Asymmetric Catalysis

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Chiral Calcium Catalysts with Neutral Coordinative Ligands: Enantioselective 1,4-Addition Reactions of 1,3-Dicarbonyl Compounds to Nitroalkenes**

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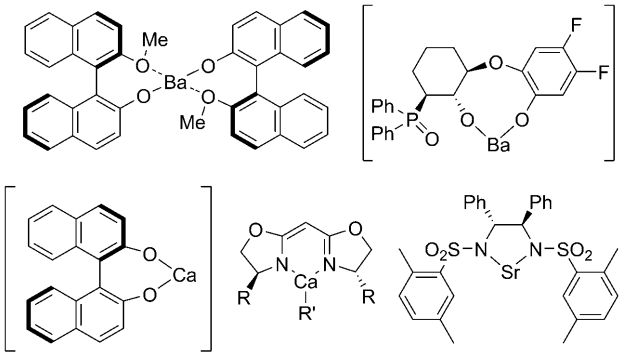
Alkaline earth metals are among the most promising metallic species in organic synthesis owing to their abundance and low toxicity. Since the first report of their use as a chiral catalyst in 1998,[1] there have been several reports of their use in asymmetric catalysis;[2–4] however, their reactivity and selectivity are lower in most cases compared with those of other chiral metal-catalyzed reactions. Recently, we developed the 1,4-addition and the [3+2]-cycloaddition reactions of glycine Schiff bases using chiral calcium catalysts.[5] We also reported the chiral strontium-catalyzed Michael reactions of malonates with chalcone derivatives,[6] in which high reactivities and selectivities were attained. Salt formation is essential in the construction of chiral alkaline earth metal catalysts; it is required to successfully connect chiral ligands to the metal centers (Scheme 1). However, in those systems shown in Scheme 1, the Brønsted basicity of the catalyst is sometimes decreased owing to the acidic nature of the chiral ligands.

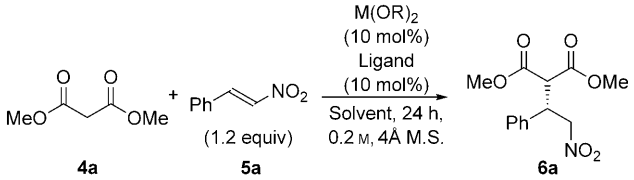


Scheme 1. Chiral alkaline earth metal salt catalysts; coordinative ligands, such as solvents, are omitted for clarity.

During the course of our investigations to develop more efficient catalysts, we envisioned that a complex between an alkaline earth metal base and a chiral coordinative ligand might act as a stronger chiral Brønsted base species, although such examples have not been reported.[7] Herein, we describe the use of chiral calcium catalysts, with neutral coordinative ligands, in 1,4-addition reactions of 1,3-dicarbonyl compounds to nitroalkenes.

Asymmetric 1,4-addition reactions of 1,3-dicarbonyl compounds to nitroalkenes are one of the most important methods for the preparation of chiral γ-nitro carbonyl compounds, which can be converted into various chiral amines by subsequent reduction.[8,9] We began by investigating the reaction of malonate **4a** with β-nitrostyrene (**5a**) in the presence of chiral catalysts, prepared from alkaline earth metal alkoxides and chiral ligands (Table 1). Although calcium complex of box ligand **1**,[5] and strontium complex of bis(sulfonamide) **2**[6] unexpectedly gave very low enantioselectivities (Table 1, entries 1 and 2; Scheme 2), calcium pybox complex (pybox = pyridinebisoxazoline; **3a**), a chiral complex with a neutral coordinative ligand, gave the desired

Table 1: Optimization of reaction conditions.



