J|A|C|S
COMMUNICATIONS

Published on Web 03/27/2003

# *anti*-Selective Direct Catalytic Asymmetric Mannich-type Reaction of Hydroxyketone Providing *β*-Amino Alcohols

Shigeki Matsunaga, Naoya Kumagai, Shinji Harada, and Masakatsu Shibasaki*

*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received February 21, 2003; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Chiral *β*-amino alcohol units are useful as chiral building blocks for various biologically active compounds. Among the methods available for their catalytic enantioselective syntheses,[1] catalytic asymmetric Mannich-type reactions[2] of α-alkoxy enolate are of particular interest, because two adjacent stereocenters are constructed simultaneously with a concomitant carbon−carbon bond formation. 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 *syn*- or *anti*-*β*-amino alcohol, respectively.[3] Recently, more atom-economical processes,[4] that is, the direct addition of *unmodified* α-hydroxyketone to imines, were reported by List,[5] Barbas,[6] and Trost.[7,8] Excellent selectivity was achieved; however, only *syn*-amino alcohols were produced in those systems.[5−7] In addition, the requirement of harsh oxidizing conditions for the cleavage of the *N*-protective groups would impose some limitations on their synthetic utility. Thus, the development of the complementary *anti*-selective direct catalytic asymmetric Mannich-type reaction of *unmodified* α-hydroxyketone using an easily removable *N*-protective group is in high demand. We report a novel *anti*-selective direct catalytic asymmetric Mannich-type reaction of 2-hydroxy-2′-methoxyacetophenone (**2**) and *N*-diphenylphosphinoyl(Dpp) imines **3** using a $Et_2Zn$/linked-BINOL **1** complex (Figure 1).[9,10]

As a part of our continuing project on asymmetric zinc catalysis, we reported direct catalytic asymmetric *syn*-selective aldol[10a,d,e] and Michael reactions[10b,c] of hydroxyketone **2** using the $Et_2Zn$/linked-BINOL **1** = 4/1 complex and 3 Å molecular sieves (MS 3A). Thus, we initiated screening using the $Et_2Zn$/**1** complex, **2**, and imines with various *N*-protective groups and determined that *N*-Dpp imine **3a** was promising. As shown in Table 1, the addition of **2** to **3a** proceeded smoothly in the presence of **1** (5 mol %), $Et_2Zn$ (20 mol %), and MS 3A to afford **4a** with high selectivity[11] (anti/syn = 94/6, 98% ee) in 97% yield (entry 1). The preferential formation of the *anti*-isomer is particularly noteworthy, because the diastereoselectivity is complementary to that observed by others.[5−7] The reaction reached completion even with reduced catalyst loading to afford **4a** 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 **2**, although there was a slight loss of reactivity at −20 °C (entry 4). At 0 °C, the reaction was completed using 1.1 equiv of **2** to afford **4a** in 97% yield; the stereoselectivity, however, decreased somewhat (entry 5). The presence of activated MS 3A enhanced the reaction rate without affecting stereoselectivity (entry 3 vs entry 6).

As summarized in Table 2, the present asymmetric zinc catalysis was applicable to various imines **3**. All reactions were performed with 1 mol % of **1**, 4 mol % of $Et_2Zn$, and MS 3A. 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 → 98/2, entries 1−10). Ortho-substituents

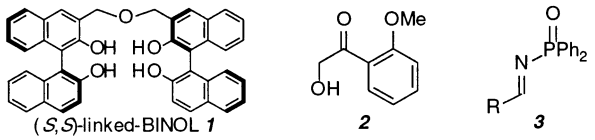
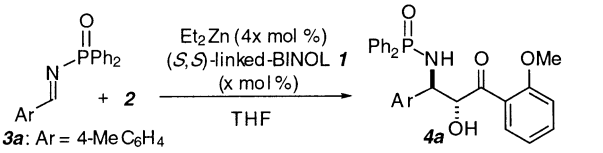



***Figure 1.*** Structures of (*S*,*S*)-linked-BINOL **1**, 2-hydroxy-2′-methoxyacetophenone (**2**), and *N*-diphenylphosphinoyl(Dpp) imine **3**.

