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Chiral Calcium Iodide for Asymmetric Mannich-type Reactions of Malonates with Imines Providing β-Aminocarbonyl Compounds

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The use of ubiquitously occurring elements is of current interest because of the scarcity of precious metals. Calcium (Ca) is one of the most promising elements; it is the fifth most abundant element in the earth's crust,[1] and is nontoxic and inexpensive. In the periodic table, it belongs to group 2 and has a unique character compared with the group 1 and 3 elements; it has both Brønsted basicity and Lewis acidity. In organic synthesis,[2] however, uses of Ca as either reagent or catalyst have been very limited.[1] Recently, we and other groups have shown the use of chiral Ca catalysts in asymmetric C–C bond-forming reactions.[1] For example, we have developed chiral Ca alkoxides and phenoxides in asymmetric 1,4-additions and [3+2]-cycloaddition reactions of glycine Schiff bases with α,β-unsaturated carbonyl compounds.[3] In these reactions, the Brønsted basicity of the Ca catalysts plays a key role. On the other hand, we have been interested in Ca halides and the use of their Lewis acidity in asymmetric catalysis.[4] Herein, we describe for the first time a chiral calcium iodide (CaI_2) catalyst and its use in asymmetric Mannich-type reactions of malonates with imines affording β-aminocarbonyl compounds.

Catalytic asymmetric Mannich-type reactions provide β-amino acid derivatives,[5] which are biologically important compounds in peptide synthesis and other reactions. To obtain β-amino acid derivatives, diastereoselective approaches starting from chiral α-amino acids[6] have conventionally been employed. In catalytic asymmetric reactions, Mannich-type reactions of imines with enolate equivalents such as silicon enolates[7] are well established with chiral metal complexes or organocatalysts. More recently, asymmetric Mannich-type reactions of malonates with imines[8] have been studied. In these reactions, malonates have an advantage over enolate equivalents in terms of availability, and give the corresponding β-aminocarbonyl compounds, which can be readily converted into free β-amino acids in a few steps.[9] However, successful examples of asymmetric Mannich-type reactions of malonates are limited.[8] Ni,[8m] Pd,[8l,n] Mg,[8o] and Ca[3e] catalysts have been reported; however, substrates have been limited to aromatic imines in most cases. For aliphatic imines, there are only a few successful examples, while some organocatalysts, sometimes with relatively high loadings, have recently been employed in those reactions.[8a,b] We focused on chiral Ca halides as potential chiral catalysts of asymmetric Mannich-type reactions and found that chiral CaI_2 catalysts were effective for the reactions.

First, we investigated the Mannich-type reaction of the imine **1a** derived from benzaldehyde with benzyl malonate. An initial trial was conducted using calcium triflate, a typical Lewis acid, and pybox **3a** (pybox = 2,6-bis(2-oxazolinyl)pyridine), and a moderate yield with moderate enantioselectivity was obtained (Table 1, entry 1). After screening several Ca salts, such as Ca halides, nitrate, carbonate, etc., it was found that calcium iodide (CaI_2)[10,11] gave the best enantioselectivity (entry 2). Conducting the reaction at higher temperature decreased the enantioselectivity because of a noncatalyzed reaction (entry 3). We then examined other solvents. While lower enantiomeric excesses were obtained using dichloromethane (DCM), tetrahydrofuran (THF), and acetonitrile (entries 4, 5, and 7), diethyl ether provided good enantioselectivity (90.5:9.5 e.r., entry 6). After screening equivalents of CaI_2, pybox, and triethylamine, it was found that 10 mol% CaI_2, 15 mol% pybox, and 60 mol% triethylamine gave the best enantioselectivity, and the product was obtained in 96:4 e.r. (entry 10). Further optimizations enabled the asymmetric reaction to be conducted using 5 mol% of the catalyst and slow addition of the imine without significant decrease in the product yield and enantioselectivity (entry 11). Furthermore, the reaction proceeded under air without any significant loss of yield and enantioselectivity (entry 12). We then conducted the reaction of the aliphatic imine **1b** derived from pentanal. The reaction proceeded smoothly under the conditions to afford the desired product in 72% yield with 82.5:17.5 e.r. (entry 13). To improve the enantioselectivity, several pybox ligands were screened, and it was found that *anti*-Ph_2- and *anti*-MePh-pybox ligands (**3d** and **3e**, respectively) resulted in better enantioselectivities of up to 91:9 e.r. (entries 16 and 17). Finally, the desired product was obtained in higher enantioselectivity using *anti*-MePh-pybox (**3e**) in diethyl ether (entry 18).

