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Direct Catalytic Asymmetric Mannich-type Reaction of Hydroxyketone Using a Et_2Zn/Linked-BINOL Complex: Synthesis of Either *anti*- or *syn*-β-Amino Alcohols

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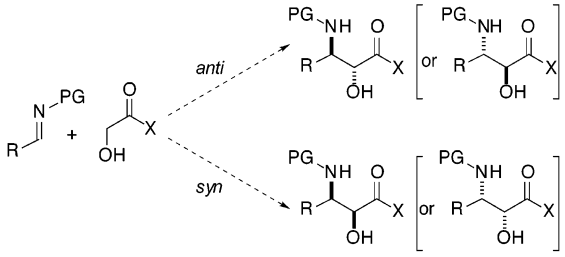
Abstract: Full details of a direct catalytic asymmetric Mannich-type reaction of a hydroxyketone using a Et_2Zn/(*S*,*S*)-linked-BINOL complex are described. By choosing the proper protective groups on imine nitrogen, either *anti*- or *syn*-β-amino alcohol was obtained in good diastereomeric ratio, yield, and excellent enantiomeric excess using the same zinc catalysis. *N*-Diphenylphosphinoyl (Dpp) imine **3** gave *anti*-β-amino alcohols in anti/syn = up to >98/2, up to >99% yield, and up to >99.5% ee, while Boc-imine **4** gave *syn*-β-amino alcohols in anti/syn = up to 5/95, up to >99% yield, and up to >99.5% ee. The high catalyst turnover number (TON) is also noteworthy. Catalyst loading was successfully reduced to 0.02 mol % (TON = up to 4920) for the *anti*-selective reaction and 0.05 mol % (TON = up to 1760) for the *syn*-selective reaction. The Et_2Zn/(*S*,*S*)-linked-BINOL complex exhibited far better TON than in previous reports of catalytic asymmetric Mannich-type reactions. Mechanistic studies to clarify the reason for the high catalyst efficiency as well as transformations of Mannich adducts are also described.

Introduction

Chiral β-amino alcohol units are useful chiral building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands.[1] Various methods have been developed over the past decade for enantioselective and diastereoselective preparation of β-amino alcohols.[2] Among the methods available for their catalytic enantioselective syntheses,[3] catalytic asymmetric Mannich-type reactions[4] of α-alkoxy enolate are of particular interest because two adjacent stereocenters are constructed simultaneously with a concomitant carbon−carbon bond formation. As shown in Scheme 1, either *anti*- or *syn*-β-amino alcohol is obtained in an optically active form using suitable chiral catalysts, imines, and nucleophiles. Toward this end, Kobayashi reported pioneering work on the Zr catalysis using preformed α-TBSO- and α-BnO-ketene silyl acetals, which selectively provided either *anti*- or *syn*-β-amino alcohol, respectively.[5] By changing the face selection of enolate, stereoselective synthesis of either *syn*- or *anti*-β-amino alcohol was achieved by the same Zr-catalysis.

Scheme 1. Catalytic Enantio- and Diastereoselective Synthesis of β-Amino Alcohol via the Mannich-type Reaction



syn-Mannich and *anti*-Mannich adducts had the same absolute configuration at the β-position of the carbonyl group. Akiyama et al. reported the *syn*-selective Mannich-type reaction of an α-Ph_3SiO-ketene silyl acetal using a chiral Brønsted acid catalyst.[6] Recently, more atom-economical processes,[7] that is, the direct addition of unmodified α-hydroxyketone[8] to imines, were reported by List,[9] Barbas,[10] and Trost.[11,12] Excellent selectivity was achieved; however, only *syn*-amino alcohols were produced in those systems.[9−11] The development of an *anti*-

(1) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*, 1st ed.; Springer: Berlin, 1999. (c) Ojima, I., Ed.; *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000.
(2) For reviews on asymmetric synthesis of vicinalamino alcohols, see: (a) Bergmeire, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Reetz, M. *Chem. Rev.* **1999**, *99*, 1121.
(3) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243.
(4) For a review on the catalytic asymmetric Mannich-type reaction, see: (a) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Supplement 1; Springer: Berlin, 2003; Chapter 29.5, p 143. See also ref 3a and: (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
(5) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.
(6) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
(7) Trost, B. M. *Science* **1991**, *254*, 1471.
(8) For the use of unmodified hydroxyketones as a donor in asymmetric carbon−carbon bond forming reactions, see, with catalytic antibodies: (a) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768 and references therein. For examples with small molecular catalysts, see reviews on direct aldol reactions: (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (c) List, B. *Tetrahedron* **2002**, *58*, 5573.
(9) (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
(10) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842.
(11) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338.

selective direct catalytic asymmetric Mannich-type reaction of α-hydroxyketone has remained problematic. In addition, catalyst loading remained unsatisfactory in the above-mentioned examples.[9−11] In the Mannich-type reaction using metal catalysis, β-amino carbonyl adducts often interact strongly with asymmetric metal complexes. Product inhibition is a formidable problem in asymmetric Mannich-type reactions. Although recent progress in asymmetric Mannich-type reactions with ketene silyl acetals and enol silyl ethers enabled catalytic use of chiral promoters (1−5 mol %) to achieve high yield (>90%),[4,13] the asymmetric catalysts for the direct Mannich-type reaction, in most cases, still require 5−20 mol % of catalyst loading (substrate/catalyst = <20) to achieve good conversion (>90% yield).[9−11,12] Thus, the development of an asymmetric catalysis that has high catalyst efficiency for direct asymmetric Mannich-type reactions is desirable. To improve the substrate/catalyst ratio, catalysts should be compatible with β-amino carbonyl adducts.

After a preliminary report[14] on *anti*-selective direct catalytic asymmetric Mannich-type reactions of hydroxyketone **2a** using a Et_2Zn/linked-BINOL **1** complex (Figure 1),[15−17] we continued studies to broaden the reaction scope and to improve the catalyst turnover number (TON). Here, we report full details of asymmetric zinc catalysis in direct catalytic asymmetric Mannich-type reactions using the Et_2Zn/linked-BINOL **1** complex. By selecting the proper protective group of imines, either *anti*- or *syn*-β-amino alcohols were selectively obtained in good diastereomeric ratio, yield, and ee while using the same zinc catalyst and ketone **2a**. Dpp-imine **3** gave *anti*-adducts in anti/syn = up to >98/2, up to >99% yield, and up to >99.5% ee, while Boc-imine **4** gave *syn*-adducts in anti/syn = up to 5/95, up to >99% yield, and up to >99.5% ee. It is noteworthy that catalyst loading was successfully reduced to 0.02 mol % for the *anti*-selective reaction (TON = up to 4920) and 0.05 mol % for the *syn*-selective reaction (TON = up to 1760). Mechanistic studies revealed that the rate-determining step differed depending on the imines used. The effects of β-amino alcohol adducts on the zinc catalysis were also discussed.

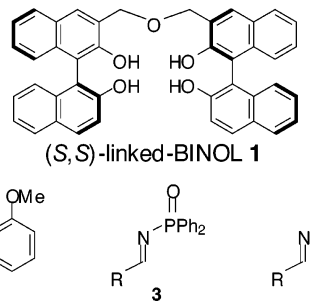
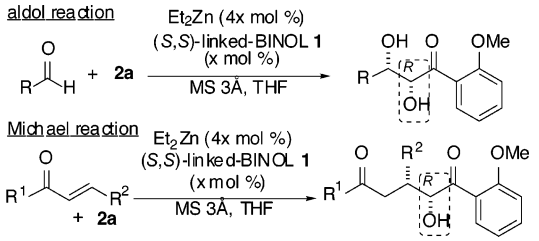


Figure 1. Structures of (*S*,*S*)-linked-BINOL **1**, 2-hydroxy-2′-methoxyacetophenone (**2a**), *N*-diphenylphosphinoyl(Dpp) imine **3**, and *N*-*tert*-butoxycarbonyl (Boc) imine **4**.

