Catalytic Enantioselective Mannich-Type Reactions Using a Novel Chiral Zirconium Catalyst

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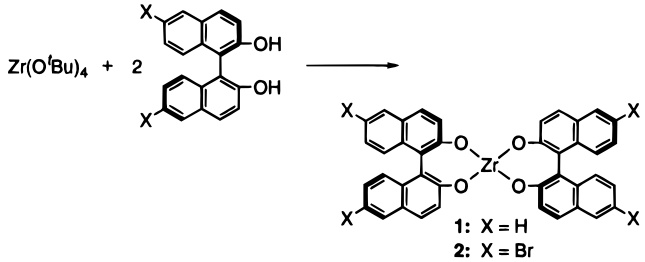
Asymmetric Mannich-type reactions provide useful routes for the synthesis of optically active β-amino ketones or esters, which are versatile chiral building blocks in the preparation of many nitrogen-containing biologically important compounds.[1] While several diastereoselective Mannich-type reactions have already been reported,[2] very little is known about the enantioselective versions. In 1991, Corey *et al.* reported the first example of the enantioselective synthesis of β-amino acid esters using chiral boron enolates.[3] Yamamoto *et al*. showed enantioselective reactions of aldimines with a ketene silyl acetal using a stoichiometric amount of a Brønsted acid-assisted chiral Lewis acid.[4] Quite recently, Enders *et al*. reported efficient enantioselective Mannich-type reactions based on the chiral hydrazone method;[5] however, a stoichiometric amount of a chiral source was needed. Asymmetric Mannich-type reactions using small amounts of chiral sources have not been reported to the best of our knowledge. In this paper, we disclose the first truly catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates using a novel zirconium catalyst.

Our approach is based on chiral Lewis acid-catalyzed reactions. Asymmetric reactions using chiral Lewis acids are of great current interest as one of the most efficient methods for the preparation of chiral compounds.[6] While rather rapid progress has been made on the enantioselective reactions of carbonyl compounds using chiral Lewis acids (aldol reactions, allylation reactions, Diels−Alder reactions, etc.),[7] very few examples have been reported for their aza analogues.[8] We thought that this was due to two main difficulties. First, many Lewis acids are deactivated or sometimes decomposed by the nitrogen atoms of starting materials or products, and even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by the nitrogen atoms. Second, aldimine−chiral Lewis acid complexes are rather flexible and often have several stable conformers (including *E*/*Z* isomers of aldimines), while aldehyde−chiral Lewis acid complexes are believed to be rigid. Therefore, in the additions to aldimines activated by chiral Lewis acids, plural transition states would exist to decrease selectivities. To solve these problems, we first screened various metal salts in the achiral reactions of aldimines with silylated nucleophiles. After careful investigation of the catalytic ability of the salts, we found unique characteristics in zirconium(IV) (Zr(IV)) and decided to design a chiral Lewis acid based on Zr(IV) as a center metal.[9,10] On the other hand, as for the problem of the conformation of the aldimine−Lewis acid complex, we planned to utilize a bidentate chelation (see below).[11] A necessary condition is easy removal of the chelation part of the substrates after the reactions.

Scheme 1. Preparation of the Catalyst



A chiral zirconium catalyst was prepared *in situ* according to Scheme 1.[12] In the presence of 20 mol % catalyst **1**, aldimine **3** prepared from 1-naphthaldehyde and 2-aminophenol was treated with the ketene silyl acetal derived from methyl isobutylate (**4**) in dichloromethane at −15 °C. The reaction proceeded smoothly to afford the corresponding adduct in a quantitative yield, and the enantiomeric excess of the product was 34% (Table 1). The ee was improved to 70% when *N*-methylimidazole (NMI) was used as an additive. Moreover, the ee was further improved when catalyst **2** was used,[13] and the desired adduct was obtained in a 95% ee when the reaction was carried out at −45 °C.[14] It should be noted that the same high level of ee was obtained when 2 mol % catalyst was employed. We then tested other aldimines and silyl enolates, and the results are summarized in Table 2. Not only aldimines derived from aromatic aldehydes but also aldimines from heterocyclic and aliphatic aldehydes[15] worked well in this reaction, and good to high yields and enantiomeric excesses

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(2) For example, (a) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. (b) Arend, M. Risch, N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2861. (c) Matsumura, Y. Tomita, T. *Tetrahedron Lett.* **1994**, *35*, 3737. (d) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902. (e) Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 83. (f) Nolen, E. G.; Aliocco, A.; Broody, M.; Zuppa, A. *Tetrahedron Lett.* **1991**, *32*, 73. (g) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (h) Katritzky, A. R.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987. (i) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, 28, 1067. (j) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (k) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227. (l) Broadley, K.; Davies, S. G. *Tetrahedron Lett.* **1984**, *25*, 1743. (m) Seebach, D.; Betschart, C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593.

