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Asymmetric Mannich Reaction of Malonates with Imines Catalyzed by a Chiral Calcium Complex

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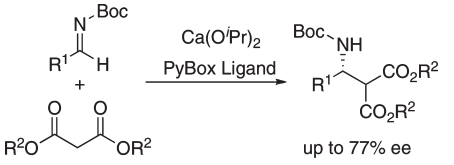
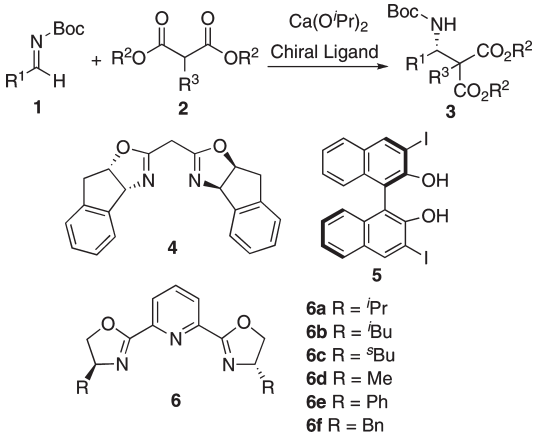


A chiral calcium complex was found to be effective for the Mannich reactions of malonates with *N*-Boc imines. The desired adducts were obtained in excellent yields (up to 95%) with moderate to good enantioselectivities (up to 77% ee).

Group 2 alkaline earth metals (calcium, strontium, and barium) are now of great interest because of the abundance and specific properties of these metals such as low electron negativity and various coordination sites.[1] The use of these metals in organic synthesis, especially as a catalyst,[2] is also beneficial from an environmental viewpoint. Since the first report of the use of alkaline earth metals in asymmetric aldol reactions,[3] chiral alkaline earth metal catalysts have been intensively investigated; however, successful examples were limited.[2,4]

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 chemistry as well as medicinal chemistry.[5] In these reactions, no preformation of enolates or naked enolates is required to access to the Mannich adducts. Despite organocatalytic pathways receiving much attention,[6] the asymmetric addition of malonates to imines catalyzed by a chiral metal complex has been under development.[7] Herein we disclose the Mannich reaction of malonates with *N*-Boc imines catalyzed by a chiral calcium complex prepared from a calcium salt and a neutral coordinative ligand (Scheme 1).[8]

SCHEME 1. Asymmetric Mannich Reaction with Chiral Ca Complexes



In the course of our investigation to expand use of alkaline earth metal complexes in organic synthesis, we studied the addition of dimethyl malonate (**2a**, R^2 = Me, R^3 = H) to *N*-Boc imine **1a** (R^1 = Ph) derived from benzaldehyde in the presence of a catalytic amount of calcium isopropoxide and a

(1) *Basic Inorganic Chemistry*, 3rd ed.; Cotton, F. A., Wilkinson, G., Gaus, P. L., Eds.; Wiley: New York, 1995.

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(3) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561.

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(6) Selected examples with organocatalysts in direct addition of malonates to imines: (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Tillman, A. L.; Yeb, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (c) Yamaoka, U.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, *22*, 2571. (d) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzanic, V. *Adv. Synth. Catal.* **2006**, *348*, 2043. (e) Marianacci, O.; Micheletti, G.; Bernardi, L.; Fini, F.; Fochi, M.; Pettersen, D.; Sgarzani, V.; Ricci, A. *Chem.—Eur. J.* **2007**, *13*, 8338. (f) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564.

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TABLE 1. Ligand Screening[a]

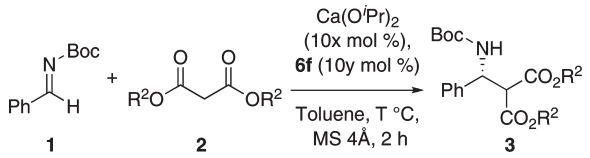
entry	ligand	yield (%)[b]	ee (%)[c]
1	**4**	85	−11
2	**5**	79	4[d]
3	**6a**	85	28[d]
4	**6b**	89	25[d]
5	**6c**	86	40[d]
6	**6d**	94	43[d]
7	**6e**	98	0
8	**6f**	99	47[d]

[a]The Mannich reaction of **1a** (0.20 mmol) with **2a** (0.24 mmol) was performed in toluene at 0 °C for 24 h in the presence of a calcium complex prepared from $Ca(O^iPr)_2$ (10 mol %), a ligand (10 mol %), and molecular sieves 4Å (10 mg/mmol). The concentration is 0.2 M. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Absolute configuration was determined to be *R* according to the literature data.[6b]

chiral ligand (Table 1). When known anionic calcium complexes derived from Bisoxazoline **4**[4f] and BINOL ligand **5**[4c] were used, very low enantioselectivities were obtained (Table 1, entries 1 and 2). After extensive screening of ligands, Ca-Pyridinebisoxazoline (PyBox) **6a** complex[8] was found to be more effective, and the Mannich adduct **3aa** was obtained in excellent yield with moderate enantioselectivity (28% ee, entry 3). This promising result led us to screen several PyBox ligands carefully. While PyBox **6b** furnished the corresponding β-aminodicarbonyl compound with similar selectivity (entry 4, 25% ee), the use of PyBox **6c** and **6d** provided significant increase of selectivity (40% ee and 43% ee, respectively). Ph-PyBox (**6e**) gave the Mannich adduct as a racemate, whereas Bn-PyBox (**6f**) gave the product in 47% ee.