Scheme 2. Direct Asymmetric Aldol Reaction and Michael Reaction Catalyzed by the Et_2Zn/(*S*,*S*)-Linked-BINOL **1** Complex



Results and Discussion

(A) Development of Enantio- and Diastereoselective Mannich-type Reactions. In our continuing investigation of a direct catalytic asymmetric aldol reaction[16] and a Michael reaction[17] of hydroxyketones, a Et_2Zn/linked-BINOL **1** complex was determined to be effective for shielding the Re-face of the zinc-enolate generated from ketone **2a**. Absolute configurations of products at the α-position of the carbonyl group were identical (2*R*) in aldol adducts and Michael adducts, as shown in Scheme 2. We anticipated that an efficient enantioface selection of the enolate would be applicable to other electrophiles, such as imines. Face selection of imines is important to achieve high diastereoselectivity. As shown in Figure 2, we hypothesized that either *anti*- or *syn*-Mannich adducts would be selectively obtained by choosing the proper protective group of imines (Scheme 3) that favored the Si-face or Re-face approach toward the Zn/linked-BINOL **1**/ketone **2a** complex, respectively. Therefore, our strategy is different from that of Kobayashi et al. employed in Zr catalysis.[5] Previous mechanistic studies on the Et_2Zn/linked-BINOL **1** complex revealed that active Zn/linked-BINOL **1**/ketone **2a** had an oligomeric structure, containing presumably seven Lewis acidic zinc centers.[16a] We assumed that the multinuclear zinc complex would enable flexible facial selection of imines depending on the protective groups. Screen-

(12) For other examples of direct catalytic asymmetric Mannich(-type) reactions using unmodified ketone and/or aldehyde as donors, see a review: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. For selected examples, see also: (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (c) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (d) Córdova, A.; Watanabe, S.-i.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (e) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749. (f) Watanabe, S.-i.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519. (g) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (h) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. For related examples, see: (i) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (j) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.-Eur. J.* **2003**, *9*, 2359. (k) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356 and references therein.

(13) For selected leading references, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (d) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (e) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271. (f) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. For examples with metal enolate, see: (g) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (h) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 728. (i) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomoika, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. For an example with organocatalyst, see: (j) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

(14) A portion of the results in this Article was reported previously as a preliminary communication: Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712.

(15) For the synthesis of linked-BINOL **1**, see: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 4. Both enantiomers of linked-BINOL are also commercially available from Wako Pure Chemical Industries, Ltd. Catalog No. for (*S*,*S*)-**5**, No. 152-02431; and for (*R*,*R*)-**5**, No. 155-02421.

(16) Et_2Zn/linked-BINOL **1** complex in direct aldol reaction: (a) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169. (b) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (c) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(17) Et_2Zn/linked-BINOL **1** complex in direct Michael reaction: (a) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251.

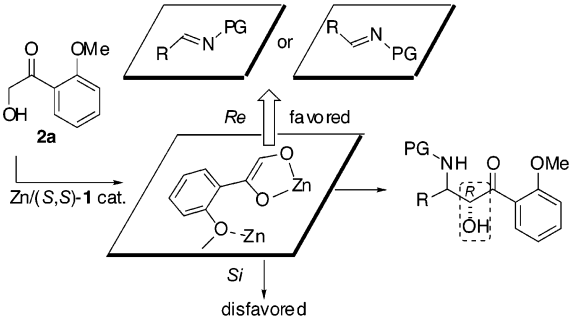
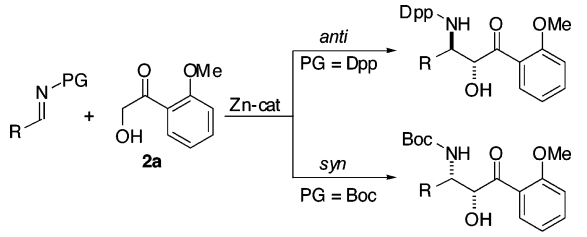


Figure 2. Strategy to achieve enantio- and diastereoselective Mannich-type reactions.

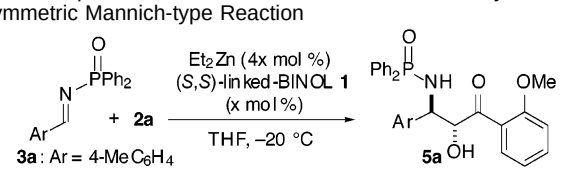
Scheme 3. Effects of Protective Group on Imine Nitrogen



ing of various imines revealed that Dpp-imines[18] afforded *anti*-β-amino alcohol, while Boc-imines[19] afforded *syn*-β-amino alcohol (Scheme 3).[20] Optimization of the reaction conditions, scopes, and limitations of substrates, and trials to reduce catalyst loading for both the *anti*- and the *syn*-selective reactions are described in this section.

Optimization of the reaction conditions for Dpp-imine **3a** is summarized in Table 1. The addition of **2a** to **3a** proceeded smoothly in the presence of 5 mol % of **1**, 20 mol % of Et_2Zn, and MS 3 Å, to afford **5a** *anti*-selectively (anti/syn = 94/6) in 97% yield and 98% ee (*anti*-**5a**) (entry 1). The reaction reached completion even with reduced catalyst loading to afford **5a** without any loss of diastereo- or enantioselectivity (entry 2, 3 mol %; entry 3, 1 mol %). The reaction proceeded well with only 1.1 equiv of **2a**, although there was a slight loss of reactivity at −20 °C (entry 4). The presence of activated MS 3 Å enhanced the reaction rate without affecting stereoselectivity (entry 3 vs entry 5). The effects of hydroxyketones are summarized in Table 2. As expected from previous results in the direct aldol reaction using Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex,[16a] ketones **2a** gave the best results (Table 2, entry 1). With 4′-methoxy-substituted ketone **2b**, the reaction rate decreased, while good ee and dr were obtained (entry 2, 92% ee, dr = 91/9). With ketones without methoxy substituents, both ee and dr were only modest (entries 3−5). These results suggested that hydroxyketones are involved in active species affecting the stereoselectivity, as was suggested in the previous mechanistic studies in the direct aldol reaction.[16a] Although applicable hydroxyketones were limited, Mannich adducts should be useful as chiral building blocks when considering the methoxy-phenyl group as an ester synthon. The methoxy substituent of **2a** is supposed to assist conversion of Mannich adducts **5** into β-amino-α-hydroxy esters through Baeyer−Villiger oxidation (see section C).

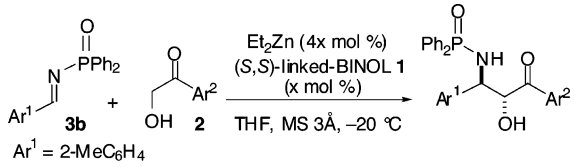
Table 1. Optimization of the *anti*-Selective Direct Catalytic Asymmetric Mannich-type Reaction



entry	ligand **1** (×mol %)	ketone **2a** (equiv)	additive	time (h)	yield[a] (%)	dr[b] (anti/syn)	ee (%) (anti)
1	5	2	MS 3 Å	2	97	94/6	98
2	3	2	MS 3 Å	3	95	94/6	98
3	1	2	MS 3 Å	9	98	96/4	98
4	1	1.1	MS 3 Å	24	87	96/4	98
5	1	2	none	18	93	96/4	98

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude mixture.

