dipolar cycloaddition reactions are some of the most efficient and often used tactics to synthesize five-membered heterocyclic rings, in regio- and stereocontrolled fashion [1, 6, 8, 9]. In particular, [3+2] cycloaddition reactions are a useful method for synthesizing chiral pyrrolidine derivatives, which are important building blocks in the syntheses of many natural products and pharmaceuticals [1, 4, 6]. Several enantioselective metal catalyst systems have been employed to these reactions, but most of these systems require additional bases [1, 10]. This inspired Kobayashi and Yamashita's investigation of asymmetric [3+2] cycloaddition reactions using chiral calcium catalysts [4, 10–13]. They successfully applied chiral Box–calcium complexes to reactions of glycine Schiff bases with β-substituted α,β-unsaturated esters, such as methyl crotonate (Scheme 1.1), and obtained the desired chiral pyrrolidine derivatives with high yields, complete diastereoselectivities, and excellent enantioselectivities (Table 1.1) [10–12].

However, the results of their research indicate that the size and character of the substituent in the aldehyde part of the imine could play an important role in the enantioselectivity of the Box–calcium complex-catalyzed [3+2] cycloaddition reactions [1, 3, 5]. In comparison with glycine Schiff bases that are prepared from aromatic aldehydes (Table 1.1, entries 1–10; Table 1.2, entries 1–10), aliphatic aldehyde derivatives (Table 1.2, entries 11–12) are less stable. This stems from possible tautomerization processes which lead to the formation of enamines. These competitive processes could be crucial in Kobayashi's group research. Moreover, aromatic substituents form better stabilized carbocations, which shifts the equilibrium of the reaction toward the formation of the cyclic adducts and induces higher enantioselectivity.

These catalytic systems have performed well in the constructing of highly substituted contiguous chiral carbon centers using amino acid derivatives containing an α-alkyl group and α,β-unsaturated carbonyl compounds (Table 1.3) [1, 4, 5].

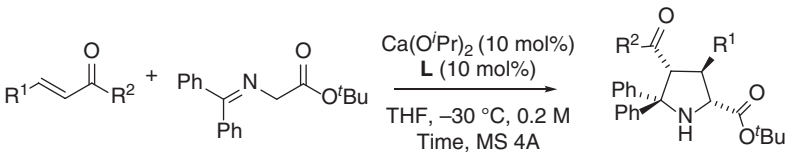
The chiral Lewis acids that were developed by Kobayashi and co-workers, prepared from calcium alkoxides with chiral bisoxazoline ligands bearing active methylene moieties, were classified as type II [3].

During the preparation of these catalysts, an anionic bidentate Box ligand is produced by deprotonation. The chiral ligand is then bound to the metal by a combination of covalent and coordinate bonds, assisted by the mild Lewis acidity of alkaline earth metals (Figure 1.2) [3].

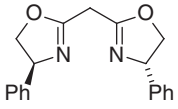


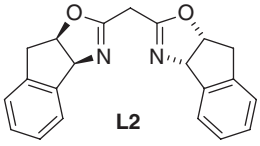
Scheme 1.1 A Box–calcium complex-catalyzed [3+2] cycloaddition reaction of amino acid Schiff bases with α,β-unsaturated carbonyl compounds [1, 4].

Table 1.1 Asymmetric [3+2] cycloaddition of a glycine ester Schiff base with α,β-unsaturated carbonyl compounds [1].



Entry	R^1	R^2	Ligand	Time (h)	Yield (%)	*ee* (%)
1	MeO	Me	**1**	3	Quant.	>99
2	EtO	Me	**1**	3	98	98
3	^{t}BuO	Me	**1**	3	77	87
4	MeO	Et	**2**	24	Quant.	95
5	MeO	^{i}Bu	**2**	24	Quant.	99
6	MeO	^{n}Heptyl	**2**	48	97	>99
7	NMe_2	H	**1**	12	83	95
8	 1: X=O 2: X=CH_2	H	**1**	24	76	98
9		H	**1**	24	84	97
10	^{c}Hex	H	**1**	24	93	91


L1

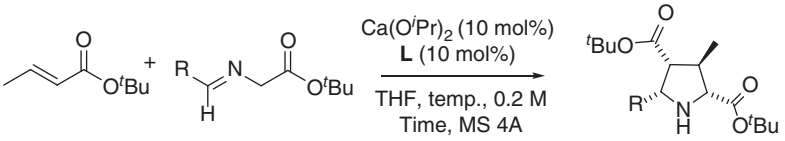

L2

This type of bonding opens up the opportunity for strict control of the effective asymmetric environment. Furthermore, the Brønsted basicity of such complexes can be controlled by changing the remaining free counterion [3].

While chiral Box–calcium complexes prepared from calcium isopropoxide worked well in asymmetric [3+2] cycloaddition reactions, further investigations showed that stronger Brønsted bases such as calcium amides (e.g., $Ca(HMDS)_2$) could be employed successfully in these types of reactions (Scheme 1.2). Moreover, they exhibit higher solubility in many solvents when compared with calcium alkoxides, which makes them more suited to organic synthesis [1, 3–5].

Examination of the chiral alkaline earth metal complexes has shown that these Lewis acids are useful catalytic systems in Diels–Alder cycloadditions as well. For years, the [4+2] cycloaddition reaction has been one of the best methods for the preparation of six-membered rings and Lewis acid-catalyzed asymmetric Diels–Alder reactions have been widely reviewed to date [13, 14]. It has been

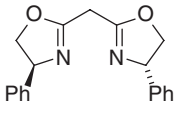
Table 1.2 Asymmetric [3+2] cycloaddition of a Schiff base of a glycine ester with *t*-butyl crotonate [1].

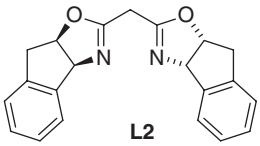


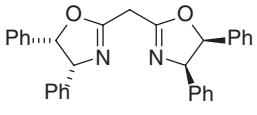
(1.2 equiv.)

Entry	*R*	Ligand	Time (h)	Temperature (°C)	Yield (%)	*ee* (%)
1	Ph	**1**	3	10	86	86
2	*p*-ClC_6H_4	**2**	8	–20	92	82
3	*p*-BrC_6H_4	**1**	3	10	95	86
4	*p*-MeC_6H_4	**3**	12	–30	92	87[a]
5	*m*-MeC_6H_4	**2**	12	–20	Quant.	91
6	*o*-MeC_6H_4	**1**	3	10	86	78
7	3,5-$Me_2C_6H_3$	**1**	12	10	Quant.	94
8	2-Naphtyl	**1**	3	10	97	92
9	*p*-$MeOC_6H_4$	**1**	12	10	76	86
10	2-Furyl	**3**	12	–30	97	90[a]
11	^{t}Bu	**2**	12	–20	80	38
12	Cy	**2**	12	–20	97	29

a) The absolute configuration of the product was reversed.


L1


L2

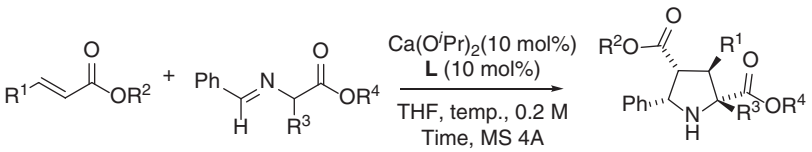

L3

frequently reported that the reaction rate and selectivity depends on the Lewis acidity of the metal and the Lewis basicity of the counterion [2]. Moreover, the HOMO–LUMO energy gap plays an important role in the pericyclic reactions. Classic Lewis acids promote these types of reactions by coordinating to the dienophile and lowering the LUMO energy. On the other hand, investigations of Shibasaki *et al*. have shown that the reaction of a silyloxydiene with fumarate is likely promoted through a HOMO-raising mechanism. This reaction catalyzed by chiral barium complexes yields a precursor for the synthesis of optically active oseltamivir (Tamiflu) (Scheme 1.3) [3, 13].