(3) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *39*, 5287.

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(6) (a) Narasaka, K. *Synthesis* **1991**, 1. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995.

(7) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993.

(8) (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (b) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1997**, 59.

(9) Different types of chiral zirconium catalysts, which are effective in ring opening reactions of epoxides, Diels−Alder reactions, and polymerization, etc.: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (c) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262, and references cited therein.

(10) Rare earths (Sc, Y, Ln) are also promising candidates for the catalytic activations of aldimines: (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773. See also ref 11.

(11) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

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(13) For the use of 6,6′-dibromo-1,1′-bi-2-naphthol, see: (a) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693. (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.

(14) When the aldimine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding β-amino esters were obtained in good yields but with less than 5% ee's.

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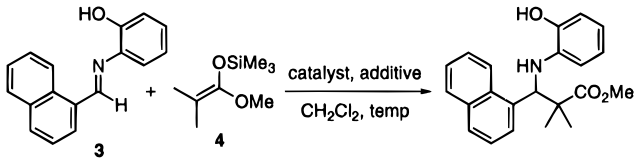
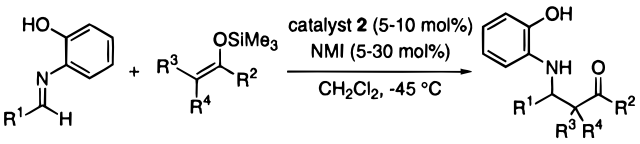
Table 1. Examination of Reaction Conditions[a]



catalyst (mol %)	additive (mol %)	temp, °C	yield, %	ee, %
1 (20)		−15	quant	34
1 (20)	NMI (20)	−15	80	70
2 (20)	NMI (20)	−15	73	90
2 (20)	NMI (20)	−45	83	95
2 (10)	NMI (10)	−45	quant	92
2 (5)	NMI (5)	−45	69	95
2 (5)	DMI (5)	−15	quant	91
2 (2)	NMI (2)	−45	75	86

[a] NMI = *N*-methylimidazole; DMI = 1,2-dimethylimidazole.

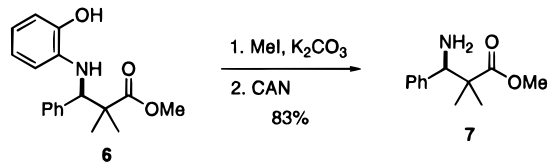
Table 2. Catalytic Enantioelective Mannich-Type Reactions



R^1	silyl enolate	yield, %[a]	ee, %[b]
Ph	**4**	70	87
p-ClPh	**4**	86	83
1-naphthyl	**4**	quant	92
Ph	$H_2C{=}C(OSiMe_3)SEt$ (**5**)	78	88
p-ClPh	**5**	88	86
1-naphthyl	**5**	quant	>98
2-furyl	**5**	89	89
c-C_6H_{11}[c]	**5**	56	80

[a] Isolated yields after acidic workup (see a typical experimental procedure). [b] Determined by HPLC analyses (see the Supporting Information). [c] The aldimine prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol was used. When the reaction was carried out at −23 °C, 71% yield and 71% ee were obtained. See ref 15.