Table 2. Effects of Hydroxyketones in the *anti*-Selective Direct Catalytic Asymmetric Mannich-type Reaction



entry	ketone:Ar^2	ligand **1** (×mol %)	time (h)	yield[a] (%)	dr[b] (anti/syn)	ee (%) (anti)
1	**2a**: 2′-MeO-C_6H_4	1	6	99	>98/2	99
2	**2b**: 4′-MeO-C_6H_4	5	24	81	91/9	92
3	**2c**: C_6H_5	5	24	83	72/28	58
4	**2d**: 4′-Me-C_6H_4	5	24	89	81/19	65
5	**2e**: 2-furyl	5	24	84	85/15	36

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude mixture.

As summarized in Table 3, the present asymmetric zinc catalysis was applicable to various Dpp-imines **3**. All reactions were performed with 1 mol % of **1**, 4 mol % of Et_2Zn, and MS 3 Å. The enantiomeric excesses were uniformly high (98 → 99.5% ee) with imines derived from α-nonenolizable aldehydes. Imines from aromatic aldehydes having various substituents (**3a**−**3j**) afforded products with high *anti*-selectivity (dr: 94/6 → 99/1, entries 1−10). *ortho*-Substituents on the aromatic rings resulted in almost exclusive formation of the *anti*-adducts (dr: >98/2, entry 2 and 98/2, entry 8). Although imine **3k** from α,β-unsaturated aldehyde had less *anti*-selectivity, diastereoselectivity was improved at a lower reaction temperature (entry 12, dr: 81/19 at −30 °C). Imine **3l** also provided the Mannich adduct in high ee (99%) with modest *anti*-selectivity (entry 13). Diastereoselectivity was improved by increasing the bulkiness of the protective group. As shown in Scheme 4, di(*o*-tolyl)-phosphinoyl imine **3m**[21] gave product **5m** in better *anti*-

(18) Dpp-imine was prepared by following the reported procedure. Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.
(19) Boc-imine was prepared by following the reported procedure. Kanazawa, A. M.; Denis, J.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238. See also ref 13j.
(20) Other imines, such as Ts-imine, PMP-imine, and Cbz-imine, gave less satisfactory results in terms of diastereoselectivity, reaction rate, and enantioselectivity.

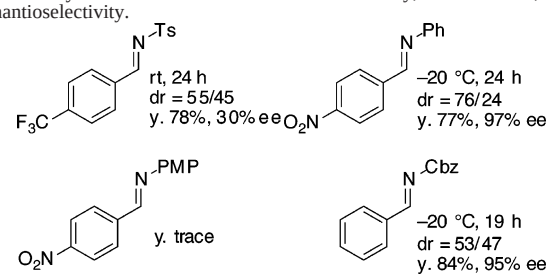
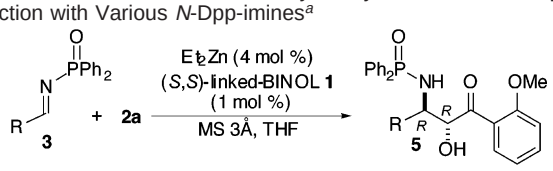


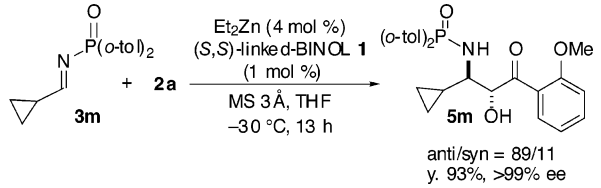
Table 3. *anti*-Selective Direct Catalytic Asymmetric Mannich-type Reaction with Various *N*-Dpp-imines[a]



entry	R		product	temp (°C)	time (h)	yield[b] (%)	dr[c] (anti/syn)	ee (%) (anti)
1	4-MeC_6H_4	**3a**	**5a**	−20	9	98	96/4	98
2	2-MeC_6H_4	**3b**	**5b**	−20	6	99	>98/2	99
3	C_6H_5	**3c**	**5c**	−20	6	98	96/4	99
4	4-$MeOC_6H_4$	**3d**	**5d**	−20	6	97	95/5	99
5	4-$NO_2C_6H_4$	**3e**	**5e**	−20	9	96	97/3	98
6	4-ClC_6H_4	**3f**	**5f**	−20	4	97	97/3	98
7	4-BrC_6H_4	**3g**	**5g**	−20	4	97	95/5	98
8	1-naphthyyl	**3h**	**5h**	−20	6	97	98/2	>99.5
9	2-naphthyl	**3i**	**5i**	−20	7	95	94/6	99
10	2-furyl	**3j**	**5j**	−20	7	98	96/4	>99.5
11	(*E*)-cinnam	**3k**	**5k**	−20	4	98	76/24	>99.5
12		**3k**	**5k**	−30	7	97	81/19	>99.5
13	*cyclo*-propyl	**3l**	**5l**	−30	5	98	80/20	99

[a] Two equivalents of **2a** was used. For less soluble imines, THF/CH_2Cl_2 mixed solvent was used. See the Supporting Information. [b] Isolated yield. [c] Determined from the ^{1}H NMR spectrum of the crude mixture.

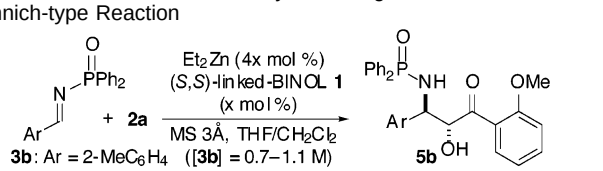
Scheme 4. Substituent Effects of the *N*-Phosphinoyl Group on Diastereoselectivity



selectivity (89/11, Scheme 4 vs 80/20, Table 3, entry 13), although reactivity decreased slightly.

The results of attempts to reduce catalyst loading are summarized in Table 4. The reactions were completed within 6 h using 0.25 mol % catalyst to afford product **5b** in excellent yield, dr, and ee (entry 2). Importantly, diastereoselectivity and enantioselectivity remained high when the reaction was performed at 0 °C (entries 3−7). Thus, the catalyst loading was reduced at 0 °C, because a higher reaction rate was observed at 0 °C. At 0 °C, the reaction proceeded smoothly with as little as 1.1 equiv of ketone **2a** using 0.5 mol % (entry 3) and 0.1 mol % catalyst (entry 4). High yield (entry 3, >99%; entry 4, 95%) and ee (entry 3, 99%; entry 4, 99%) were achieved. The reaction rate, however, decreased slightly with 0.05 mol % catalyst and 1.1 equiv of **2a** (entry 5). Thus, 1.5 equiv of **2a** was used to achieve a good reaction rate. As shown in entry 6, the reaction was completed within 6 h using 0.05 mol % catalyst, affording the product in >99% yield, anti/syn = 94/6, and 96% ee. The high catalyst turnover frequency (>300 h^{-1}) is noteworthy. In entry 7, the reaction was performed on a >10 g scale with 0.02 mol % catalyst; 11.9 g of **5b** (TON = 4920, yield 98.4%, anti/syn = 98/2, 97% ee) was obtained using 3.1 mg of (*S*,*S*)-linked-BINOL **1** (0.005 mmol) and 20 μL of Et_2Zn in hexanes (0.02 mmol). The TON of the present reaction (up to 4920) was far better than in previous reports of catalytic asymmetric Mannich-type reactions. The commercial availability of both (*S*,*S*)-linked-BINOL **1**[15] and Et_2Zn solution is also practically useful.