The catalytic cycle of the Diels–Alder type reaction postulated by Shibasaki and co-workers is based on the formation of a chiral barium-activated diene (Figure 1.3) [13].

First, the silyloxydiene is activated by the fluoride cocatalyst, which facilitates the formation of a barium dienolate through transmetalation with the barium

Table 1.3 Asymmetric [3+2] cycloaddition of a Schiff base of α-amino esters with α,β-unsaturated carbonyl compounds [1].



Entry	R^1	R^2	R^3	R^4	Ligand	Time (h)	Temperature (°C)	Yield (%)	*ee* (%)
1	H	^{t}Bu	Me	Me	**1**	12	10	Quant.	90
2	H	^{t}Bu	Me	Et	**1**	3	10	Quant.	91
3	H	^{t}Bu	Me	Bn	**1**	3	10	93	90
4	H	^{t}Bu	^{i}Pr	Me	**1**	3	10	32	59
5	H	^{t}Bu	Et	Me	**2**	12	−30	82	96
6	H	^{t}Bu	Bn	^{t}Bu	**2**	12	−30	90	92
7	H	^{t}Bu	^{n}Bu	Me	**2**	12	−20	94	94
8	H	^{t}Bu	^{i}Bu	Me	**2**	12	−30	98	87
9	H	^{t}Bu	CH_2CH_2SMe	Me	**2**	12	−20	81	81
10[a]	H	^{t}Bu	CH_2O^tBu	^{t}Bu	**2**	12	−20	80	93
11	Me	Me	Me	Me	**2**	12	0	79	96
12	Et	Me	Me	Me	**2**	12	0	64	96
13[b]	^{n}Bu	Me	Me	Me	**2**	18	0	81	98
14	Me	Me	Et	Me	**2**	24	−20	42	89
15[b]	Me	Me	^{n}Bu	Me	**2**	72	−30	50	93
16[b]	Me	Me	Bn	^{t}Bu	**2**	72	−30	98	85
17[a]	Me	Me	CH_2O^tBu	^{t}Bu	**2**	24	10	80	97
18[a,b]	^{i}Bu	Me	CH_2O^tBu	^{t}Bu	**2**	24	0	87	95

a) L-Amino acid was used.
b) 20 mol% of catalyst was used.

alkoxide. This achiral diene is reactive enough to produce the barium alkoxide intermediate with the dienophile in a concerted or stepwise manner. Finally, the free oxygen electron pair attacks the trimethylsilyl group that is attached to the ligand, leading to catalyst regeneration and formation of an optically active silylated cyclohexane derivative [3, 13].

Investigations of Shibasaki *et al.* have proved that asymmetric Diels–Alder reactions with ketone-derived silyloxydienes do not depend on acid catalysis. Moreover, unlike chiral barium catalytic systems, calcium, strontium, and magnesium complexes were not effective (Table 1.4). Only Lewis acids prepared from a barium alkoxide and a chiral diol bearing a phosphine oxide moiety gave the expected product [13]. This result shows the importance of the metal Brønsted basicity for the development of effective metal catalysis [1].

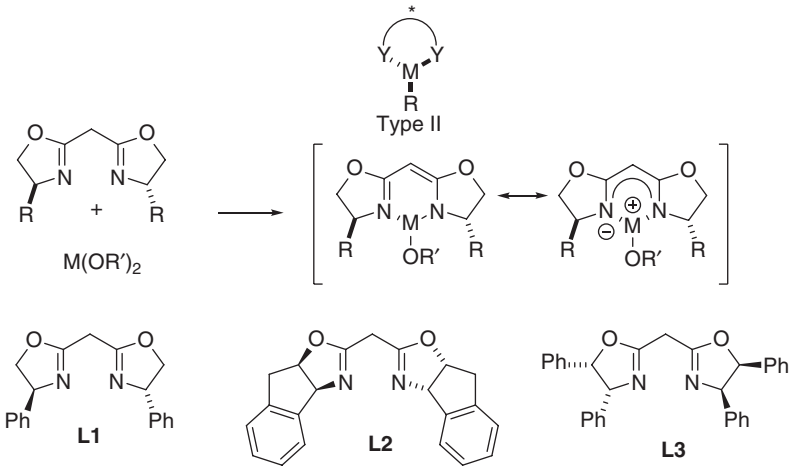
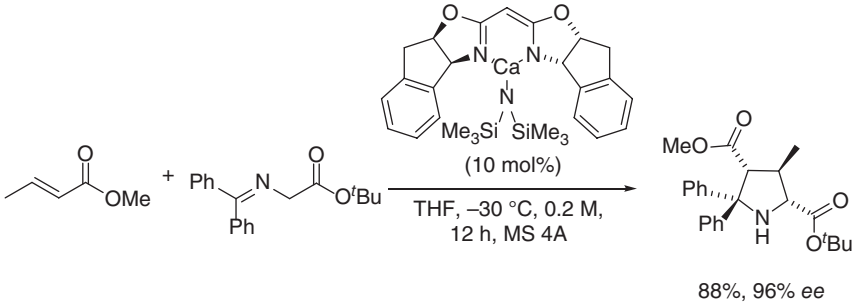
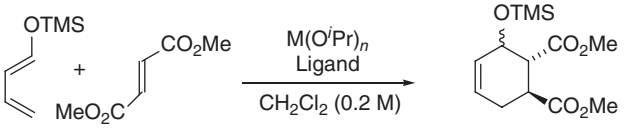


Figure 1.2 Type II chiral alkaline earth metal complexes. Alkaline earth metal–chiral bisoxazoline complexes [1, 3].



Scheme 1.2 Catalytic [3+2] cycloaddition reaction using a Box–calcium complex prepared from calcium amide and bisoxazoline derivative.



Scheme 1.3 Asymmetric Diels–Alder reaction of a silyloxydiene with fumarate catalyzed by chiral alkaline earth metal complexes.

A great deal of attention has been given to hetero-Diels–Alder reactions [2, 15] because of their potential for efficiently constructing functionalized six-membered heterocyclic rings in an enantioselective fashion. Despite many developments in this field and the large number of catalytic systems that have been developed, many groups still carry out research focused on this powerful method of heterocycle synthesis. The investigations of Zhu *et al.* on the enantioselective construction of dihydropyran derivatives are an excellent example. Working toward an effective

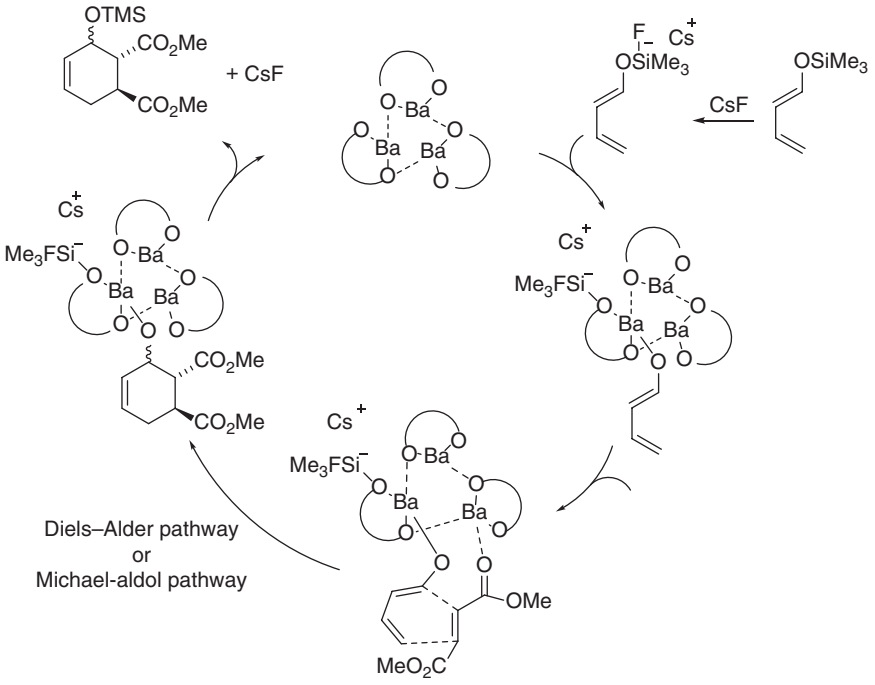


Figure 1.3 The catalytic cycle of asymmetric Diels–Alder-type reaction postulated by Shibasaki.

method for the construction of optically pure oxygen-containing cycloalka[2,3-b] indoles, they have reported that chiral calcium phosphate catalytic systems could be successfully employed in the reaction of oxindole heterodienes with vinyl ethers (Scheme 1.4) [3, 15].

