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Chiral Zirconium Complex as Brønsted Base Catalyst in Asymmetric Direct-type Mannich Reactions

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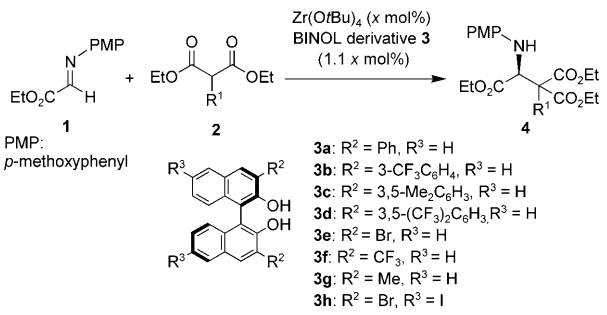
Dedicated to the 150th anniversary of Japan–UK diplomatic relations

Development of efficient methods for preparation of optically active amino acids is one of the most important topics in synthetic organic chemistry. Asymmetric Mannich-type reactions have been recognized as one of the most efficient methods to provide optically active β-amino esters, because new carbon–carbon bond formation and chiral induction are achieved at the same time in a single reaction step. Recently, several types of catalytic asymmetric Mannich-type reactions have been reported;[1] among them, direct-type Mannich reactions are the most attractive from an atom economical point of view, because no stoichiometric amounts of bases or metals for pre-activation of carbonyl donors are required.[2]

In previous papers, our group has reported asymmetric Mannich-type reactions using chiral zirconium Lewis acid catalysts prepared from zirconium alkoxides and BINOL derivatives.[3,4] The zirconium catalysts could interact with imines and their equivalents to create excellent asymmetric environments, realizing high enantioselection. On the other hand, some zirconium catalysts possess alkoxide parts on their structure, suggesting that such catalysts could potentially work as Brønsted bases. While it was already disclosed that zirconium alkoxides worked as Brønsted bases in direct-type aldol reactions, few successful examples of catalytic asymmetric direct-type reactions using chiral zirconium catalysts as Brønsted bases were reported.[5] Herein, we describe a successful example of catalytic asymmetric, direct-type Mannich reactions using a chiral zirconium catalyst as Brønsted base.

We selected the Mannich-type reaction of malonate with α-iminoester as a model, providing an efficient method for preparation of optically active α-amino acid derivatives (Scheme 1).[6] While asymmetric variants of this reaction



Scheme 1. Asymmetric Direct-type Mannich Reaction Using a Chiral Zirconium Catalyst.

were reported using chiral Cu[6a], Pd[6b], Ni[6c] catalysts or organocatalysts[6d–n] and high enantioselectivities were observed, scope of substrates is still limited in some cases. We decided to employ a zirconium complex prepared from zirconium *tert*-butoxide and 3,3′-disubstituted BINOL derivative, which could form a 1:1 complex with the remaining two alkoxide parts in their structure. In this complex, we expected that the BINOL part could increase the Lewis acidity of the zirconium metal (compared with the alkoxide parts) to assist activation of electrophiles, and at the same time that the *tert*-butoxide group could work as a Brønsted base to activate carbonyl compounds effectively.

In the reaction of ethyl 2-(4-methoxyphenylimino)acetate (**1**) with diethyl methyl malonate (**2a**, R^1 = Me), the catalyst prepared from $Zr(OtBu)_4$ and 3,3′-Ph_2BINOL (**3a**) worked