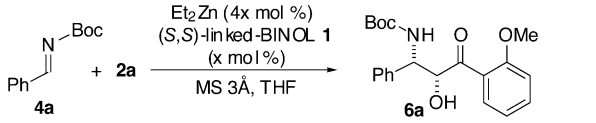
Table 4. Trials To Reduce Catalyst Loading in the *anti*-Selective Mannich-type Reaction



entry	ligand **1** (×mol %)	ketone **2a** (equiv)	temp (°C)	time (h)	yield[a] (%)	dr[b] (anti/syn)	ee (%) (anti)
1	1	2	−20	6	99	>98/2	99
2	0.25	2	−20	6	99	>98/2	99
3	0.5	1.1	0	2	>99	95/5	99
4	0.1	1.1	0	6	95	96/4	99
5	0.05	1.1	0	14	89	97/3	97
6	0.05	1.5	0	6	>99	94/6	96
7[c]	0.02	1.5	0	24	98	98/2	97

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude mixture. [c] Reaction was performed on the 25 mmol scale at 1.1 M on imine.

Table 5. Optimization of the *syn*-Selective Direct Catalytic Asymmetric Mannich-type Reaction



entry	ligand **1** (×mol %)	ketone **2a** (equiv)	temp (°C)	time (h)	yield[a] (%)	dr[b] (syn/anti)	ee (%) (syn/anti)
1	5	2	−40	19	94	88/12	99/95
2	5	1.1	−40	40	>99	79/21	97/92
3	1	2	−40	36	91	89/11	99/95
4	1	1.1	−40	40	90	84/16	95/94
5	1	2	−20	1.5	84	87/13	98/93
6	0.5	2	−20	2.5	86	86/14	99/ND
7	0.1	2	−20	15	90	83/17	99/ND
8	0.05	2	−20	48	88	84/15	98/ND

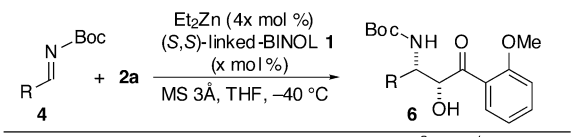
[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude mixture.

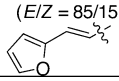
Boc-imine **4** was most promising for *syn*-selective reactions. The attempts to optimize the reaction conditions are summarized in Table 5. The best diastereoselectivity was achieved at −40 °C using 2 equiv of ketone **2a** (entry 1, 88/12; entry 3, 89/11). The diastereoselectivity and enantioselectivity decreased with 1.1 equiv of **2a**, although good yield was achieved (entries 2 and 4). At −20 °C, the reaction rate was much higher, albeit with slightly decreased diastereoselectivity (entries 5−8). Trials to reduce catalyst loading were performed at −20 °C, because turnover frequency of the zinc catalyst was rather slow at −40 °C. At −20 °C, the reaction reached completion within 1.5−2.5 h with 1 mol % (entry 5) and 0.5 mol % (entry 6) catalyst. The *syn*-adduct was obtained in high ee (98−99% ee) and good dr (83/17−86/14) using 0.5 mol % (entry 6), 0.1 mol % (entry 7), and 0.05 mol % (entry 8) catalyst loading. Although *syn*-selectivity of the present reaction was not as high as a previous report of direct catalytic asymmetric Mannich-type reactions,[9−11] the far better TON in the present system is noteworthy. Another advantage of the present reaction is the use of Boc-imine as a substrate, because the Boc group is one of the most frequently used protective groups for amines.

Substrate scope and limitations were examined at −40 °C with 5 mol % catalyst and 2 equiv of **2a**, which afforded the best diastereoselectivity (Table 5). The results are summarized

(21) Positive effects of sterically demanding di(*o*-tolyl)phosphinoyl imine over Dpp-imine were reported. Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura I.; Ikeno, T.; Yamada, T. *Org. Lett.* **2003**, *5*, 3555 and references therein.

Table 6. *syn*-Selective Direct Catalytic Asymmetric Mannich-type Reaction with Various *N*-Boc-imines **4**



entry	R	product		ligand **1** (x mol %)	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	C_6H_5	**4a**	**6a**	5	19	94	88/12	99
2	C_6H_5	**4a**	**6a**	1	36	91	89/11	99
3	4-MeOC_6H_4	**4b**	**6b**	5	25	>99	85/15	99
4	4-MeOC_6H_4	**4b**	**9b**	1	51	91	85/15	99
5	4-MeC_6H_4	**4c**	**6c**	5	20	>99	87/13	>99.5
6	3-MeC_6H_4	**4d**	**6d**	5	20	80	83/17	99
7	2-MeC_6H_4	**4e**	**6e**	5	21	87	93/7	>99.5
8	2-MeC_6H_4	**4e**	**6e**	1	35	89	94/6	99
9	4-ClC_6H_4	**4f**	**6f**	5	27	82	83/17	98
10	1-naphthyl	**4g**	**6g**	5	27	85	95/5	99
11	2-naphthyl	**4h**	**6h**	5	26	80	85/15	99
12	2-furyl	**4i**	**6i**	5	26	>99	82/18	>99.5
13	2-thienyl	**4j**	**6j**	5	21	>99	86/14	99
14	3-pyridyl	**4k**	**6k**	5	21	67	72/28	89
15	(*E*)-cinnam	**4l**	**6l**	5	30	81	63/37	99
16[c]	Ph (*E*/*Z* = 85/15)	**4m**	**6m**	5	26	95	80/20	>99.5
17		**4n**	**6n**	5	30	79	58/42	99

[a] Isolated yield. [b] Determined from the ^{1}H NMR spectrum of the crude mixture. [c] **4m** was used as *E*/*Z* = (85/15) mixture. Product was obtained in *E*-*syn*/*E*-*anti*/*Z*-*syn*/*Z*-*anti* = 70/16/10/4 as determined (syn/anti = 80/20) by NMR analysis.

in Table 6. *syn*-Adducts were obtained in good yield (entries 1−11: 80−>99%), dr (entries 1−11: syn/anti = 83/17−95/5), and ee (entries 1−11: 98 → 99.5% ee) using imines prepared from aromatic aldehydes. For selected examples, the reaction was also performed with 1 mol % catalyst and still afforded a good yield, dr, and ee (entries 2, 4, and 8). Heteroaromatic imines were also applicable (entries 12−14). Imines **4i** and **4j** had good reactivity and enantioselectivity, although **4k** with a 3-pyridyl group resulted in a modest yield (67%) and ee (89%). Imines **4l**, **4m**, and **4n** from α,β-unsaturated aldehydes gave products in high ee, although the diastereoselectivity was poor to modest (entries 15−17).