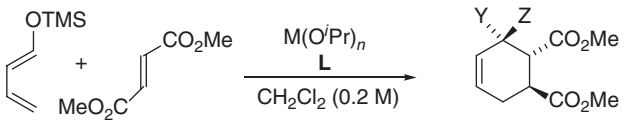
The results of Cheng's group have shown the importance of Lewis acid heterodiene activation in achieving the desired product formation [3]. Moreover, the screening of catalysts for the hetero-Diels–Alder reactions revealed that strontium and barium compounds could also catalyze this class of reactions [15]. However, the lower yields and enantioselectivities that were obtained from strontium- and barium-based catalysts, versus calcium-based ones, indicate that the Lewis acidity of the metal plays an important role in this type of catalysis.

1.3.2 Carbonyl and Imine Addition Reactions

However, chiral strontium catalysts proved to be successful in Mannich-type reactions. This approach is the first example of this kind of catalytic reaction on sulfonylimidates and provides the desired addition product, of *N*-Boc-imines to the ester surrogate, with good yields and moderate enantioselectivity (Table 1.5) [16, 17].

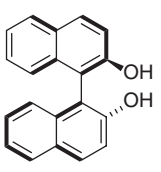
Moreover, further works have revealed that high enantioselectivity could be induced using a combination of $Sr(O^iPr)_2$ and a bis(sulfonamide) chiral ligand which bears a diphenylethylenediamine backbone (Scheme 1.5). In this catalytic system, the strontium complex coordinates to the nitrogen of the sulfonylimidate and increases the acidity of the α-proton of the sulfonylimidate, allowing deprotonation by Et_3N [16, 17].

Table 1.4 Influence of the alkaline earth metal complexes on the enantio- and diastereoselectivity of the asymmetric Diels–Alder reaction.

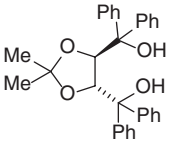


Y = OTMS, Z = H (*endo*: desired)
Y = H, Z = OTMS (*exo*: undesired)

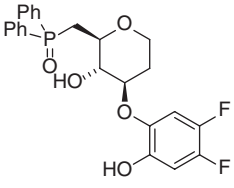
Entry	M	Ligand	Time (h)	Yield (%)	*dr* (%) *endo*/*exo*	*ee* (%) *endo*
1	Mg	**4**	17	0	—	—
2	Ba	**4**	17	45	3/1	4
3	Sc	**4**	17	0	—	—
4	Gd	**4**	17	0	—	—
5	Ba	**5**	0.5	97	4/1	1
6	Ba	**6**	2.5	72	3/1	77
7	Ba	**6**	42	74	3/1	61
8	Ba	**7**	1.5	34	5/1	73
9	Ba	**8**	17	62	6/1	73
10	Ba	**8**	23	64	3/1	88



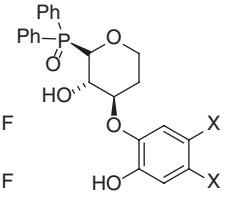
BINOL: **L4**



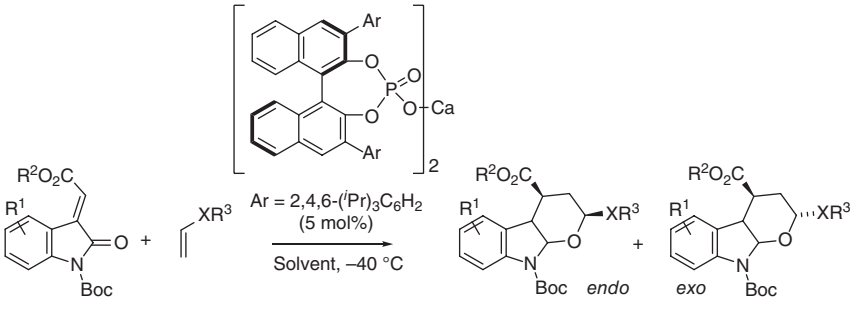
TADDOL: **L5**



F_2-GluCAPO: **L6**



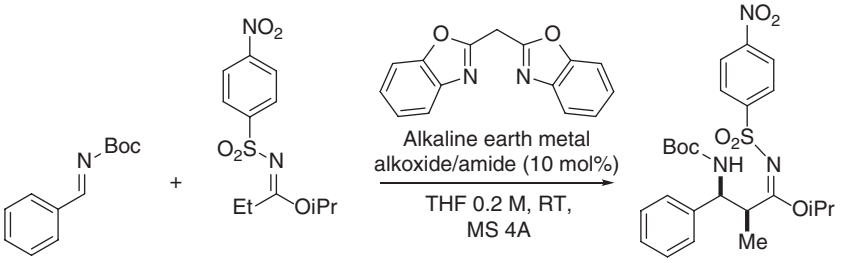
FujiCAPO: **L7** (X = H)
F_2-FujiCAPO: **L8** (X = F)



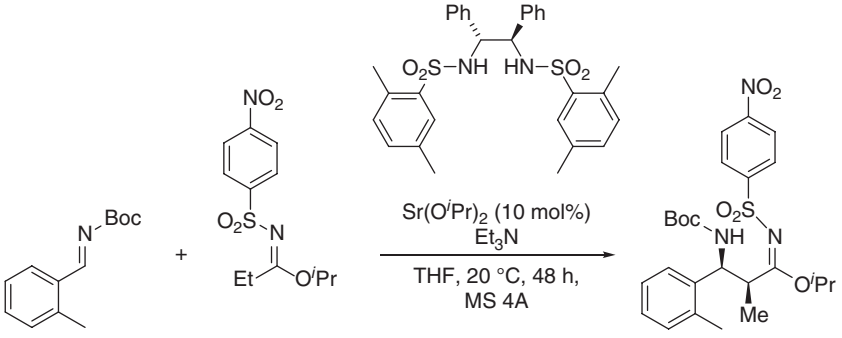
Endo/*exo* > 99 : 1
Up to 99% *ee*

Scheme 1.4 Asymmetric hetero-Diels–Alder reactions of heterodienes with vinyl ethers.

Table 1.5 Chiral alkaline earth metal complex-catalyzed catalytic Mannich reactions of sulfonylimidates with *N*-Boc-imines.