With ligand **6f** in hand, we investigated the optimization of reaction conditions and influence of the malonate moiety on selectivity (Table 2). The first examination of reaction temperature revealed that −20 °C was the optimum temperature for the reaction. Indeed decrease of the temperature to −40 °C induced a drop of enantioselectivity from 50% ee (at −20 °C) to 40% ee (entry 4). This might be explained by partial decomplexation of the Ca-PyBox complex; free calcium alkoxide could catalyze a racemic background reaction.[9] A study of the ratio of calcium vs. ligand at −20 °C revealed an optimum of 1 to 1.5; in that case the selectivity increased to 55% ee (entry 3). On the other hand, we observed a significant influence of the malonate part on selectivity. The reaction of diethyl malonate (**2b**) provided almost the same enantioselectivity (entry 5), whereas those of secondary and tertiary esters (**2c** and **2d**) gave lower selectivities (entries 6 and 7). Finally, dibenzyl malonate **2e** was found to be the most efficient furnishing the product in 68% ee (entry 8). To improve the enantioselectivity further, use of additives was investigated. Unfortunately, use of molecular sieves was ineffective on the selectivity (entries 9 and 10), and the same selectivity was observed without addition of molecular sieves (entry 11). Furthermore, solvent screening revealed that xylene was more effective than toluene and mesitylene (entries 11 and 12, respectively), providing the corresponding product in excellent yield with 73% ee (entry 13).[10] Interestingly, decrease of concentration to 0.02 M led to similar results (entry 14).

TABLE 2. Optimization of the Reaction Conditions[a]



entry	R^2	*x*:*y*	temp (°C)	yield (%)[b]	ee (%)[c]
1	Me (**2a**)	1:1	0	99	47
2	Me (**2a**)	1:1	−20	83	50
3	Me (**2a**)	1:1.5	−20	99	55
4	Me (**2a**)	1:1	−40	83	40
5	Et (**2b**)	1:1.5	−20	95	54
6	^{i}Pr (**2c**)	1:1.5	−20	95	51
7	^{t}Bu (**2d**)	1:1.5	−20	92	43
8	Bn (**2e**)	1:1.5	−20	91	68
9[d]	Bn (**2e**)	1:1.5	−20	82	69
10[e]	Bn (**2e**)	1:1.5	−20	75	69
11[i]	Bn (**2e**)	1:1.5	−20	83	69
12[f,i]	Bn (**2e**)	1:1.5	−20	88	65
13[g,i]	Bn (**2e**)	1:1.5	−20	90	73
14[g−i]	Bn (**2e**)	1:1.5	−20	89	73

[a]The Mannich reaction of **1a** (0.20 mmol) with **2** (R^3 = H, 0.24 mmol) was performed in toluene at 0.2 M for 2 h in the presence of a calcium complex prepared from $Ca(O^iPr)_2$ (10*x* mol %) and **6f** (10*y* mol %) and molecular sieves 4 Å (10 mg/mmol), unless otherwise noted. [b]Isolated yield. [c]Determined by HPLC analysis. [d]MS 3 Å was used as additive, [e]MS 5 Å was used as additive, [f]Mesitylene was used as a solvent, [g]Xylene was used as a solvent. [h]The concentration was 0.02 M. [i]Reaction conducted without MS 4 Å.

After these optimizations, we decided the use of 10 mol % of $Ca(O^iPr)_2$ in the presence of 15 mol % of PyBox **6f** in xylene at −20 °C was the best system for the Mannich reaction of the malonate with the *N*-Boc imine. With this system in hand, the substrate scope of several *N*-Boc imines[11,12] and malonates was investigated (Table 3).

First, the α-substitution of dibenzylmalonate was examined, and it was found that this substitution was important for obtaining good enantioselection. Indeed, methyl malonate **2f** (Table 3, entry 2) provided a significant loss of selectivity, whereas the use of malonate **2g** with a bulkier benzyl group as a substituent provided a dramatic drop of enantioselectivity (entry 3). We examined several substituted imines with **2e** as a nucleophile. It was revealed that substitution at the para position of the aromatic ring provided a decrease of selectivity (entries 6, 9, and 10) except for the fluoro analogue (entry 8), while a meta substitution did not have any significant effect (entry 5). A methyl substitution at the ortho position of the aromatic ring was found to have a beneficial effect on enantioselectivity; 77% ee was obtained as shown in entry 4. Unexpectedly, when the methyl substituent was replaced by a methoxy substitution (entry 7), the selectivity decreased to 56%, probably due to the steric hindrance of the methoxy group. The use of the *N*-Boc imine derived from 1-naphthaldehyde revealed the same trend; the selectivity also dropped to 66% (entry 11).