4a **5a** **6a**

Entry	Ligand	$M(OR)_2$	Conditions	Yield [%]	*ee* [%]
1	**1**	$Ca(OiPr)_2$	THF, 0°C	49	0
2	**2**	$Sr(OiPr)_2$	Toluene, 20°C	88	−8
3	**3a**	$Ca(OiPr)_2$	Toluene, 0°C	70	44
4	**3a**	$Mg(OtBu)_2$	Toluene, 0°C	32	2
5	**3a**	$Sr(OiPr)_2$	Toluene, 0°C	32	8
6	**3a**	$Ba(OiPr)_2$	Toluene, 0°C	35	3
7	**3a**	$Ca(OiPr)_2$	THF, 0°C	54	18
8	**3a**	$Ca(OiPr)_2$	Ether, 0°C	33	51
9	**3a**	$Ca(OiPr)_2$	DCM, 0°C	43	28
10	**3b**	$Ca(OiPr)_2$	Toluene, 0°C	53	32
11	**3c**	$Ca(OiPr)_2$	Toluene, 0°C	45	4
12	*anti*-**3e**	$Ca(OiPr)_2$	Toluene, 0°C	84	91
13	**3d**	$Ca(OiPr)_2$	Toluene, 0°C	27	19
14	*syn*-**3e**	$Ca(OiPr)_2$	Toluene, 0°C	72	50
15	*anti*-**3e**	$Ca(OAr)_2$[a]	Toluene, 0°C	94	91
16	*anti*-**3e**	$Ca(OAr)_2$[a]	Toluene, −20°C	80	96
17	*anti*-**3e**	$Ca(OAr)_2$[a]	Toluene, −30°C	68	96[b]

[a] Ar = *p*-$MeOC_6H_4$. [b] 48 h.

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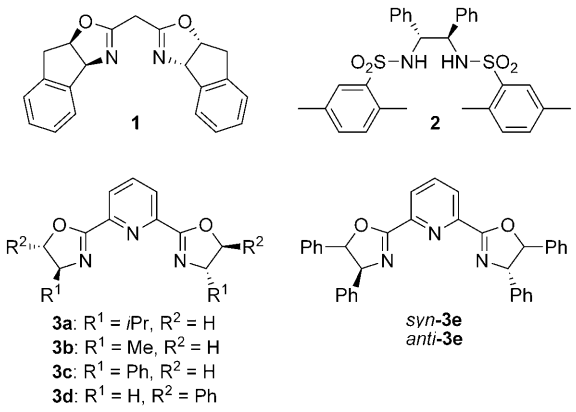
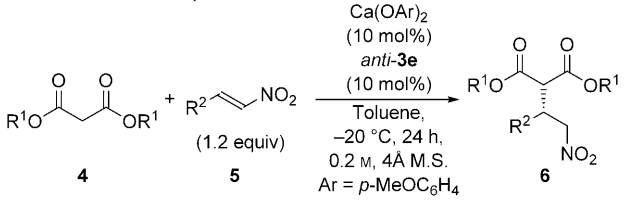


Scheme 2. Chiral ligands that are employed herein.

1,4-addition product **6a** with moderate enantioselectivity (Table 1, entry 3). Among the alkaline earth metal alkoxides examined, calcium showed the highest enantioselectivity (Table 1, entries 3–6). We also examined the effect of solvent on the reaction, and found that the best result was obtained using toluene (Table 1, entries 3, 7–9). To consider the effect of the chiral ligand, several pybox ligands, prepared from chiral amino alcohols, were synthesized and tested.[10] Although pybox ligands **3a**–**3c** gave low enantioselectivities (Table 1, entries 3, 10, and 11), *anti*-5,4-diphenyl pybox (*anti*-**3e**) afforded the product in high *ee* (91%; Table 1, entry 12). We also conducted the reaction using *syn*-5,4-diphenyl pybox (*syn*-**3e**) and 5-phenyl pybox (**3d**) to examine the effect of placing substituents at the 5-positions on the two oxazoline rings. Interestingly, although a very low enantioselectivity was obtained using **3d** (19%; Table 1, entry 13), *syn*-**3e** afforded a more moderate *ee* value (50%; Table 1, entry 14). These results show that substituents with an *anti* configuration at the 4- and 5-positions of the oxazoline ring are very important for high enantioselectivity, and that the phenyl group at the 5-position has a significant influence on the structure of the calcium pybox complex. Furthermore, the yield improved when $Ca(OAr)_2$ (Ar = *p*-$MeOC_6H_4$) was used instead of $Ca(OiPr)_2$ (Table 1, entry 15). The reactions at lower temperatures gave higher enantioselectivities (Table 1, entries 16 and 17), although the rate of reaction decreased at −30 °C (Table 1, entry 17).