Entry	Catalyst	Time (h)	Yield (%)	*Anti/syn*
1	$Ca(O^iPr)_2$	48	68	11/89
2	$Sr(O^iPr)_2$	48	45	7/93
3	$Ba(O^iPr)_2$	48	65	9/91
4	$1/2[[Sr(HMDS)_2]_2]$	24	92	7/93
5	$1/2[[Sr(HMDS)_2]_2]$	48	76	6/94
6	$1/2[[Sr(HMDS)_2]_2]$	72	65	6/94

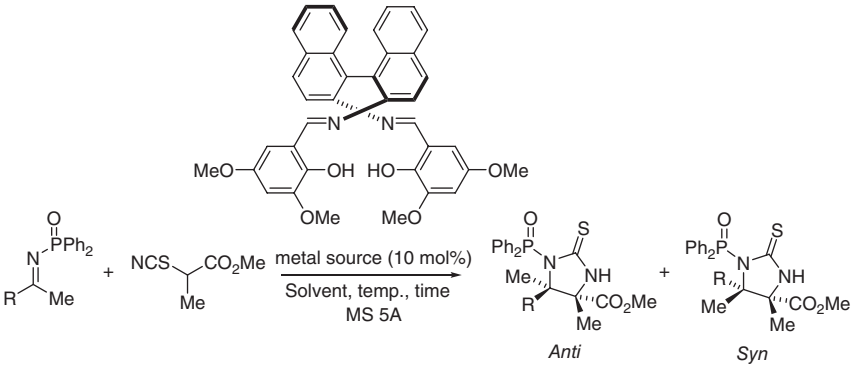


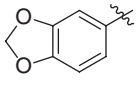
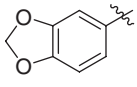
Scheme 1.5 Chiral strontium complex-catalyzed asymmetric Mannich reaction of sulfonylimidates.

Shibasaki *et al.* have also reported that chiral strontium complexes could be applied to asymmetric Mannich reactions. They found that, unlike $Ca(O^iPr)_2$ and $Ba(O^iPr)_2$, the use of Sr or Mg compounds as metal sources gives good results in asymmetric reactions of α-isothiocyanate esters with ketimines. Moreover, the obtained results have shown that the type of metal has an influence on the ratio of *syn* and *anti*-products. Compared with magnesium complexes, the application of strontium complexes reverses the diastereoselectivity and promotes the formation of *anti*-products (Table 1.6) [18].

Likewise, chiral barium complexes which are prepared from a barium alkoxide and optically active BINOL or aryloxide derivatives have been found to be effective

Table 1.6 Catalytic asymmetric Mannich reactions of α-isothiocyanate esters with ketimines.



Entry	Catalyst	*R*	Solvent	Temp (°C)	Time (h)	Yield (%)	*dr syn*/anti	*ee (%)*
1	$Sr(O^iPr)_2$	*p*-BrC_6H_4	$CHCl_3$	r.t.	48	86	6/94	92
2	$Sr(O^iPr)_2$	*p*-ClC_6H_4	$CHCl_3$	r.t.	48	82	10/90	87
3	$Sr(O^iPr)_2$	*p*-FC_6H_4	$CHCl_3$	r.t.	48	71	6/94	90
4	$Sr(O^iPr)_2$	*p*-$CF_3C_6H_4$	$CHCl_3$	r.t.	48	85	11/89	92
5[a]	$Sr(O^iPr)_2$	*p*-MeC_6H_4	$CHCl_3$/THF	r.t.	20	97	6/94	95
6[a]	$Sr(O^iPr)_2$	*p*-MeC_6H_4	$CHCl_3$/THF	r.t.	24	99	8/92	93
7[a]	$Sr(O^iPr)_2$	*p*-$MeOC_6H_4$	$CHCl_3$/THF	r.t.	24	91	4/96	97
8[a]	$Sr(O^iPr)_2$	*p*-$Me_2NC_6H_4$	$CHCl_3$/THF	r.t.	69	45	4/96	97
9[a]	$Sr(O^iPr)_2$		$CHCl_3$/THF	−5	47	76	6/94	95
10[a]	$Sr(O^iPr)_2$	2-Thienyl	$CHCl_3$/THF	0	48	70	13/87	90
11[a]	$Sr(O^iPr)_2$	3-Thienyl	$CHCl_3$/THF	−5	48	74	12/88	92
12[a]	$Sr(O^iPr)_2$	2-Furyl	$CHCl_3$/THF	−10	48	84	17/83	84
13	Bu_2Mg	*p*-BrC_6H_4	$CHCl_3$	−10	48	87	91/9	84
14	Bu_2Mg	*p*-ClC_6H_4	$CHCl_3$	−10	48	90	92/8	85
15	Bu_2Mg	*p*-FC_6H_4	$CHCl_3$	0	44	96	93/7	84
16	Bu_2Mg	*p*-MeC_6H_4	THF	−25	48	99	90/10	82
17	Bu_2Mg		THF	−5	17	96	92/8	81

(Continued)

Table 1.6 (Continued)

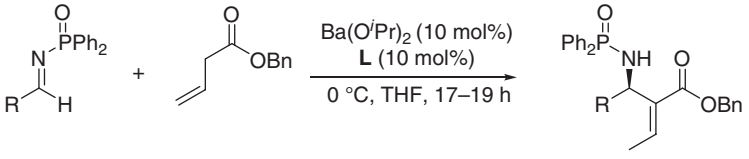
Entry	Catalyst	*R*	Solvent	Temp (°C)	Time (h)	Yield (%)	*dr syn*/anti	*ee* (%)
18	Bu_2Mg	2-Naphtyl	$CHCl_3$	0	48	99	93/7	95
19	Bu_2Mg	3-Thienyl	THF	–25	48	80	93/7	81
20	Bu_2Mg	2-Furyl	$CHCl_3$	–5	48	70	93/7	80

a) $CHCl_3$/THF (2/1).

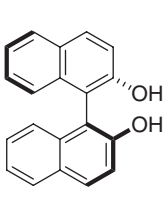
in reactions of β,γ-unsaturated esters with imines, leading to an aza-Morita–Baylis–Hillman-type product *via* isomerization of the initially formed Mannich adducts (Table 1.7) [19].

Alkaline earth metal catalysis have been widely investigated in recent years also by Ishihara *et al*. Their research has revealed that a chiral calcium phosphate, prepared from a calcium alkoxide and phosphoric acid bearing a chiral BINOL backbone, could be successfully applied in asymmetric Mannich reactions of 1,3-dicarbonyl compounds with *N*-Boc-imines. In particular, these Lewis acids were effective for enantioselective Mannich-type reactions with less acidic 1,3-dicarbonyl compounds, including β-ketoesters and thiomalonates (Table 1.8) [20–22].

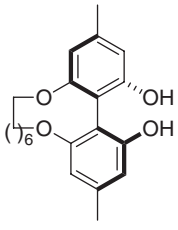
Table 1.7 Chiral barium aryloxide-catalyzed Mannich reactions of β,γ-unsaturated esters with imines.



Entry	Ligand	R	Time (h)	Yield (%)	α/γ	*ee* (%)
1	(*S*)-BINOL	Ph	19	58	>15/1	14
2	(*S*)-Biaryldiol	Ph	17	69	9/1	77
3	(*S*)-Biaryldiol	*p*-MeC_6H_4	19	78	>15/1	80
4	(*S*)-Biaryldiol	2-Thienyl	17	73	>15/1	78

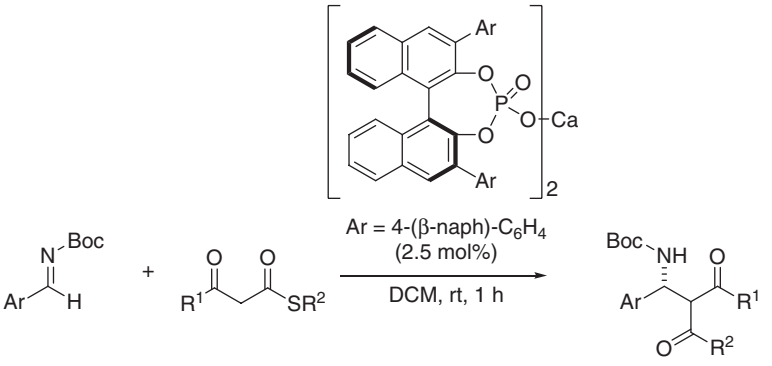


(*S*)-BINOL



(*S*)-Biaryldiol

Table 1.8 Chiral calcium phosphate-catalyzed asymmetric Mannich reactions.