We then surveyed the substrate scope of these chiral CaI_2-catalyzed asymmetric Mannich-type reactions. First, aromatic imine substrates were investigated (Table 2). When we investigated the substitution positions of the benzene ring of

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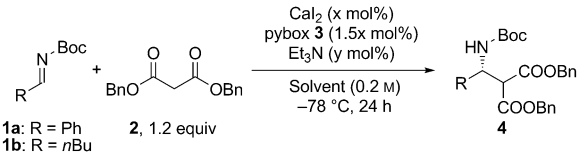
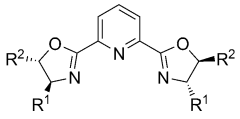
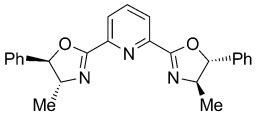
Table 1. Optimization of reaction conditions.



Entry	1	Conditions	x	y	Product	Yield [%]	e.r.
1[a]	**1a**	Tol, **3a**	10	10	**4a**	57	71:29
2	**1a**	Tol, **3a**	10	10	**4a**	78	94.5:5.5
3[b]	**1a**	Tol, **3a**	10	10	**4a**	85	88.5:11.5
4	**1a**	DCM, **3a**	10	10	**4a**	82	84.5:15.5
5	**1a**	THF, **3a**	10	10	**4a**	87	56.5:43.5
6	**1a**	Et_2O, **3a**	10	10	**4a**	50	90.5:9.5
7[b]	**1a**	MeCN, **3a**	10	10	**4a**	81	77.5:22.5
8[c]	**1a**	Tol, **3a**	10	10	**4a**	81	75.5:24.5
9[d]	**1a**	Tol, **3a**	10	10	**4a**	81	94:6
10	**1a**	Tol, **3a**	10	60	**4a**	79	96:4
11[e]	**1a**	Tol, **3a**	5	30	**4a**	89	96:4
12[f]	**1a**	Tol, **3a**	5	30	**4a**	84	96:4
13[e]	**1b**	Tol, **3a**	5	30	**4b**	72	82.5:17.5
14[e]	**1b**	Tol, **3b**	5	30	**4b**	77	76:24
15[e]	**1b**	Tol, **3c**	5	30	**4b**	72	74:26
16[e]	**1b**	Tol, **3d**	5	30	**4b**	76	90:10
17[g]	**1b**	Tol, **3e**	5	30	**4b**	62	91:9
18[h]	**1b**	Et_2O, **3e**	5	30	**4b**	62	94:6

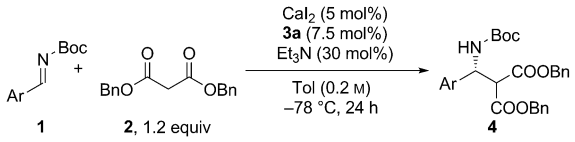
[a] $Ca(OTf)_2$. [b] −40 °C. [c] 10 mol% of pybox. [d] 20 mol% of pybox. [e] Slow addition of imine over 14 h. [f] Slow addition of imine over 14 h. Under air. [g] Slow addition of imine over 14 h. The opposite enantiomer was obtained. [h] Slow addition of imine over 14 h. The opposite enantiomer was obtained after 48 h.