(B) Mechanistic Studies. In the present Mannich-type reactions, either *anti*- or *syn*-β-amino alcohol was selectively obtained using the same Et_2Zn/linked-BINOL **1** complex. In addition, a high catalyst TON was achieved in both *anti*- and *syn*-selective reactions. The results summarized in Tables 4 and 5 suggest that the Et_2Zn/linked-BINOL **1** complex is compatible with both *anti*- and *syn*-β-amino alcohols. In our previous studies on the direct aldol[16a] and Michael reaction[17a] of ketone **2a** using the Et_2Zn/linked-BINOL **1** complex, the strong affinity of ketone **2a** over aldol and Michael adducts had a key role in achieving a high catalyst TON. Because β-amino alcohols are often utilized as good ligands for zinc complexes,[1] investigations on the effects of the Mannich adducts on the Et_2Zn/linked-BINOL **1** complex were essential to clarify the origin of the high catalyst efficiency.

Relative configurations of Mannich adducts, *anti*-**5b** and *syn*-**6h**, were unequivocally determined by X-ray crystallographic

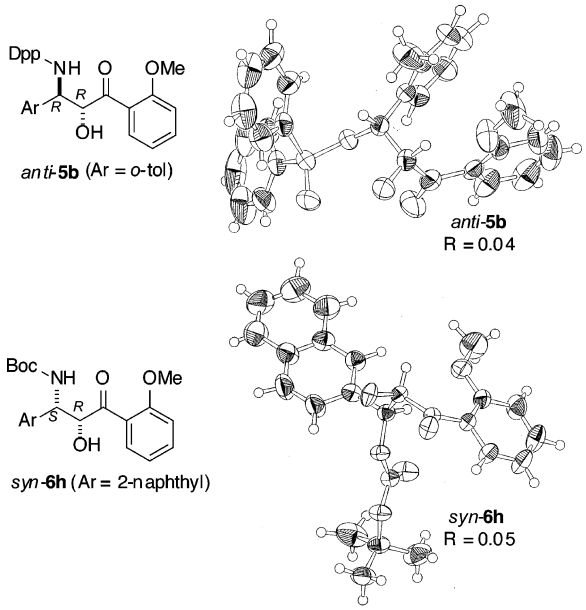


Figure 3. X-ray structures of *anti*-**5b** and *syn*-**6h**.

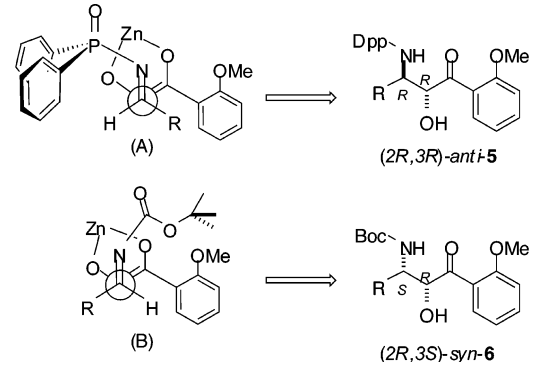


Figure 4. Transition state models of Mannich-type reactions.

analysis as shown in Figure 3.[22,23] Absolute configurations were determined using the MTPA method or by derivatization into known compounds (vide infra, section C).[23] As expected, the absolute configurations at the α-position of the carbonyl group were identical in both *anti*-**5** and *syn*-**6**, supporting our working hypothesis (see Figure 2). Figure 4 illustrates the postulated transition state models for the *anti*-selective reaction from Dpp-imine **3** and for the *syn*-selective reaction from Boc-imine **4**. The *anti*-selectivity with Dpp-imine might be due to the bulky Dpp-group on the imine nitrogen. To avoid steric repulsion between the Dpp-group and zinc-enolate, the Mannich-type reaction would proceed via transition state A in Figure 4, preferentially affording *anti*-adducts. The positive effects of the sterically more hindered di-*o*-tolyl-phosphinoyl group on diastereoselectivity (Scheme 4) also support our assumption. When using less sterically demanding Boc-imine **4**, the facial selectivity of imine should be opposite. To avoid steric repulsion between a substituent (R) of imine and zinc-enolate, the Mannich-type reaction would proceed via transition state B in Figure 4, giving *syn*-adducts.[24]

(22) CIF files of **5b** and **6h** are available as Supporting Information.
(23) Relative configurations of **5a**, **5b**, **5j**, **5k**, **5l**, **6e**, **6g**, and **6i** were determined by NOE experiments of corresponding cyclic carbamates. Absolute and relative configurations of **6a** and **6b** were determined by comparison of α_D value and NMR after conversion into **10** and **12** (Scheme 9). Absolute configurations of **5b**, **6h**, **6j**, and **6l** were determined by Mosher's method. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

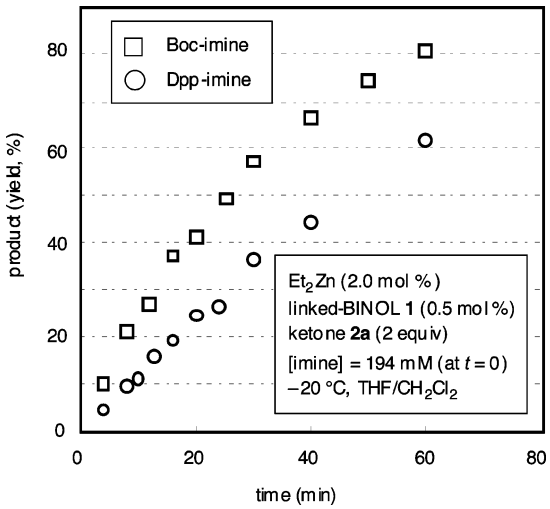
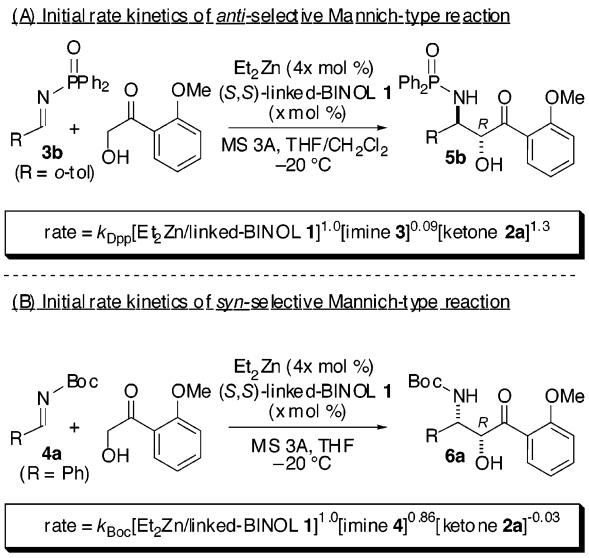


Figure 5. Reaction profiles of Mannich-type reactions.