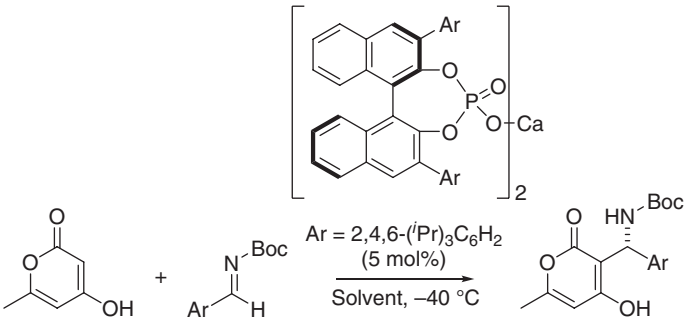
Entry	Ar	R^1	R^2	Yield (%)	*ee (%)*
1	Ph	Ac	Ph	>99	90
2	*p*-MeC_6H_4	Ac	2,6-Xyl	>99	94
3	*p*-$MeOC_6H_4$	Ac	2,6-Xyl	94	92
4	Ph	Ac	2,6-Xyl	>99 (>99)[a]	94 (98)[a]
5	*p*-ClC_6H_4	Ac	2,6-Xyl	90	90
6	*p*-BrC_6H_4	Ac	2,6-Xyl	99	91
7	1-Naphtyl	Ac	2,6-Xyl	88	97
8	3-Thionyl	Ac	2,6-Xyl	>99	96
9	Ph	2,6-Xyl	2,6-Xyl	94	95
10	*p*-$MeOC_6H_4$	2,6-Xyl	2,6-Xyl	81	91
11	*p*-BrC_6H_4	2,6-Xyl	2,6-Xyl	89	95

a) 0.5 mol% of the catalyst was used.

Rueping *et al*. confirmed that the BINOL-phosphoric acid calcium salt is a valuable catalytic system in asymmetric Mannich reactions. However, in contrast with the work of Ishihara *et al*., their investigations have been based on using pyrone (Table 1.9) and 1,3-cyclohexadione (Table 1.10) as carbonyl donors. This approach yielded intermediates that are valuable in organic synthesis with high enantioselectivities [22].

Alkaline earth metals possess multiple coordination sites, which enables them to accept multidentate ligands; Kobayashi *et al*. used this concept to develop chiral calcium catalysts such as (PyBox)-calcium complexes with neutral ligands. They have reported that complexes constructed with a ligand that binds *via* only coordinate bonds are useful in the addition of malonates to imines (Table 1.11). However, only aromatic-substituted *N*-Boc imines yielded the Mannich-type product in high yields and with moderate-to-good enantioselectivities [23].

Table 1.9 Chiral calcium phosphate-catalyzed asymmetric Mannich reaction of *N*-Boc-imine with pyrone.



Entry	Ar	Solvent	Yield (%)	*ee* (%)
1	*p*-MeC_6H_4	Bu_2O	49	88
2	*p*-MeC_6H_4	$CHCl_3$	62	82
3[a]	*p*-MeC_6H_4	$CHCl_3$	45	39
4	*m*-ClC_6H_4	Bu_2O	43	76
5	*o*-BrC_6H_4	Bu_2O	55	86
6	*o*-BrC_6H_4	Bu_2O	43	73
7[a]	*o*-BrC_6H_4	$CHCl_3$	67	84
8	Ph	Bu_2O	43	52

a) 10 mol% phosphoric acid **1** was added.

1.3.3 Conjugate Addition Reactions

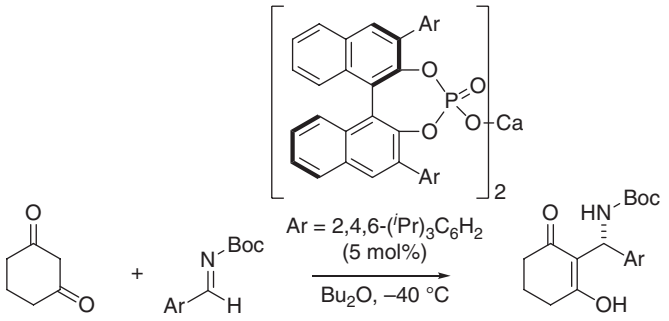
Conjugate addition reactions are one of the most powerful carbon–carbon and carbon–heteroatom bond forming strategies known in organic chemistry. Numerous examples are known in the literature, some of which have been reviewed [24, 25]. Asymmetric Michael additions are crucial transformations in the syntheses of medicinally relevant compounds and natural products [26].

The first example of an asymmetric Michael addition catalyzed by a chiral alkaline earth metal complex was described by Kumaraswamy and co-workers in 2001 (Scheme 1.6). They developed an addition of malonates to α,β-unsaturated acyclic/cyclic ketones and aldehydes, catalyzed by a calcium-BINOL complex, and obtained the conjugate addition products with modest yields and enantioselectivities [27].

In the same report, thiophenol was used as a substrate, although furnishing a racemic product. Addition of ethanol was found to be advantageous, increasing the reaction rate and enantioselectivity.

In their next report, in 2003, the Kumaraswamy group proposed an asymmetric epoxidation of chalcones using ^{t}BuOOH as the oxidizer (Scheme 1.7). A similar calcium-BINOL complex was used in the reaction [28]. However, in contrast to the previous report, most additives were found to have a deleterious effect on

Table 1.10 Chiral calcium phosphate-catalyzed asymmetric Mannich reaction of *N*-Boc-imine with 1,3-cyclohexadione.



Entry	Ar	Yield (%)	*ee* (%)
1	*p*-MeC_6H_4	47	73
2	*o*-BrC_6H_4	49	83
3	*o*-BrC_6H_4	53	72
4	*o*-BrC_6H_4	48	62
5	*p*-$CF_3C_6H_4$	48	88

the process. Ultimately, molecular sieves were found to be instrumental for the initiation of the reaction.

The products were obtained with good yields and modest enantioselectivities. The authors also carried out preliminary investigations on the structure of the active catalyst and proposed on the basis of mass spectrometry analysis, that it was an oligomer.

The same authors have used a calcium octahydro-BINOL complex in the addition of cyclic β-ketoesters to methyl vinyl ketone, furnishing quaternary stereocenters (Scheme 1.8) [29].

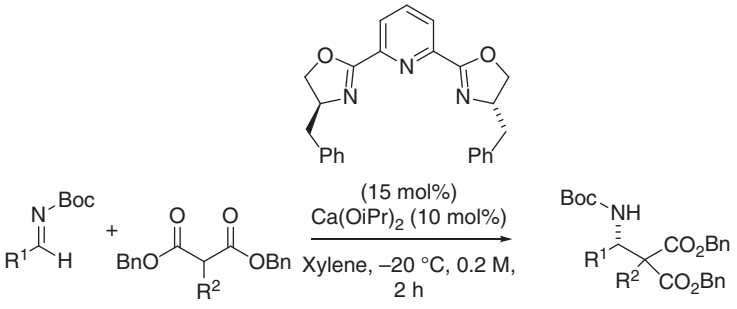
The products were obtained with very good yields and good enantioselectivities. The authors found that the more rigid five-membered β-ketoesters gave better enantioselectivities than their six-membered congeners. The direction of asymmetric induction was found to vary depending on the substrate. Acyclic substrates gave negligible enantioselectivities.

Another class of calcium catalysts have been used by the Kobayashi group in the synthesis of glutamic acid derivatives from protected glycines (Scheme 1.9) [11]. The authors have employed a calcium bisoxazoline complex and obtained the products with excellent yields and enantioselectivities. Strontium and barium were also examined, but only calcium gave good outcomes for the reaction.