the benzaldehyde-derived imines, high yields and high enantioselectivities were observed in all cases; in particular, the *para*-tolylaldehyde-derived substrate gave the best enantioselectivity (entries 2–4). Then, we investigated imines derived from benzaldehyde derivatives bearing electron-donating and -withdrawing substituents. Aryl imines with electron-rich substituents gave good to high yields with high enantioselectivities (entries 2–6). When *para*-halogenated benzaldehyde-derived imines were employed, the enantioselectivities of the products were also high (entries 7 and 9). We further examined trifluoromethyl benzaldehyde-derived imines, which resulted in high enantioselectivities as well (entries 10 and 11). The 2-naphthylaldehyde-derived imine gave the best enantioselectivities (entries 12 and 13). It is noted that a gram-scale experiment was also performed, and the desired product was obtained in high yield with high enantioselectivity (entry 13). The imines derived from heteroaromatic aldehydes were also investigated. In the case of the 2-furylaldehyde-derived imine, the enantioselectivity was high (entry 14). When we used the 2-thienylaldehyde-derived imine, the enantioselectivity of the product was still high (entry 15). Finally, we attempted to reduce the catalyst

Table 2. Substrate scope for aryl imines.



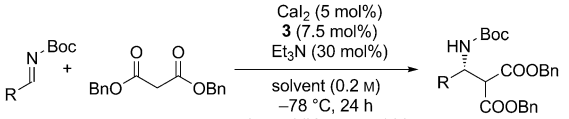
Entry	Ar	Product	Yield [%]	e.r.
1[a]	Ph	**4a**	89	96:4
2[a,b]	*o*-MeC_6H_4	**4c**	86	92:8
3[a]	*m*-MeC_6H_4	**4d**	91	94:6
4[a]	*p*-MeC_6H_4	**4e**	89	96:4
5[c]	*p*-$MeOC_6H_4$	**4f**	71	90.5:9.5
6[a]	3,4-$(OCH_2O)C_6H_3$	**4g**	66	92:8
7[c]	*p*-ClC_6H_4	**4h**	87	96.5:3.5
8[c,d]	*p*-ClC_6H_4	**4h**	90	95:5
9[c]	*p*-FC_6H_4	**4i**	88	96:4
10[a]	*m*-$CF_3C_6H_4$	**4j**	91	94.5:5.5
11[c]	*p*-$CF_3C_6H_4$	**4k**	82	95.5:4.5
12[e]	2-naphthyl	**4l**	84	97:3
13[e,f]	2-naphthyl	**4l**	95 (88)[g]	98:2 (98.5:1.5)[g]
14[a]	2-furyl	**4m**	99	96:4
15[a]	2-thienyl	**4n**	76	93:7

[a] Slow addition of imine over 14 h. [b] Diethyl ether was used. [c] Slow addition of imine over 7 h. [d] Catalyst (2 mol%). [e] Slow addition of imine over 6 h. [f] Gram scale (1.51 g was obtained). [g] After recrystallization.

loading. In the presence of 2 mol% of the catalyst, the corresponding product was obtained in high yield with 95:5 e.r. (entry 8).

Next, we investigated imines derived from aliphatic aldehydes, and the results are summarized in Table 3. We tested several *n*-alkyl aldehyde-derived imines, and the products were obtained in moderate to good yields with high enantio-

Table 3. Substrate scope for aliphatic imines.



Entry	R	Conditions	Product	Yield [%]	e.r.
1	Et	Tol, **3d**	**4o**	64	95.5:4.5
2	*n*Pr	Et_2O, **3e**	**4p**	48	94.5:5.5[a]
3[b]	*n*Bu	Et_2O, **3e**	**4b**	62	94:6[a]
4	*n*Pentyl	Et_2O, **3e**	**4q**	53	93.5:6.5[a]
5	$Ph(CH_2)_2$	Et_2O, **3e**	**4r**	53	91:9[a]
6	*i*Bu	Et_2O, **3e**	**4s**	57	96.5:3.5[a]

[a] The opposite enantiomer was observed. [b] 48 h.

selectivities (entries 1–4). Interestingly, the propionaldehyde-derived imine, one of the most difficult substrates because of side reactions, gave the second highest enantioselectivity among the aliphatic substrates tested (entry 1). The imine derived from 3-phenylpropanal could be applied to the Mannich-type reaction, affording the corresponding adduct in 53% yield with 91:9 e.r. (entry 5). In the case of

a β-branched imine, the imine derived from isovaleraldehyde, the desired β-amino carbonyl product was obtained in 96.5:3.5 e.r. (entry 6). Thus, we could establish a wide substrate scope of chiral CaI_2-catalyzed asymmetric Mannich-type reactions.