We then investigated the substrate scope of the 1,4-addition reaction using our optimized reaction conditions (Table 2). The malonate methyl ester gave the highest enantioselectivity of those tested (Table 2, entries 1–4). Impressively, it was found that nitroalkenes with substituted phenyl groups reacted with methyl malonate smoothly, to afford the desired 1,4-adducts in high yields, with high enantioselectivities (Table 2, entries 5–7, 9). Substituted aromatic nitroalkenes bearing either electron-donating or electron-withdrawing groups reacted without any significant loss of enantioselectivity. In the case of an *ortho*-substituted nitroalkene (Table 2, entry 8), the enantioselectivity was moderate, presumably owing to steric constraints imposed by the aromatic moiety. Nitroalkenes bearing heteroaromatics (Table 2, entry 10), or an aliphatic ring (Table 2, entry 11)

Table 2: Substrate scope for malonates and nitroalkenes.



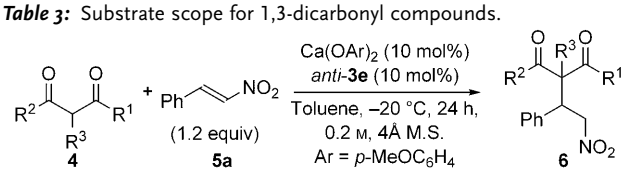
Entry	R^1	R^2	Product	Yield [%]	*ee* [%]
1	Me	Ph	**6a**	80 (quant.)[a]	96 (94)[a]
2	Et	Ph	**6b**	95	92
3	iPr	Ph	**6c**	91	87
4	tBu	Ph	**6d**	50	18
5[b]	Me	*p*-$MeOC_6H_4$	**6f**	95	93
6[b]	Me	*p*-MeC_6H_4	**6g**	92	94
7[b]	Me	*m*-MeC_6H_4	**6h**	quant.	94
8[b]	Me	*o*-MeC_6H_4	**6i**	97	65
9	Me	*p*-BrC_6H_4	**6j**	93	93
10	Me	2-furyl	**6k**	96	94
11[c]	Me	Cy	**6l**	73	87

[a] 1.0 mol%, 0.6 M. 18 days. [b] 48 h. [c] 72 h.

also worked well. The reaction proceeded smoothly even in the presence of only 1.0 mol% of catalyst (Table 2, entry 1, in the parenthesis); the reaction time was 18 days.

We also investigated other 1,3-dicarbonyl compounds as nucleophiles under the same conditions (Table 3). β-Ketoesters afforded both high yields and high enantioselectivities

Table 3: Substrate scope for 1,3-dicarbonyl compounds.



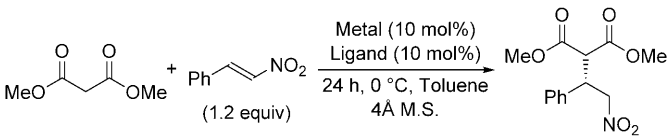
Entry	R^1	R^2	R^3	Product	Yield [%]	*ee*[a] [%]
1	OMe	OMe	H	**6a**	80	96
2[b]	OMe	Me	H	**6m**	90	93 (93)
3[c]	OtBu	Me	H	**6n**	91	90 (90)
4[d]	Me	Me	H	**6o**	54	78
5[e]	OEt	OEt	Me	**6p**	quant.	87
6[e]	OMe	OMe	OMe	**6q**	84	87

[a] Parentheses indicate *ee* of minor distereoisomer. [b] d.r. = 51:49. [c] d.r. = 76:24. [d] −45 °C, 72 h. [e] 72 h.