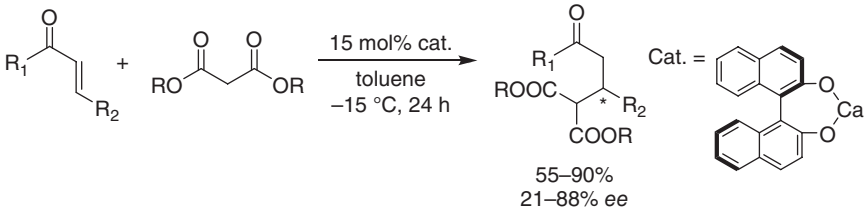
Esters, Weinreb amides, and sulfones have been used as the Michael acceptors. Where applicable, the products were normally obtained with good diastereoselectivities.

Switching to a more bulky ligand, the same authors have described an extension of this methodology to 3-substituted Michael acceptors (Scheme 1.10) [12].

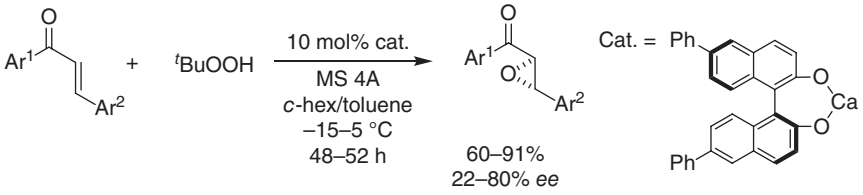
Table 1.11 Asymmetric Mannich reactions of malonates with *N*-Boc imines catalyzed by a chiral PyBox–calcium complex.



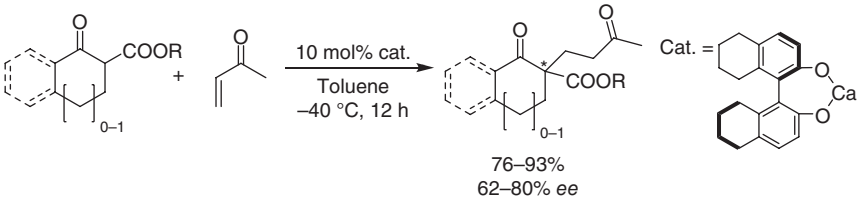
Entry	R^1	R^2	Yield (%)	*ee* (%)
1	Ph	H	90	73
2	Ph	Me	84	62
3	Ph	Bn	95	16
4	*o*-MeC_6H_4	H	90	77
5	*m*-MeC_6H_4	H	93	71
6	*p*-$MeOC_6H_4$	H	75	66
7	*o*-$MeOC_6H_4$	H	92	56
8	*p*-FC_6H_4	H	91	72
9	*p*-ClC_6H_4	H	82	61
10	3,4-$(OCH_2O)C_6H_3$	H	92	67
11	1-Naphtyl	H	73	66
12	1-Furyl	H	95	76
13	2-Thienyl	H	89	54
14	^{c}Hex	H	80	4



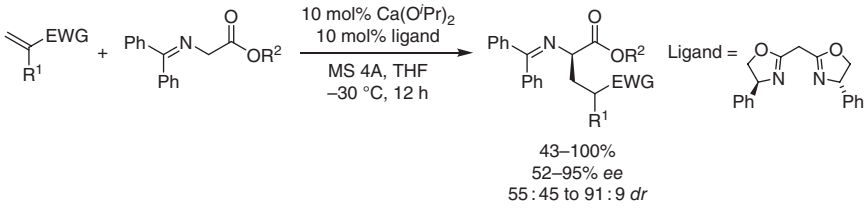
Scheme 1.6 The calcium-catalyzed asymmetric addition of malonates to α,β-unsaturated ketones.



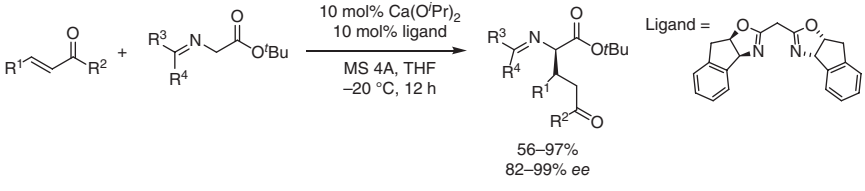
Scheme 1.7 The calcium-catalyzed epoxidation of chalcones.



Scheme 1.8 The asymmetric addition of β-ketoesters to methyl vinyl ketone.



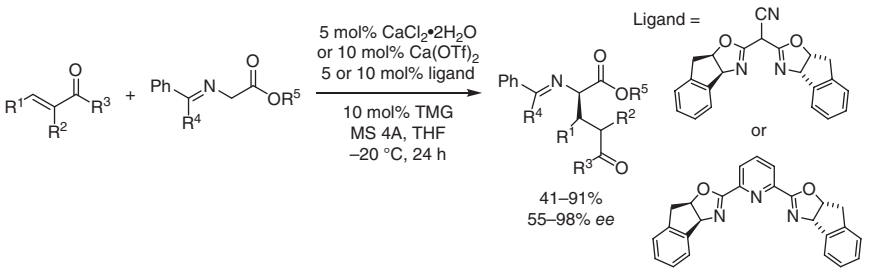
Scheme 1.9 The Box–calcium-catalyzed addition of protected glycines to Michael acceptors.



Scheme 1.10 The asymmetric synthesis of substituted glutamic acids.

Excellent diastereo- and enantioselectivities were obtained. This reaction was then used by the authors to propose a high-yielding synthesis of a chiral 3-methylglutamic acid. In the same report, the authors observed the formation of 1,3-dipolar addition side products, a reaction they subsequently investigated more extensively (see Section ***1.3.1***).

Kobayashi *et al*. have also reported that by switching to a nitrile-substituted Box ligand or to a PyBox ligand, the reaction can be rendered moisture- and air-insensitive by substituting a calcium chloride hydrate catalyst for the previously used isopropoxide (Scheme 1.11) [30]. Alternatively, calcium triflate was used.



Scheme 1.11 $CaCl_2$ as the basis of a moisture-tolerant catalytic system.

The authors have investigated the formation of the active catalytic species by NMR through titration of the free ligand by $CaCl_2$, finding that two equivalents of the salt effect full consumption of the free ligand in the presence of TMG and molecular sieves. Again, [3+2] cycloaddition was observed as a competing reaction.

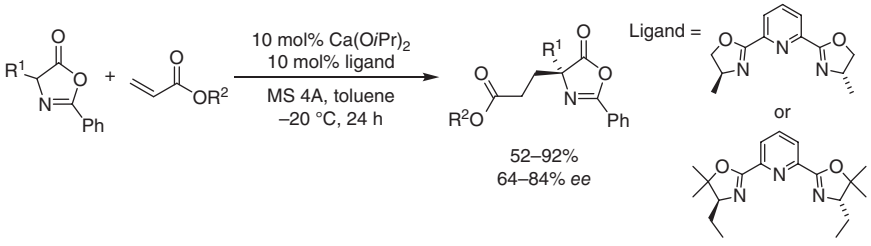
In an innovative extension of this methodology, the Kobayashi group have reported a synthesis of glutamic acids containing a quaternary stereocenter (Scheme 1.12) [31]. By utilizing a calcium–PyBox catalyst, they have obtained a number of adducts between substituted oxazolidones and acrylates.

The Kobayashi group have also used similar PyBox–calcium catalysts for the asymmetric addition of 1,3-dicarbonyl compounds to nitrostyrenes. In their first report [7], they used calcium *p*-methoxyphenoxide as the metal source, but later found that it could be replaced by calcium chloride dihydrate to render the reaction insensitive to moisture and air (Scheme 1.13) [32].