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well in toluene at −45 °C to afford the Mannich-type adduct in good yield with moderate enantioselectivity (Table 1, entry 1). It was found that the 3,5-disubstituted benzenes at the R^2 parts did not increase the enantioselectivity significantly (entries 2–4). On the other hand, it was revealed that Br, CF_3, and Me groups at the R^2 parts were effective, and high enantioselectivities were obtained (entries 5–7). Interestingly, no reaction occurred when $Zr(OiPr)_4$ was used instead of $Zr(OtBu)_4$, suggesting that Brønsted basicity of the *tert*-butoxy group was very important in this catalyst system (entry 8). When the catalyst prepared from **3g** was used, excellent enantioselectivity (97 % *ee*) was obtained when THF was used as a solvent (entry 10). For improvement of the yield, addition of MS 3 Å was effective to afford the desired Mannich-type product in 86 % yield with 96 % *ee* (entry 11). We then investigated the reduction of the catalyst loading. In the reaction using 10 mol % of the catalyst, significant decrease of the yield was observed; however, the reactivity was improved by conducting the reaction in higher concentration (entries 12, 13). While 5 mol % of the catalyst also worked at higher concentration, both yield and selectivity decreased (entry 14). Use of a slight excess amount of malonate improved the yield (entry 15). Finally, it was found that slow addition of the iminoester was very effective to improve the enantioselectivity dramatically, and that the highest enantioselectivity (98 % *ee*) was obtained (entry 16). Under the reaction conditions, even 2 mol % of the catalyst also worked well to give the product in moderate yield while keeping a high enantioselectivity (entry 17).

Table 1. Optimization of the reaction conditions.[a]

Entry	3	x	Solvent	Additive	Yield [%][b]	ee [%]
1	**3a**	20	toluene	–	76	61
2	**3b**	20	toluene	–	89	52
3	**3c**	20	toluene	–	83	37
4	**3d**	20	toluene	–	78	60
5	**3e**	20	toluene	–	78	90
6	**3f**	20	toluene	–	89	90
7	**3g**	20	toluene	–	62	92
8[c]	**3g**	20	toluene	–	trace	-
9	**3g**	20	DCM	–	41	91
10	**3g**	20	THF	–	66	97
11[d]	**3g**	20	THF	MS 3Å	86	96
12[d]	**3g**	10	THF	MS 3Å	47	91
13[d,f]	**3g**	10	THF	MS 3Å	78	96
14[d,g]	**3g**	5	THF	MS 3Å	53	87
15[d,g,h]	**3g**	5	THF	MS 3Å	63	87
16[d,g,h,i]	**3g**	5	THF	MS 3Å	86	98
17[e,g,h,j]	**3g**	2	THF	MS 3Å	60	95

[a] The reaction of **1** (0.600 mmol) with **2a** (R^1 = Me, 0.600 mmol) was conducted by using a chiral Zr complex prepared from $Zr(OtBu)_4$ (*x* mol %) and BINOL derivative **3** (1.1*x* mol %) at −45 °C for 24 h in 0.25 M unless otherwise noted. The concentration was based on **1**. [b] Yield of isolated product. [c] $Zr(OiPr)_4{\cdot}i$PrOH complex was used instead of $Zr(OtBu)_4$. [d] 18 h. [e] 46 h. [f] 0.4 M. [g] 0.8 M. [h] 1.2 equivalents of **2a** were added. [i] **1** was slowly added over 10 h. [j] **1** was slowly added over 20 h.

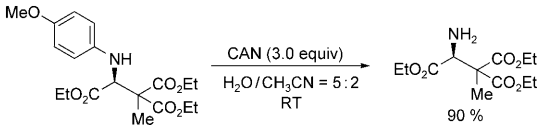
Substrate scope of β-dicarbonyl compounds was then examined. The malonates with primary alkyl chains, Er, Pr, and Bu, worked well, and high enantioselectivities (95–98 % *ee*) were obtained (Table 2, entries 1–3). The allyl substituent also worked well (entry 4). On the other hand, the benzyl substituent decreased the reactivity, although good enantioselectivity was maintained (entry 5). When the malonate bearing the *i*Pr group was examined, good results were obtained by using BINOL **3h** (entry 6). The substrate containing aromatic or halogen substituent did not work well (entries 7, 8). The reaction of β-ketoester **5** was also investigated, however selectivities were not sufficient (entry 9).