The reaction profiles of *anti*- and *syn*-selective Mannich-type reactions are summarized in Figure 5. When the Mannich-type reactions of imines **3c** and **4a** derived from benzaldehyde were performed under identical conditions [2 mol % of Et_2Zn, 0.5 mol % of (*S*,*S*)-linked-BINOL, 2 equiv of **2a**, 0.194 M, at −20 °C], Boc-imine **4a** had a 1.9-fold higher reaction rate (v_{Boc} = 4.27 mM min^{-1} vs v_{Dpp} = 2.30 mM min^{-1}) at the initial stage (yield < 30%). Interestingly, the initial rate kinetic studies of *anti*- and *syn*-selective Mannich-type reactions had a completely different tendency. As summarized in Figure 6 and Scheme 5,[25] the reaction rate of the *anti*-selective Mannich-type reaction of Dpp-imine **3b** had 1.0 order dependency on the concentration of the zinc catalyst, 0.09 order dependency on the concentration of the Dpp-imine **3b**, and 1.3 order dependency on the concentration of ketone **2a** (Scheme 5A). On the other hand, the reaction rate of the *syn*-selective Mannich-type reaction of

Scheme 5. Initial Rate Kinetics of Mannich-type Reactions with (A) Dpp-imine **3b** and (B) Boc-imine **4a**



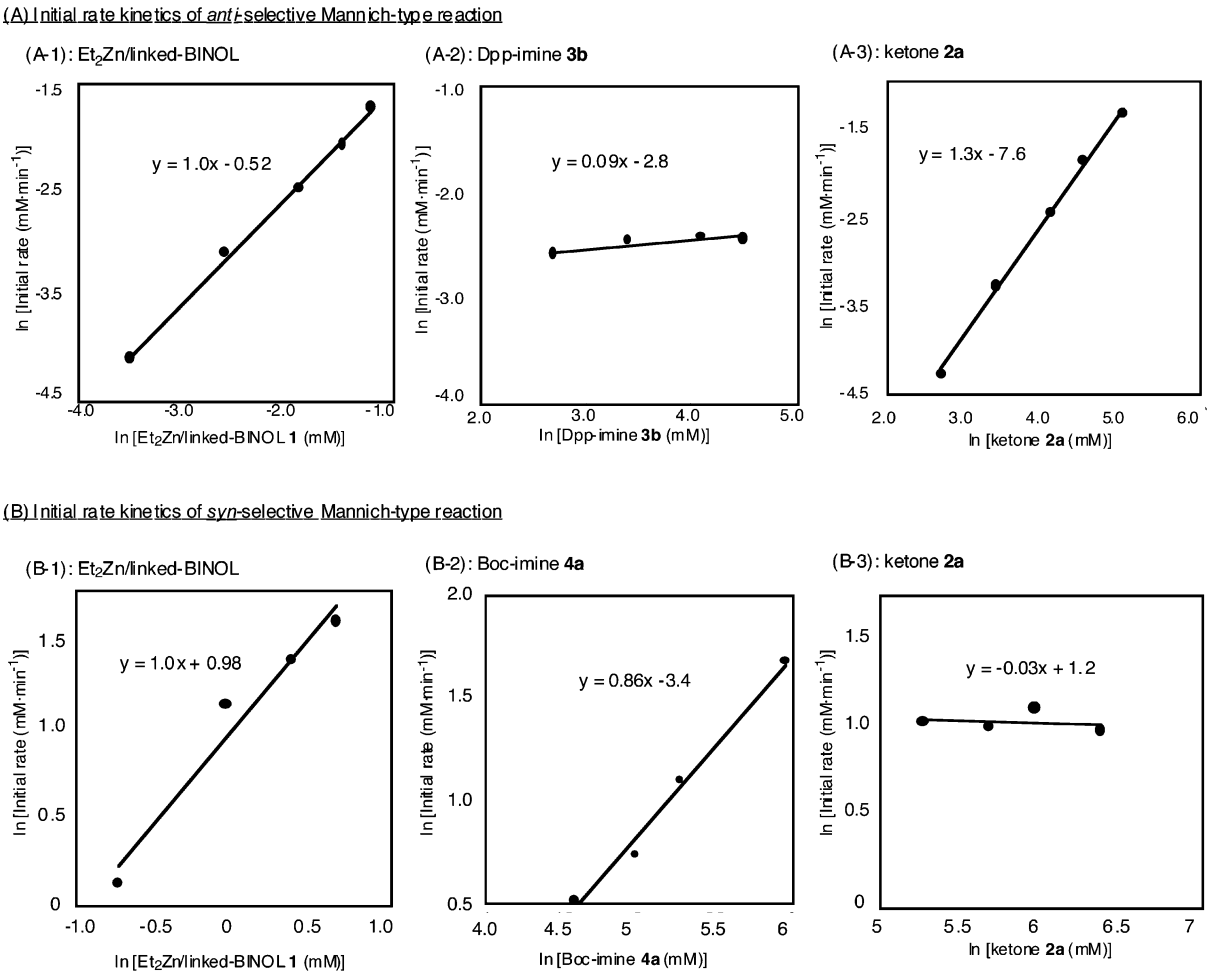
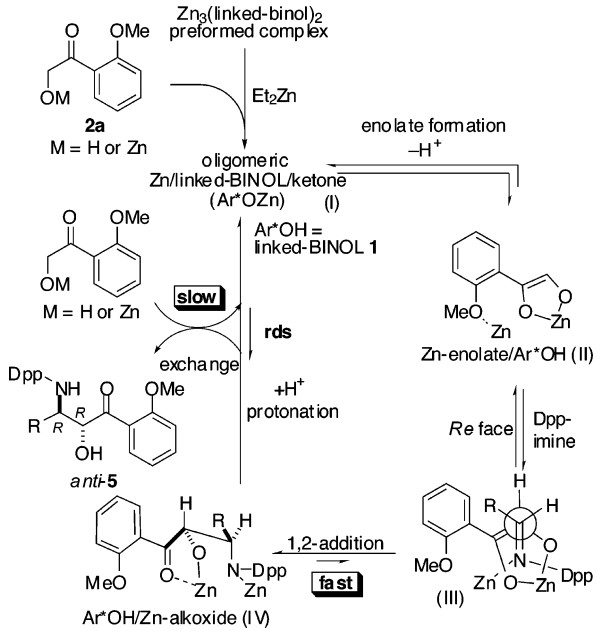
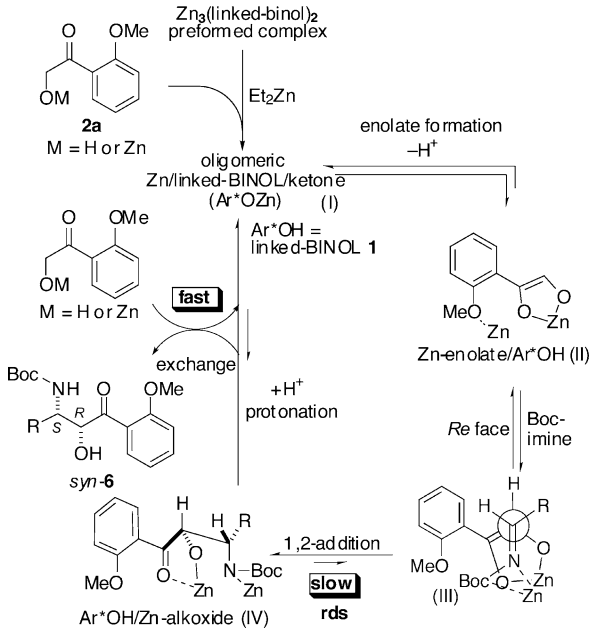


Figure 6. Initial rate kinetics of Mannich-type reactions.

Scheme 6. Proposed Catalytic Cycle of the *anti*-Selective Mannich-type Reaction of Dpp-imine **3**



Scheme 7. Proposed Catalytic Cycle of the *syn*-Selective Mannich-type Reaction of Boc-imine **4**



Boc-imine **4a** had 1.0 order dependency on the concentration of the zinc catalyst, 0.86 order dependency on the concentration of the Boc-imine **4a**, and −0.03 order dependency on the concentration of ketone **2a** (Scheme 5B). These results indicate that the rate-determining step of the Mannich-type reaction is different depending on the imine used. The proposed catalytic cycle of the Mannich-type reactions is summarized in Scheme 6 (*anti*-selective) and Scheme 7 (*syn*-selective). On the basis of detailed mechanistic studies of the direct aldol reaction,[16a] the active species of Et_2Zn/(*S*,*S*)-linked-BINOL **1** are postulated to be a Zn/linked-BINOL/ketone oligomeric, probably heptanuclear, complex [Ar*OZn (I), in Schemes 6 and 7].[26] Zinc-phenoxide would act as a Brønsted base to deprotonate the α-proton of the ketone, affording a zinc-enolate (II). Zinc would also function as a Lewis acid to activate imines (III), and then 1,2-addition would give (IV). Subsequent protonation and ligand exchange of (IV) with ketone **2a** would regenerate (I). The rate-determining step in Scheme 6 is the product dissociation step [from (IV) to (I)], while the rate-determining step in Scheme 7 is the 1,2-addition step [from (III) to (IV)].