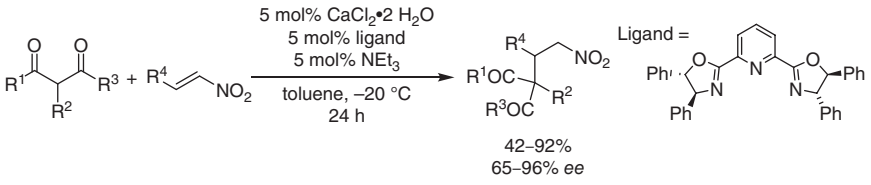
2-Substituted dicarbonyl compounds could be used in the reaction, but the diastereoselectivities that were obtained were mediocre.

The authors have utilized a solid-supported PyBox ligand to carry out the transformation under continuous flow conditions [33]. After 216 h, a TON of 228 was achieved, and the authors note that the catalyst was still active after that time. The developed conditions have been used by the authors to develop a continuous-flow synthesis of chiral rolipram (Scheme 1.14) [34].

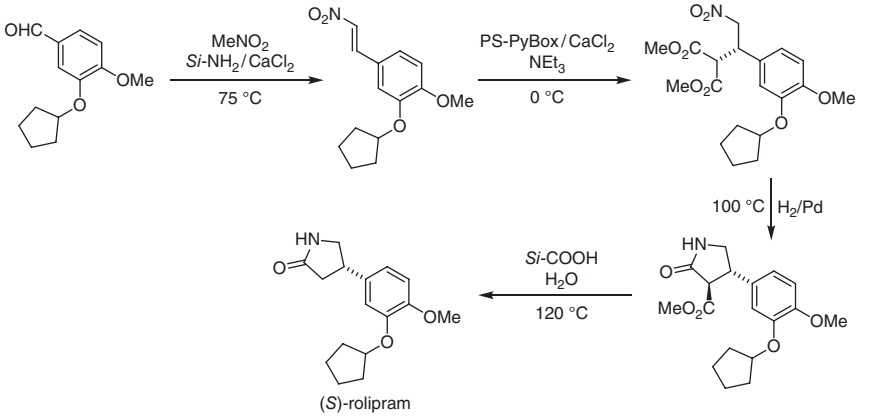
The synthesis of (*S*)-rolipram was carried out using a four-stage flow system. The aldehyde was condensed with nitromethane on a column filled with amine-modified silica coordinated with $CaCl_2$ as the stationary phase. Next, asymmetric Michael addition was carried out using the previously developed Ca-PyBox



Scheme 1.12 Formation of quaternary stereocenters in the synthesis of glutamic acid derivatives from azlactones.



Scheme 1.13 The asymmetric addition of malonates to nitroalkenes.



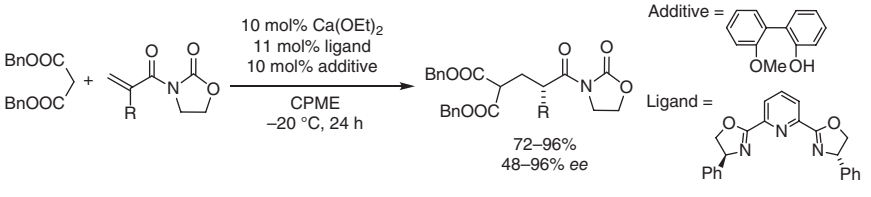
Scheme 1.14 Kobayashi's approach to flow synthesis of rolipram.

system. The addition product was hydrogenated on a palladium column and, finally, decarboxylation was carried out on carboxylic acid-modified silica. The product was obtained with 50% yield from the aldehyde and in 96% *ee* (>99% after recrystallization). In the same manner, the authors synthesized (*R*)-rolipram by simply utilizing the enantiomer of the chiral ligand. (*R*)-phenibut was also synthesized using a slightly modified flow system.

A calcium–PyBox system has also been used by the Kobayashi group for the asymmetric addition of malonates to 2-substituted acrylamides (Scheme 1.15) [35].

The authors suggest that in this transformation, the final protonation of the chiral calcium enolate is the rate-determining step and is responsible for the asymmetric induction in the final product. They have also used this methodology in the synthesis of chiral diacid derivatives.

An aza-Michael addition of enamides to azodicarboxylates has been described by Masson and co-workers [36, 37]. They have employed calcium-BINOL phosphate



Scheme 1.15 The asymmetric addition of malonates to acrylamides.

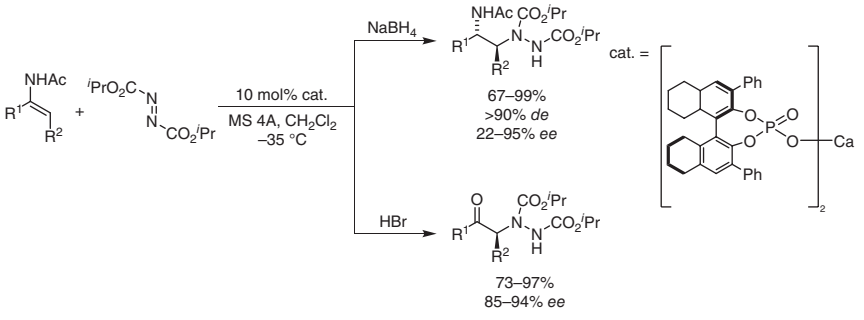
in this transformation and obtained either protected hydrazinoketones or diamines by varying the reaction conditions (Scheme 1.16).

Excellent yields and enantioselectivities have been achieved in this methodology. The diamine products have also been obtained with high diastereoselectivity after $NaBH_4$ reduction.

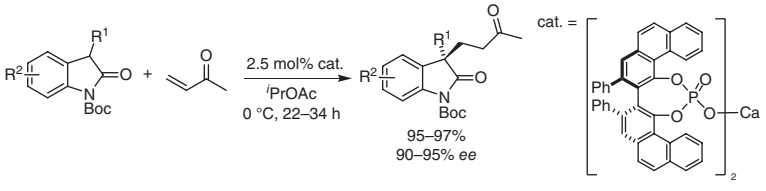
A similar catalytic system has been employed by the Antilla group in the synthesis of 3,3-disubstituted oxindoles by the Michael reaction of monosubstituted oxindoles with methyl vinyl ketone (Scheme 1.17) [38]. Excellent yields and enantioselectivities were reported, although relatively few examples were examined.

Beside calcium catalysts, strontium and barium have also been employed in asymmetric Michael reactions. In 2009, Kobayashi *et al*. reported an addition of malonates to chalcones that is catalyzed by a strontium sulfonamide complex (Scheme 1.18) [39].

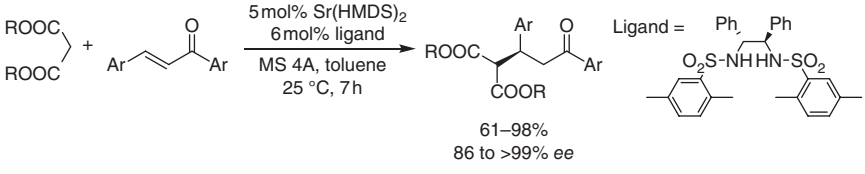
The authors have examined the formation of the catalyst by NMR, proposing that the active form of the catalyst bears the sulfonamide as a bidentate ligand. The coordination of the malonate has subsequently been studied (Scheme 1.19).



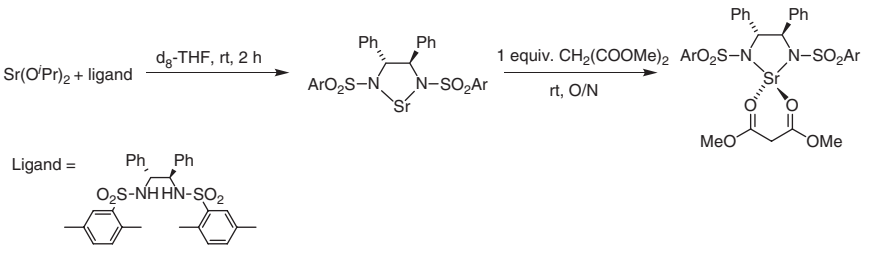
Scheme 1.16 The divergent amination of enamides.