Table 2. Substrate scope of β-dicarbonyl compounds.[a]

Entry	2 (R^1)	x	3	Solvent	Yield[b] [%]	ee [%]
1	**2b** (Et)	5	**3g**	THF	80	96
2	**2c** (Pr)	5	**3g**	THF	72	95
3	**2d** (Bu)	5	**3g**	THF	78	98
4	**2e** (Allyl)	5	**3g**	THF	60	95
5	**2f** (Bn)	10	**3g**	THF	25	87
6[c]	**2g** (*i*Pr)	10	**3h**	toluene	47	89
7[c]	**2h** (Ph)	10	**3h**	toluene	40	10
8[c,d]	**2i** (Cl)	10	**3e**	toluene	72	22
9[e]	**5**	20	**3h**	toluene	50[f]	79[g]

[a] The reaction of **1** (0.600 mmol) with **2** (0.720 mol) was conducted by using a chiral Zr complex prepared from $Zr(OtBu)$ (*x* mol %) and BINOL derivative **3** (1.1*x* mol %) at −20 °C for 18 h in 0.25 M in the presence of MS 3Å unless otherwise noted. **1** was slowly added during the reaction time (18 h). [b] Yield of isolated product. [c] Without MS 3 Å. [d] Dimethyl ester was used. [e] Benzyl 2-oxocyclohexanecarboxylate (**5**) was used as a substrate. The reaction was conducted at 0 °C for 24 h without slow addition using a zirconium catalyst (20 mol %). [f] As a diastereomixture. Diastereomer ratio was 3:1. [g] *ee* of major diastereomer.

Next, deprotection of the obtained product was investigated. Oxidative cleavage of the PMP group using celium ammonium nitrate (CAN) proceeded smoothly to afford the desired primary amine in high yield under standard conditions (in a water–acetonitrile mixture at room temperature) (Scheme 2).[7,8]



Scheme 2. Deprotection of *p*-methoxyphenyl group.

A proposed catalytic cycle was shown in Scheme 3. First the malonate interacts with the zirconium catalyst in a bidentate fashion to form the active zirconium enolate (**A**) selectively. The iminoester then coordinates to the zirconium and is activated. Finally, the zirconium enolate attacks the imine part of the iminoester to afford the desired product. Formation of the zirconium enolate was confirmed by ^{1}H

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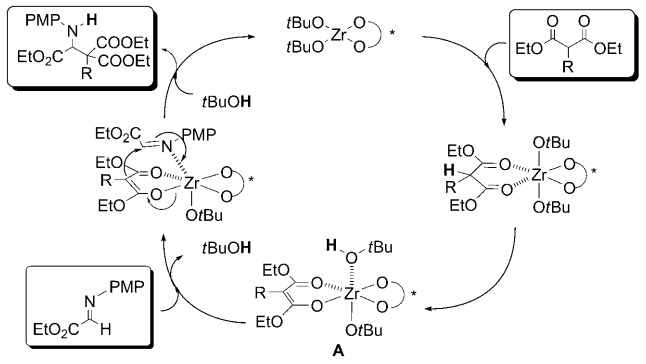

Scheme 3. Proposed catalytic cycle.

and ^{13}C NMR analysis of a mixture of the malonate and the zirconium complex.

In conclusion, we have demonstrated that the zirconium complex prepared from $Zr(OtBu)_4$ and 3,3′-disubstituted BINOL was a good chiral Brønsted base catalyst and that the asymmetric direct-type Mannich reactions of malonates with an iminoester proceeded in high yields with high enantioselectivities. To the best of our knowledge, this is the first example of successful catalytic direct activation of carbonyl compounds using chiral zirconium Brønsted base catalysts. Further investigation using zirconium alkoxides in asymmetric catalysis is now in progress.

Experimental Section

Typical experimental procedure is described for the reaction shown in Table 1, entry 16. Under argon atmosphere, to a well-dried flask were added ligand **3g** (0.0330 mmol), MS 3 Å (50 mg), and THF (0.5 mL), and the mixture was stirred at room temperature. $Zr(OtBu)_4$ (0.0300 mmol) was added, and the catalyst solution was stirred for 1 h at the same temperature. After adding **2a** (0.720 mmol) to this solution, the whole was cooled at −45 °C. A solution of **1** (0.600 mmol) in THF (0.5 mL) was slowly added to the mixture over 18 h. The reaction was stopped by addition of water, and the mixture was separated after addition of dichloromethane. The aqueous phase was extracted with dichloromethane, then the organic phases were combined and dried over anhydrous sodium sulfate. After filtration and concentration in vacuo, the crude mixture was purified by silica gel column chromatography to afford the corresponding product. The optical purity was determined by HPLC analysis using a chiral column.

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Keywords: asymmetric catalysis · Brønsted base · mannich reaction · zirconium

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