***Table 1.*** Direct Catalytic Asymmetric Mannich-type Reaction of **3a** with a $Et_2Zn$/(*S*,*S*)-linked-BINOL **1** = 4/1 Complex




| entry | ligand **1** (× mol%) | ketone **2** (equiv) | additive | temp (°C) | time (h) | yield[a] (%) | dr[b] (anti/syn) | ee (%) (anti) |
|---|---|---|---|---|---|---|---|---|
| 1 | 5 | 2 | MS 3A | −20 | 2 | 97 | 94/6 | 98 |
| 2 | 3 | 2 | MS 3A | −20 | 3 | 95 | 94/6 | 98 |
| 3 | 1 | 2 | MS 3A | −20 | 9 | 98 | 96/4 | 98 |
| 4 | 1 | 1.1 | MS 3A | −20 | 24 | 87 | 96/4 | 98 |
| 5 | 1 | 1.1 | MS 3A | 0 | 8 | 97 | 88/12 | 95 |
| 6 | 1 | 2 | none | −20 | 18 | 93 | 96/4 | 98 |

[a] Isolated yield. [b] Determined by the $^1H$ NMR of the crude mixture.

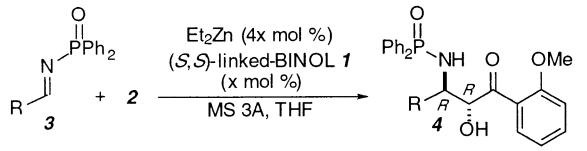
on the aromatic rings resulted in almost exclusive formation of the *anti*-adducts (dr: >98/2, entry 2 and 98/2, entry 8). Although imine **3k** from α,*β*-unsaturated aldehyde had less *anti*-selectivity, diastereoselectivity was improved at a lower reaction temperature (entry 12, dr: 81/19 at −30 °C). Imine **3l** also provided Mannich adduct in high ee (99%) with modest *anti*-selectivity (entry 13). To demonstrate the practical utility, the reaction was performed on a gram scale with as little as 0.25 mol % of **1** (6.2 mg) to afford **4b** in excellent yield (99%, 1.92 g), dr (>98/2), and ee (99%) after 6 h (entry 14). Commercial availability of both $Et_2Zn$ solution and linked-BINOL **1** also makes the present system advantageous from a practical viewpoint.[9]

The opposite diastereoselectivity between the present Mannich-type reaction (*anti*-selective) and the previously reported aldol reaction (*syn*-selective)[10a] using the same $Et_2Zn$/**1** complex is interesting. Because the absolute configurations at the α-position of both the aldol- and the Mannich-products are identical (2*R*),[12] the facial selection of the Zn-enolate generated from **2** should be same (*Si*-face shielding), and the electrophiles should approach in a different manner in these two reactions. We speculate that the *anti*-selectivity in the present Mannich-type reaction would be due to the bulky Dpp group on the imine nitrogen. To avoid steric repulsion, the Mannich-type reaction would proceed via the transition state as shown in Figure 2, preferentially affording *anti*-**4**.[12]

Facile deprotection of the *N*-Dpp group and transformation of the ketone to an ester produce a protected α-hydroxy-*β*-amino acid


10.1021/ja034787f CCC: $25.00 

***Table 2.*** Direct Mannich-type Reaction with Various *N*-Dpp Imines **3**[a]




| entry | R | | ligand **1** (× mol %) | product | temp (°C) | time (h) | yield[b] (%) | dr[c] (anti/syn) | ee (%) (anti) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 4-$MeC_6H_4$ | **3a** | 1 | **4a** | −20 | 9 | 98 | 96/4 | 98 |
| 2 | 2-$MeC_6H_4$ | **3b** | 1 | **4b** | −20 | 6 | 99 | >98/2 | 99 |
| 3 | $C_6H_5$ | **3c** | 1 | **4c** | −20 | 6 | 98 | 96/4 | 99 |
| 4 | 4-$MeOC_6H_4$ | **3d** | 1 | **4d** | −20 | 6 | 97 | 95/5 | 99 |
| 5 | 4-$NO_2C_6H_4$ | **3e** | 1 | **4e** | −20 | 9 | 96 | 97/3 | 98 |
| 6 | 4-$ClC_6H_4$ | **3f** | 1 | **4f** | −20 | 4 | 97 | 97/3 | 98 |
| 7 | 4-$BrC_6H_4$ | **3g** | 1 | **4g** | −20 | 4 | 97 | 95/5 | 98 |
| 8 | 1-naphthyl | **3h** | 1 | **4h** | −20 | 6 | 97 | 98/2 | >99.5 |
| 9 | 2-naphthyl | **3i** | 1 | **4i** | −20 | 7 | 95 | 94/6 | 99 |
| 10 | 2-furyl | **3j** | 1 | **4j** | −20 | 7 | 98 | 96/4 | >99.5 |
| 11 | (*E*)-cinnam | **3k** | 1 | **4k** | −20 | 4 | 98 | 76/24 | >99.5 |
| 12 | | **3k** | 1 | **4k** | −30 | 7 | 97 | 81/19 | >99.5 |
| 13 | *cyclo*-propyl | **3l** | 1 | **4l** | −30 | 5 | 98 | 80/20 | 99 |
| 14[d] | 2-$MeC_6H_4$ | **3b** | 0.25 | **4b** | −20 | 6 | 99 | >98/2 | 99 |