Scheme 1.17 The asymmetric synthesis of disubstituted oxindoles.



Scheme 1.18 Strontium-catalyzed addition of malonates to chalcones.



Scheme 1.19 The formation of active strontium species.

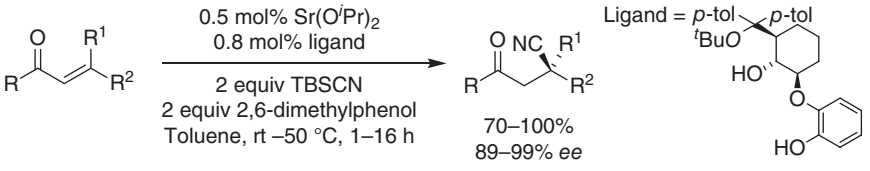
A strontium catalyst bearing an unusual phenol ligand has also been employed by Shibasaki's group in the formation of quaternary stereocenters by β,β-disubstituted Michael acceptor cyanation (Scheme 1.20) [40].

In the same report, the authors have described the asymmetric rearrangement of racemic cyanide 1,2-adducts (Scheme 1.21).

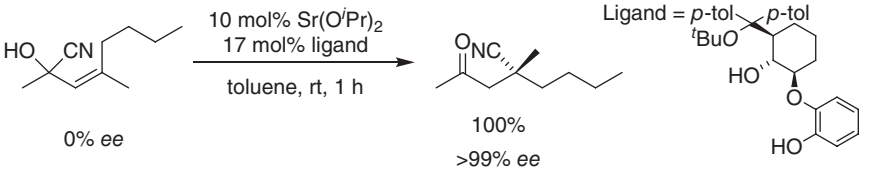
Finally, Kobayashi and co-workers have developed a Friedel-Crafts-type alkylation of indoles with chalcones utilizing a barium-BINOL catalyst (Scheme 1.22) [41].

1.3.4 Other Reactions

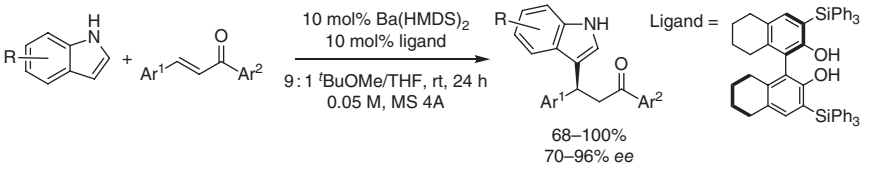
A small number of other processes which do not fit neatly into the categories discussed previously have also been reported in the literature. Antilla and co-workers



Scheme 1.20 Quaternary stereocenter formation in the course of asymmetric cyanation.



Scheme 1.21 The enantioselective rearrangement of cyanohydrins with a Sr catalyst.



Scheme 1.22 The Friedel–Crafts-type alkylation of indoles with chalcones.

have proposed an approach to the asymmetric modification of 3-monosubstituted oxindoles. In addition to previously discussed Michael reactions, they have employed chiral VAPOL calcium phosphates for the oxidative chlorination [38] and benzoyloxylation [42] of these compounds (Scheme 1.23).

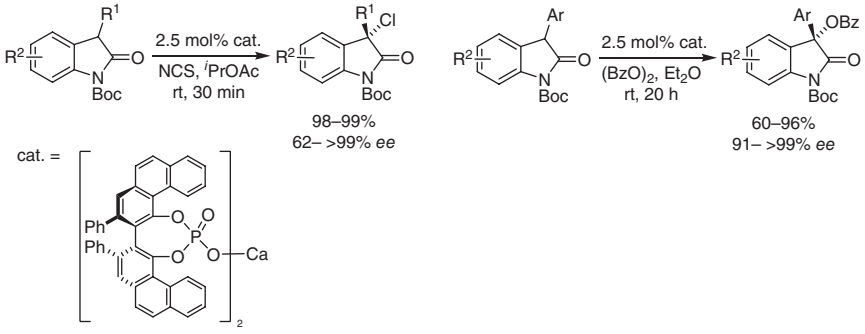
The transformations proceeded with low catalyst loading and under mild conditions. The yields and enantioselectivities were good to excellent.

Masson and co-workers have reported the enantioselective aminobromination of enecarbamates with N-bromosuccinimide (NBS) [43]. Most of their reactions were catalyzed by a chiral BINOL-phosphoric acid, but a small number of reactions were performed using the cognate calcium-BINOL phosphate (Scheme 1.24).

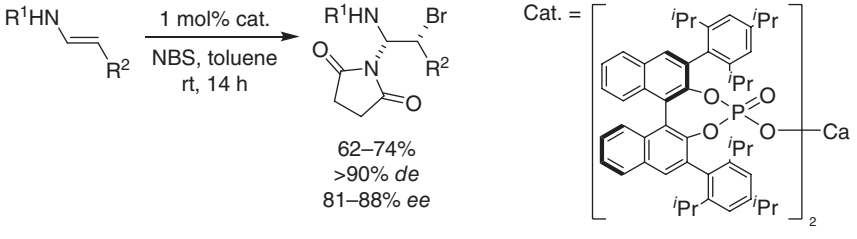
The authors observed a reversal of enantioselectivity when switching from a free acid catalyst to a calcium salt. The authors have proposed that this is due to differential shielding of the reagent faces in the transition states. In the transition state involving a free acid catalyst, the *Re* face of NBS is hindered by the bulky triisopropylphenyl group, forcing the enecarbamate to attach from the *Si* face. That is not the case in the transition state involving the calcium salt. Thus, the enecarbamate substrate attacks the *Re* face, resulting in the enantioselectivity reversal.

A highly enantioselective desymmetrization of meso-aziridines has been reported by the Nakamura group [44]. They have employed a chiral calcium imidazoline-BINOL phosphate generated *in situ* from the phosphoric acid and calcium methoxide for the opening of bicyclic aziridines with TMSNCS (Scheme 1.25).

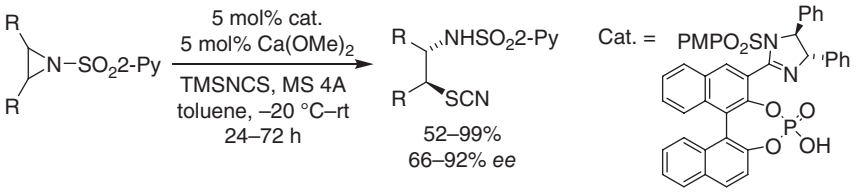
The yields and enantioselectivities were normally good to excellent. The authors have also shown that this transformation can be employed in the synthesis of



Scheme 1.23 The asymmetric oxidation of oxindoles.



Scheme 1.24 The asymmetric aminobromination of alkenes.



Scheme 1.25 The desymmetrization of aziridines with thiocyanate.

enantioenriched aminothiols and aminosulfonic acids. The pyridylsulfonyl substituent is instrumental in the catalytic cycle proposed by the authors as it provides additional calcium chelation in the transition state, affecting enantioselectivity. The authors have examined a number of chiral phosphoric acids for this reaction, but none of them came close to providing enantioselectivities as high as the one shown.

Finally, Buch and Harder have reported the hydrosilylation and hydroamination of styrenes catalyzed by calcium bis(oxazoline) complexes [45]. The conversions reported were normally very high. However, the authors obtained virtually no stereodiscrimination as the enantioselectivities were never higher than 10% *ee*. In addition, the crystal structures and dynamic behavior of the catalysts were discussed at length. The authors have concluded that the poor enantioselectivities are explained by the catalyst existing as a homoleptic calcium complex with the active species being achiral and proposed searching for a method to stabilize the nascent heteroleptic species as a possible further research direction.

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