NMR studies were conducted to obtain information on the CaI_2–pybox catalyst. For the NMR studies, acetonitrile-d_3 was used as a solvent instead of toluene-d_8 because of the solubility of the Ca catalysts. ^1H and ^{13}C NMR resonances of the Ca complexes in toluene-d_8 were weak; however, they almost corresponded to those in acetonitrile-d_3. NMR charts of several ratios of CaI_2 to pybox are shown in the Supporting Information. When a 1:1 ratio of CaI_2 to pybox was used, (pybox)·CaI_2 (**A**), in which two iodides, pybox, and acetonitrile-d_3 are ligands,[12] might be formed (Figure 1).

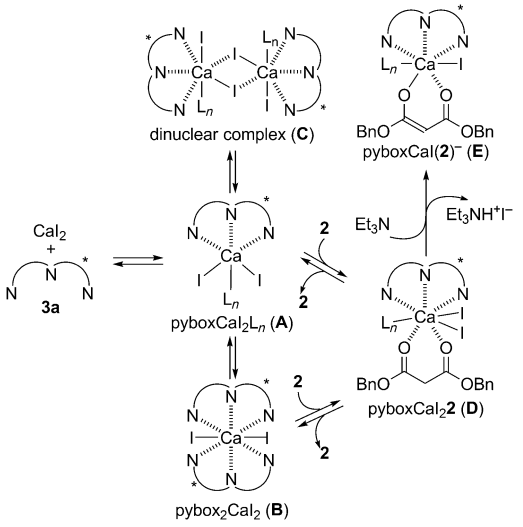
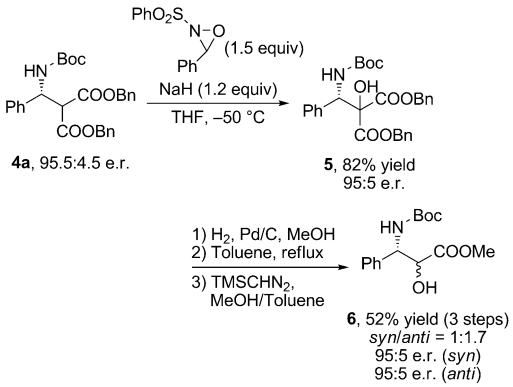


Figure 1. Assumed catalyst species.

Judging from the NMR spectrum, the formation of **A** was incomplete, and this corresponds to the lower enantioselectivity in the experiment (see Table 1, entry 8). In addition, other resonances were observed in the chart, and we assumed the formation of dinuclear complex **C** under equilibrium conditions.[13] On the other hand, only the 1:2 complex, (pybox)$_2$·CaI_2 (**B**), was obtained when 1:2 and 1:3 ratios of CaI_2 to pybox were combined (see the Supporting Information). Complex **B** has eight coordination sites occupied by two iodides and two pybox. A complex containing one calcium perchlorate and two pybox ((pybox)$_2$·$Ca(ClO_4)_2$) has recently been reported[14] and characterized by X-ray crystallographic analysis. When a 1:1.5 ratio of CaI_2 to pybox was used, two complexes, (pybox)·CaI_2 (**A**) and (pybox)$_2$·CaI_2 (**B**), were observed (see the Supporting Information). We have already shown that the 1:1.5 ratio of CaI_2 to pybox was important for obtaining high enantioselectivity (Table 1, entry 2). We then added malonate **2** to this solution and recorded the NMR spectrum (see the Supporting Information), which showed one species, which might be assigned as the Ca/pybox/malonate (1:1:1) complex ((pybox)·CaI_2·**2** (**D**)). It is noted that both the 1:1 complex (**A**) and the 1:2 complex (**B**) were converted into only one complex (**D**) after the addition of malonate **2**. This assumption corresponds to the experimental results that both 15 mol% and 20 mol% of pybox afforded the same results (Table 1, entries 2 and 9). The new resonances derived from the Ca/pybox/malonate (1:1:1) complex were also observed in toluene-d_8 (see the Supporting Information). We then added Et_3N (1 equiv) to the solution and recorded the NMR spectrum. The resonances of enolate complex **E** appeared; however, complex **D** still remained. The addition of an excess amount of Et_3N to the solution provided almost one species (see the Supporting Information), which was assigned as the Ca/pybox/enolate complex ((pybox)·CaI·(**2**)$^-$ (**E**)). These observations also correspond to the experimental results that an excess amount of Et_3N was necessary for high performance of the catalyst (Table 1, entry 10).