The difference in the initial rate kinetics between Dpp-imine **3** and Boc-imine **4** is not explained well by the difference in the reactivity of the imines.[27] The different observed kinetic tendencies might derive from the difference in interactions between amino alcohol adducts and the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex. Initial rate kinetics indicated that *syn*-β-amino alcohol **6** would have a relatively weak affinity for the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex and that the dissociation of (2*R*,3*S*)-*syn*-β-amino alcohol **6** would proceed smoothly. Thus, the high TON observed in the *syn*-selective Mannich-type reaction of Boc-imine **4** is reasonable. The mechanistic studies of the direct Michael reaction of methyl vinyl ketone using the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex revealed the same tendency previously.[28] On the other hand, initial rate kinetics indicated that the dissociation of (2*R*,3*R*)-*anti*-β-amino alcohol **5** is the rate-determining step and that the affinity of *anti*-β-amino alcohol **5** to the Et_2Zn/(*S*,*S*)-linked-BINOL **1** complex is stronger than that of *syn*-β-amino alcohol **6**. To evaluate whether *anti*-β-amino alcohol **5** had negative or positive effects on the Mannich-type reaction, we performed further mechanistic studies.

During the initial rate kinetics studies, we found that initiation time existed in the *anti*-selective Mannich-type reaction of Dpp-imine **3**. The reaction profile of the reaction at the initial stage (yield < 8%, with 0.25 mol % ligand loading) is shown in Figure 7. Acceleration of the reaction was observed after 15 min. We hypothesized that *anti*-β-amino alcohol **5** accelerated the reaction. The experiments shown in Figure 8 indicated that *anti*-β-amino alcohol had positive effects on the reaction rate. When the reaction rate was compared with and without additional product (20 mol %) using 0.5 mol % (*S*,*S*)-linked-BINOL **1** and 2 mol % of Et_2Zn, the reaction rate increased 1.4-fold in the presence of 20 mol % of **5b** (Figure 8, 0.112 mM min^{-1} vs 0.078 mM min^{-1}). When the Mannich-type reaction of **3d** and **2a** (3 equiv) was performed using 8 mol % of Et_2Zn, and 1 equiv of optically active *anti*-β-amino alcohol **5b** [(2*R*,3*R*) prepared by (*S*,*S*)-cat: 99% ee], in the absence of (*S*,*S*)-linked-BINOL **1**, reaction proceeded at a much lower reaction rate than

(24) The precise coordination mode of imines to Zn catalyst is unclear. Imines would possibly coordinate to Zn through either the oxygen atom of the protective group or the nitrogen atom of imines. Because the present Zn/linked-BINOL/ketone **2a** complex is oligomeric with as much as seven zinc metals, flexible coordination of imines to the Zn/linked-BINOL/ketone **2a** complex seems possible.

(25) For detailed results of initial rate kinetics, see the Supporting Information.

(26) Although mechanistic studies including X-ray crystallography, mass, and kinetic profiles suggested oligomeric active species (see ref 16a), a linear relationship between the ee of linked-BINOL and the ee of product was observed. The linear relationship would suggest that the formation of hetero-complex from (*S*,*S*)-**1** and (*R*,*R*)-**1** would be negligible. See the Supporting Information for the detailed results.

(27) Both Dpp-imine **3** and Boc-imine **4** are known as highly electrophilic imines. On the basis of its stability on silica gel against hydrolysis (Dpp-imine, stable; Boc-imine, decomposed), we speculate Boc-imine **4** would be more electrophilic than Dpp-imine **3**.

(28) In the mechanistic studies of Michael reaction of **2a**, we found that Zn-(*S*,*S*)-linked-BINOL catalyst recognized the absolute configuration of α-hydroxyketone unit well, and therefore the affinity of the Michael adduct to zinc catalyst was low. Thus, high catalyst TON was achieved in the Michael reaction of **2a** and methyl vinyl ketone. See ref 17a.

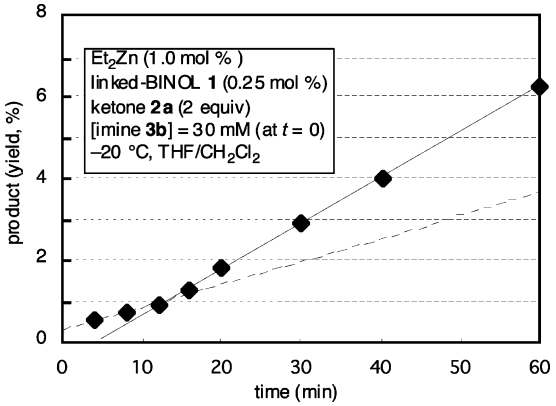


Figure 7. Reaction profile (yield < 8%) of the *anti*-selective Mannich-type reaction of Dpp-imine **3b**.

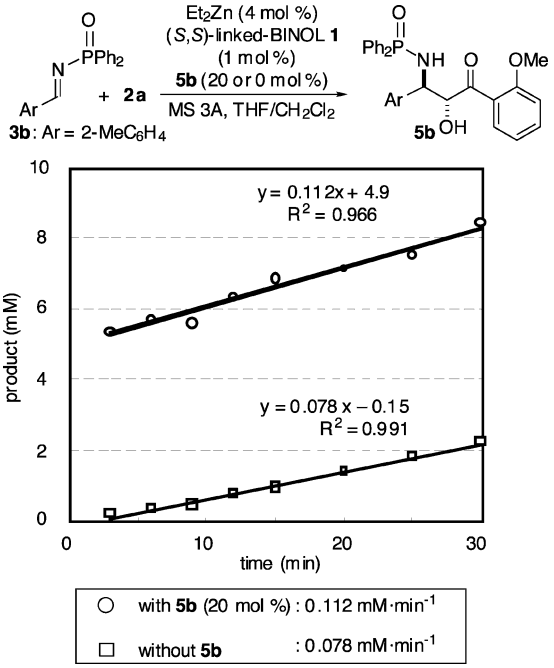
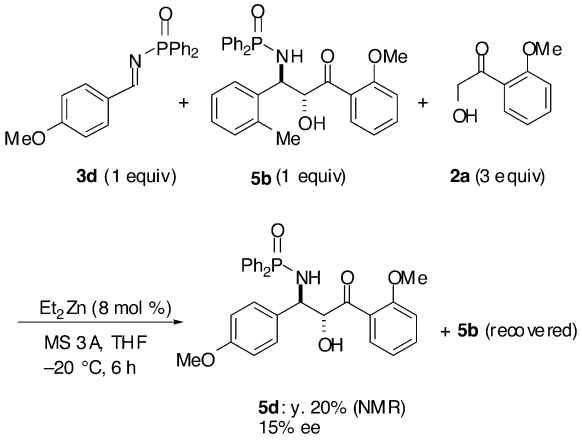