(Table 3, entries 2 and 3). However, the reaction involving a β-diketone, namely acetylacetone, proceeded with lower yield and enantioselectivity, even at −45 °C (Table 3, entry 4). α-Methyl malonate and α-methoxy malonate reacted with **5a** to afford their corresponding adducts in high yields, and with high enantioselectivities (Table 3, entries 5 and 6).

Neutral coordinative ligands worked well in these reactions, with a noticeably faster rate of reaction relative to the ligand-free system clearly observed (Table 4). In the absence of any other ligands, $Ca(OiPr)_2$ and $Ca(OAr)_2$ (Ar = *p*-$MeOC_6H_4$) both furnished the desired product **6** in 40%

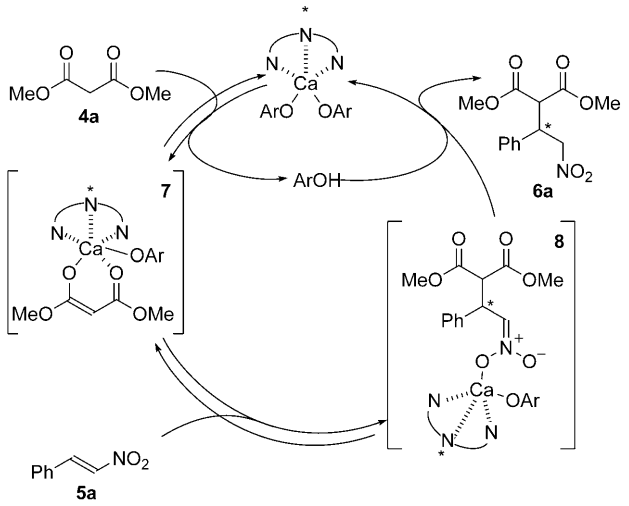
Table 4: Effect of ligand.



Entry	Metal	Ligand	Yield [%]	*ee* [%]
1	$Ca(OiPr)_2$	none	40	–
2	$Ca(OiPr)_2$	iPr-pybox	70	44
3	$Ca(OAr)_2$	none	74	–
4	$Ca(OAr)_2$	iPr-pybox	quant.	54

and 74% yield, respectively (Table 4, entries 1 and 3). Under the same reaction conditions, the corresponding calcium pybox complexes provided **6** in 70% and quantitative yield, respectively (Table 4, entries 2 and 4). These results demonstrate that pybox worked well as a Lewis base to increase the Brønsted basicity of the calcium.[11]

We assume that a catalytic cycle is operating for this reaction (Scheme 3). The calcium pybox complex deprotonates the α position of malonate **4a** to give chiral calcium



Scheme 3. Proposed catalytic cycle.

enolate **7** in situ. The chiral calcium enolate, thus formed, reacts with β-nitrostyrene (**5a**) to afford the initial 1,4-addition adduct **8**;[12] subsequent protonation by a phenol derivative affords the Michael adduct **6a**, and regenerates the catalyst. The fact that the phenol proton is more acidic than the alcohol proton may be another key to accelerate the catalyst turnover.

In summary, we have developed novel coordinative calcium pybox catalysts that effectively mediate catalytic asymmetric additions of 1,3-dicarbonyl compounds to nitroalkenes. This reaction is the first example of using a chiral, coordinative alkaline earth metal catalyst in catalytic asymmetric carbon–carbon bond-forming reactions. It should be noted that the reaction does not require excess amounts of electrophiles or external addition of bases. Further investigation of other reactions using alkaline earth metal coordinative ligand complexes are now in progress.

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[12] A mechanism that involves direct protonation of the nitronate anion by ArOH without formation of **8** was suggested by a referee.