Finally, we transformed the obtained Mannich product (**4a**) to a β-amino acid derivative (Scheme 1).[15] β-Amino acid derivatives are important in the synthesis of drugs and



Scheme 1. Transformations of a Mannich product.

peptides, including the well-known taxol derivatives bearing β-amino acid skeletons, which have hydroxy groups at the α-position. We therefore focused on the synthesis of α-hydroxy β-amino acid derivatives from the Mannich product (**4a**). Some transformations of Mannich adducts derived from malonates have already been reported;[9] however, transformations to α-hydroxy β-amino acids have not been discussed.[16] We succeeded in introducing a hydroxy group at the α-position of the malonate derivative **4a** using Davis oxaziridine,[17] thereby affording the desired product **5** in high yield without any loss of enantioselectivity. After this transformation, deprotection, decarboxylation, and esterification were conducted to afford the desired α-hydroxy β-amino acid derivative **6** in good yield (three steps) with high enantioselectivity.

In conclusion, we have developed a novel chiral calcium iodide catalyst prepared from CaI_2 and pybox that is stable under moisture and oxygen. This catalyst was applied to catalytic asymmetric Mannich-type reactions of malonates with

both *N*-Boc-protected aromatic and aliphatic imines, and gave moderate to high yields with high enantioselectivities. To the best of our knowledge, this is the first example of highly enantioselective metal-catalyzed asymmetric Mannich-type reactions of malonates with *N*-Boc-protected aliphatic imines. The Mannich adduct was successfully converted into an α-hydroxy β-amino acid derivative. We have also shown the unique structure of the chiral Ca complexes with malonates. Further investigations of other reactions using these types of calcium catalysts are now in progress.

Experimental Section

A typical experimental procedure for the catalytic asymmetric Mannich reaction of malonate **2** with *N*-Boc-protected imine **1a** is as follows: A 10 mL flask was charged with CaI_2 (0.015 mmol) and Bn-pybox (**3a**, 0.0225 mmol), and toluene (0.75 mL) was added under an argon atmosphere. The reaction mixture was heated at 80 °C for 2 h. Then dibenzyl malonate (**2**, 0.36 mmol, neat) and triethylamine (0.09 mmol, 100 μL of 0.9 M toluene solution) were added successively. After the reaction mixture was heated at 80 °C for 0.5 h, it was cooled to −78 °C; subsequently, an imine solution (**1a**, 0.30 mmol, 0.70 mL of 0.43 M toluene solution) was slowly added over 14 h. After the addition, the mixture was stirred for another 10 h at the same temperature and then quenched with saturated ammonium chloride (NH_4Cl, 3 mL). Dichloromethane (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin-layer chromatography (hexane:diethyl ether = 4:1) to afford the desired product **4a**. The enantioselectivity was determined by HPLC analysis of the product.

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Keywords: air-stable catalysts · alkaline earth metals · calcium iodide · C–C bond formation · Mannich-type reactions

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