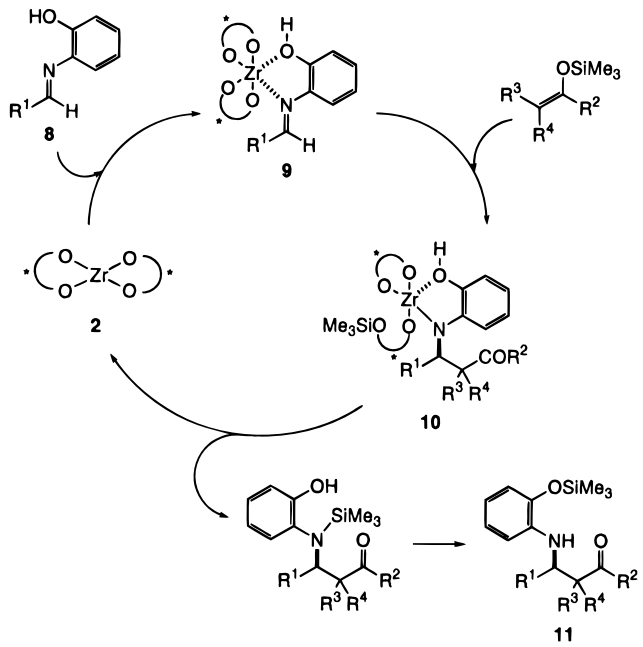
Scheme 2. Conversion to *β*-Amino Ester



were obtained. Similar high levels of ee's were also obtained when the silyl enol ether derived from *S*-ethyl thioacetate (**5**) was used. The *N*-substituent of the product was easily removed according to Scheme 2. Thus, methylation of the phenolic OH of **6** using methyl iodide and potassium bicarbonate and deprotection using cerium ammonium nitrate (CAN)[16] gave *β*-amino ester **7**. The absolute configuration assignment was made by comparison of the optical rotation of **7** with that in the literature.[17]

A typical experimental procedure is described for the reaction of aldimine **3** with ketene silyl acetal **4**. To $Zr(O^tBu)_4$ (0.04 mmol) in dichloromethane (0.25 mL) were added 6,6′-dibromo-1,1′-bi-2-naphthol (0.088 mmol) in dichloromethane (0.5 mL) and *N*-methylimidazole (0.048 mmol) in dichloromethane (0.25 mL) at room temperature. The mixture was stirred for 1 h at the same temperature and cooled to −45 °C. Dichloromethane solutions (0.75 mL) of **3** (0.8 mmol) and **4** (0.96 mmol) were successively added. The mixture was stirred for 10 h, and saturated $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude adduct was treated with THF−1N HCl (10:1) at 0 °C for 30 min. After a usual workup, the crude product was chromatographed on silica gel to give the desired adduct. The optical purity was determined by HPLC analysis using a chiral column.[18]

Scheme 3. Assumed Catalytic Cycle



The assumed catalytic cycle of this enantioselective reaction is shown in Scheme 3. Catalyst **2**[19] is postulated to coordinate aldimine **8** to form zirconium complex **9**. A silyl enolate attacks the aldimine to produce **10**, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with the regeneration of catalyst **2**. The product was obtained as a trimethylsilylated form (**11**) without the acidic workup (see a typical experimental procedure).

In summary, the first catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates have been achieved by using a novel chiral zirconium catalyst. High levels of enantioselectivities in the synthesis of chiral *β*-amino ester derivatives have been obtained according to these reactions. The novel zirconium catalyst has been shown to be effective for the catalytic activation of aldimines. Further investigations to clarify the precise structure of the catalyst and mechanism of these reactions as well as to develop other enantioselective reactions using this catalyst are now in progress.

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Supporting Information Available: Text describing the experimental procedure and NMR and HPLC data (5 pages). See any current masthead page for ordering and Internet access instructions.

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(15) It was found that the aldimine prepared from cyclohexanecarboxaldehyde and 2-aminophenol was unstable and was difficult to supply the reaction. On the other hand, high ee shown in Table 2 was obtained by using the aldimine prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol.

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(18) Details are shown in the Supporting Information.

(19) The role of NMI or DMI is not clear at this stage. White precipitates were observed after combining $Zr(O^tBu)_4$ and 6,6′-dibromo-1,1′-bi-2-naphthol in dichloromethane, and the precipitates dissolved completely when NMI or DMI was added. From this observation, although the precise structure of the catalyst has not yet been clarified, it is assumed that a monomeric catalyst may be produced by adding NMI or DMI, while an oligomeric structure may be formed without the ligand. We also found that the catalyst was obtained as a white powder after removal of the solvent. The powder did not contain *t*-BuOH and was effective in the present asymmetric Mannich-type reactions.