[a] 2 equiv of **2** was used. For less soluble imines, THF/$CH_2Cl_2$ mixed solvent was used. See Supporting Information. [b] Isolated yield. [c] Determined by the $^1H$ NMR of the crude mixture. [d] 1.28 g of **3b** was used.

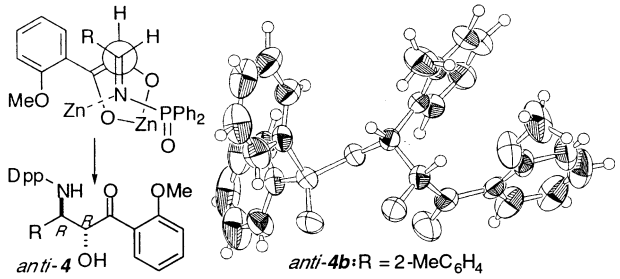
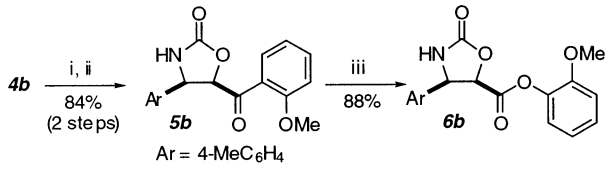



***Figure 2.*** Working transition state model to afford *anti*-**4** and X-ray structure of *anti*-**4b**.

***Scheme 1.*** Transformation of Mannich Adduct[a]




[a] (i) Concentrated HCl(aq)/THF, room temperature, 1 h; (ii) triphosgene, pyridine, $CH_2Cl_2$, −78 °C, 0.5 h, yield 84% (two steps); (iii) *m*CPBA, $Cl(CH_2)_2Cl$, 60 °C, 3 h, yield 88%.

in high yield. As shown in Scheme 1, **4b** was readily converted to cyclic carbamate **5b** in 84% yield (two steps) after removal of the *N*-Dpp group under acidic conditions,[13] followed by treatment with triphosgene. Baeyer−Villiger oxidation of **5b** proceeded with *m*CPBA to afford ester **6b** in 88% yield without any epimerization, as confirmed by NOE.

In summary, we developed a highly enantio- and diastereoselective direct catalytic asymmetric Mannich-type reaction to provide *anti*-amino alcohols (yield up to 99%, dr up to >98/2, ee up to >99.5%). The process worked well with from as little as 0.25 to 1 mol % of catalyst loading. The observed complementary *anti*-selectivity, in combination with the facile removal of the Dpp group, makes the present reaction synthetically useful. Detailed mechanistic studies of the present reaction, especially to clarify the origin of the *anti*-selectivity, are ongoing.

**Acknowledgment.** We are thankful for financial support by RFTF and Grant-in-Aid for Encouragements for Young Scientists (B) (for S.M.) from JSPS. N.K. thanks JSPS Research Fellowships for Young Scientists. We thank Prof. S. Kobayashi at the University of Tokyo for support in the X-ray analysis of **4b**.

**Supporting Information Available:** Experimental procedures, characterization of the products, determination of absolute and relative configurations of the products, and X-ray data of **4b** (CIF and PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) For reviews on asymmetric synthesis of vicinalamino alcohols, see: (a) Bergmeire, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243.
(2) For reviews on catalytic asymmetric Mannich-type Reaction, see: (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 954. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
(3) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.
(4) Trost, B. M. *Science* **1991**, *254*, 1471.
(5) (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.
(6) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842.
(7) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338.
(8) For other examples of direct catalytic asymmetric Mannich reaction using unmodified ketone and/or aldehyde as donors, see: (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307. (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.
(9) 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. Linked-BINOL is also commercially available from Wako Pure Chemical Industries, Ltd. Catalog No. for (*S*,*S*)-**1**: No. 152-02431.
(10) (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) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (d) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (e) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.
(11) Determined by NOE enhancement of cyclic carbamate synthesized from **4a**.
(12) The absolute configuration of **4b** was determined by Mosher's method. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. The relative configuration of **4b** was determined by X-ray analysis (see Figure 2).
(13) Ramage, R.; Hopton, D.; Parrott, M. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.

JA034787F