Heteroaromatic substitutions were also investigated. Impressively, the *N*-Boc imine derived from furfural provided a good selectivity (76% ee, entry 12), whereas 2-thienyl-*N*-Boc-imine

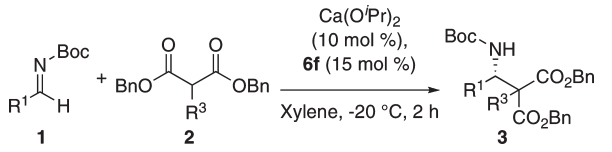
(9) The calcium−PyBox complex might exist in equilibrium with the ligand and free $Ca(O^iPr)_2$, and the decrease of temperature led to a displacement of this equilibrium in favor of free $Ca(O^iPr)_2$, which was found to be efficient as catalyst in the direct addition of malonates to *N*-Boc imines.

(10) Previous optimizations revealed that aromatic solvents were the most efficient.

(11) For an efficient preparation of *N*-Boc imines, see: Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964 and ref 6a.

(12) Boc was found to be the most efficient *N*-protecting group under conditions described in Table 2, entry 11. The *N*-Cbz analogue of **1a** furnished the corresponding product in 54% ee.

TABLE 3. Substrates Scope[a]



entry	R^1	R^3	yield (%)[b]	ee (%)[c]
1	Ph (**1a**)	H (**2e**)	90	73[c]
2	Ph (**1a**)	Me (**2f**)	84	62
3	Ph (**1a**)	Bn (**2g**)	95	16
4	*o*-MeC_6H_4 (**1b**)	H (**2e**)	90	77
5	*m*-MeC_6H_4 (**1c**)	H (**2e**)	93	71
6	*p*-$MeOC_6H_4$ (**1d**)	H (**2e**)	75	66
7	*o*-$MeOC_6H_4$ (**1e**)	H (**2e**)	92	56
8	*p*-FC_6H_4 (**1f**)	H (**2e**)	91	72
9	*p*-ClC_6H_4 (**1g**)	H (**2e**)	82	61
10	3,4-$(OCH_2O)C_6H_3$ (**1h**)	H (**2e**)	92	67
11	1-naphthyl (**1i**)	H (**2e**)	73	66
12	2-furyl (**1j**)	H (**2e**)	95	76
13	2-thienyl (**1k**)	H (**2e**)	89	54
14	C_6H_{11} (**1*l***)	H (**2e**)	80	5

[a]The Mannich reaction of **1** (0.20 mmol) with **2** (0.24 mmol) was performed in xylene at 0.2 M at −20 °C for 2 h in the presence of a calcium complex prepared from $Ca(O^iPr)_2$ (10 mol %) and **6f** (15 mol %), unless otherwise noted. [b]Isolated yield. [c]Determined by HPLC analysis. Absolute configuration was determined to be *R* according to the literature data.[6e]

gave the Mannich adduct in 54% ee (entry 13). Finally, aliphatic *N*-Boc imine derived from cyclohexanecarboxaldehyde was engaged in the Mannich reaction. Unfortunately, our catalytic system was found to be ineffective for this substrate furnishing the corresponding aminodicarbonyl compound with only 5% ee despite an acceptable yield (entry 14).

In summary, we have shown the first use of the chiral Ca-PyBox complex in the Mannich reaction of malonates with *N*-Boc imines. The corresponding adducts were obtained within 2 h in high yields with good to moderate enantioselectivities (up to 77% ee). This work could expand the use of alkaline earth metals in organic synthesis.

Experimental Section

Representative Procedure (Entry 13 in Table 2). In a flame-dried glass tube, a suspension of $Ca(O^iPr)_2$ (3.1 mg, 0.020 mmol) and PyBox **6f** (12 mg, 0.030 mmol) in dry xylene (0.5 mL) was heated at 80 °C for 2 h. Dibenzylmalonate **2e** (neat, 58 μL, 0.24 mmol) was then added, and the resulting solution was stirred at the same temperature for 0.5 h. The reaction solution was cooled to −20 °C, and the corresponding imine (0.20 mmol) was added as a solution of xylene (0.5 mL). After 2 h, the reaction was quenched with aq NH_4Cl (saturated, 3 mL). After addition of DCM, the organic layer was separated and the aqueous layer was extracted with DCM (three times). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (PTLC, hexane−Et_2O = 4:1) to afford the desired product (88 mg, 90% yield). HPLC analysis of the product (Daicel Chiralpak AS-H, hexane/^{i}PrOH = 40/1, 1.0 mL/min, 254 nm, t_R = 24.1 min (major isomer) and t_R = 30.9 min (minor isomer)) indicated that the optical purity was 73% ee.

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Supporting Information Available: Proposed catalytic cycle, general experimental procedure, characterization data of the products including new compounds, separation conditions of each enantiomer of the products in HPLC analysis, and ^1H and ^{13}C NMR charts of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.