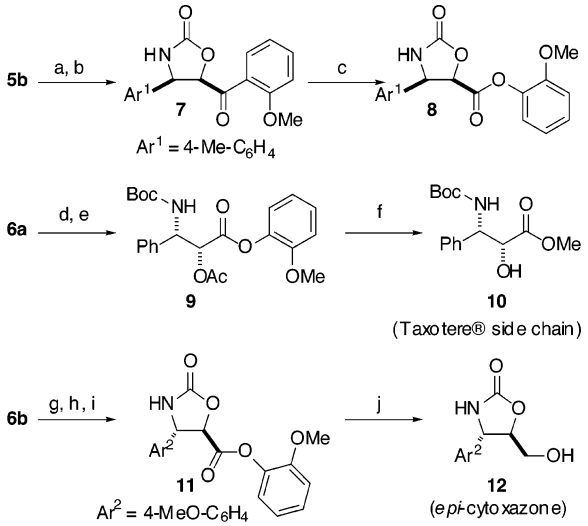
Figure 8. Effects of *anti*-β-amino alcohol **5b** on the initial reaction rate of the *anti*-selective Mannich-type reaction.

Scheme 8 *anti*-Selective Mannich-type Reaction of Imine **3d** Using *anti*-β-Amino Alcohol **5b** and Et_2Zn, in the Absence of (*S*,*S*)-Linked-BINOL **1**



in the presence of (*S*,*S*)-linked-BINOL **1** (Scheme 8 vs Table 3). Product **5d** was obtained in approximately 20% yield after 6 h at −20 °C, and the ee value of the product was only 15% ee [(2*R*,3*R*)-major]. Because the Mannich-type reaction in Tables 2 and 3 gave products in 99% ee, the possibility of asymmetric autocatalysis[29] without the participation of (*S*,*S*)-linked-BINOL **1** was ruled out. The difference in ee value (99% ee vs 15% ee) suggested that the affinity of (*S*,*S*)-linked-BINOL **1** to Zn metal is strong enough even in the presence of a large excess amount of (2*R*,3*R*)-*anti*-β-amino alcohol **5**. On the basis of these results, we speculated that *anti*-β-amino alcohol **5b** would be involved in the active species consisting of Zn/(*S*,*S*)-linked-BINOL **1**/ketone **2a** and that (2*R*,3*R*)-*anti*-β-amino alcohol had positive effects on the reaction rate when using (*S*,*S*)-linked-BINOL **1**. For achieving high TON, the affinity of ketone **2a** to Zn catalyst should be strong enough to regenerate active species via exchange with (2*R*,3*R*)-*anti*-β-amino alcohol **5**. Although the exact role of the coordinated *anti*-β-amino alcohol is not clear, we suppose that the steric bulkiness of the (2*R*,3*R*)-*anti*-β-amino alcohol coordinated to Zn catalyst might have positive effects on the exchange process between another bulky (2*R*,3*R*)-*anti*-β-amino alcohol and less sterically demanding ketone **2a**. Thus, product inhibition with *anti*-β-amino-alcohol was negligible in the *anti*-selective Mannich-type reaction of imine **3**, and high catalyst efficiency (TON up to 4920) was achieved.

Scheme 9. Transformations of Mannich Adducts to α-Hydroxy-β-amino Carboxylic Acid Derivative **8**, a Side Chain of Taxotere **10**, and *epi*-Cytoxazone **12**[a]



[a] Conditions: (a) concentrated HCl(aq)/THF, room temperature, 1 h; (b) triphosgene, pyridine, CH_2Cl_2, −78 °C, 0.5 h, yield 84% (two steps); (c) *m*CPBA, NaH_2PO_4, $Cl(CH_2)_2Cl$, 60 °C, 3 h, yield 88%; (d) Ac_2O, cat. DMAP, Py, 25 °C, 12 h, yield 94%; (e) *m*CPBA, Na_2HPO_4, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), $Cl(CH_2)_2Cl$, 60 °C, 10 h, yield 97%; (f) K_2CO_3, CH_3OH, 25 °C, yield quant; (g) TFA, anisole, 25 °C, 2 h; (h) triphosgene, Py, CH_2Cl_2, −78 °C, 2 h, yield 92% (two steps); (i) *m*CPBA, NaH_2PO_4, $Cl(CH_2)_2Cl$, 60 °C, 3 h, yield 63%; (j) $NaBH_4$, AcOH, THF, 25 °C, 2 h, yield 88%.

(C) Transformation of Mannich Adducts. Facile deprotection of the *N*-Dpp and *N*-Boc groups and transformation of the ketone to an ester should make the present Mannich-type reactions synthetically more useful. As shown in Scheme 9, *anti*-Mannich adduct **5b** was readily converted to cyclic carbamate **7** in 84% yield (two steps) after removal of the *N*-Dpp group under acidic conditions, followed by treatment with triphosgene.

(29) Review: Soai, K.; Shibata, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 9, p 699.

Baeyer−Villiger oxidation of **7** proceeded with *m*CPBA to afford ester **8** in 88% yield without any epimerization, as confirmed by NOE. *syn*-Mannich adducts are also synthetically useful, because the Boc group is one of the most frequently utilized protective groups for amines. *syn*-Mannich adduct **6a** was readily converted into a side chain of Taxotere **10**. For the Baeyer−Villiger oxidation of acetylated adduct of **6a**, the addition of 4,4′-thiobis(6-*tert*-butyl-*m*-cresol) was effective,[30] affording **9** in 97% yield. **10** was obtained in quantitative yield by treatment with K_2CO_3 in CH_3OH.[31] Baeyer−Villiger oxidation of cyclic carbamate derived from *syn*-Mannich adduct **6b** afforded **11** in 63% yield, and successive treatment with $NaBH_4$/AcOH gave *epi*-cytoxazone **12** in 88% yield.[32]

In summary, we achieved highly efficient direct catalytic enantio- and diastereoselective Mannich-type reactions of a hydroxyketone using a Et_2Zn/linked-BINOL complex. Dpp-imine **3** gave *anti*-β-amino alcohols in anti/syn = up to >98/2, up to >99% yield, and up to >99.5% ee, while Boc-imine **4** gave *syn*-β-amino alcohols in anti/syn = up to 5/95, up to >99% yield, and up to >99.5% ee. It is noteworthy that the high catalyst TON was achieved in both *anti*- and *syn*-selective Mannich-type reactions (TON = up to 4920 for anti and up to 1760 for syn). Mechanistic studies provided clues to the origin of the high TON. Application of asymmetric zinc catalysis to other reactions such as carbon−carbon bond forming reactions using unmodified carboxylic acid derivatives is in progress.

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Supporting Information Available: Experimental procedures, characterization of the products, detailed data for the reaction kinetic studies, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, *64*.

(31) $[\alpha]^{24}_D$ −6.1 (*c* 1.4, $CHCl_3$); spectral data matched well with the reported data. lit. $[\alpha]^{24}_D$ −7 (*c* 1.2, $CHCl_3$): (a) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. $[\alpha]^{20}_D$ −6.81 (*c* 1.0, $CHCl_3$): (b) Hamamoto, H.; Mamedov, V. A.; Kitamoto, M.; Hayashi, N.; Tsuboi, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4485.

(32) $[\alpha]^{25}_D$ −27.2 (*c* 1.1, MeOH); spectral data matched well with the reported data. lit. $[\alpha]^{28}_D$ −30.4 (*c* 1.0, MeOH): Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203.