ORGANIC LETTERS

2006
Vol. 8, No. 17
3817−3819

# Enantioselective Alkylation of Aldehydes Catalyzed by a Highly Active Titanium Complex of 3-Substituted Unsymmetric BINOL

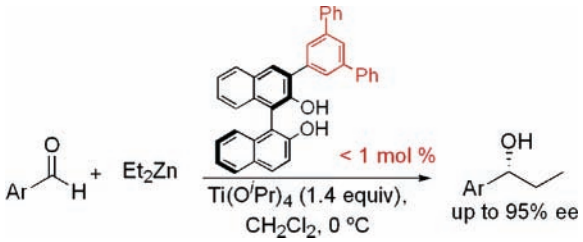
**Toshiro Harada* and Kousou Kanda**

*Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan*

*harada@chem.kit.ac.jp*

**Received June 9, 2006**

## ABSTRACT




**A titanium complex derived from 3-(3,5-diphenylphenyl)-BINOL exhibits an enhanced catalytic activity in the asymmetric alkylation of aldehydes, allowing the reduction of the catalyst amount to less than 1 mol % without deterioration in enantioselectivity.**

Titanium(IV) complexes of 1,1′-bi-2-naphthol (BINOL, **1**) and its derivatives are one of the most versatile chiral Lewis acid catalysts employed in a number of useful asymmetric processes.[1] Much effort has been directed toward the modification of the parent BINOL to optimize catalysts to specific enantioselective reactions. In 1997, Nakai and Chan et al. reported that the reaction of aldehydes with diorganozincs enantioselectively gave the alkylation products in the presence of a catalytic amount of BINOL and a stoichiometric amount of titanium tetraisopropoxide.[2] Since these initial reports, a variety of BINOL derivatives have been examined as chiral ligands for the reaction.[3,4] Although considerable improvements in enantioselectivity have been achieved by the modification of the parent BINOL framework, 10−20 mol % of catalysts need to be used. Because these modified BINOLs are less accessible, a reduction in the amount of catalysts remains an important issue for the practicality of this useful asymmetric transformation.

Herein, we wish to report that the titanium catalysts derived from 3-substituted unsymmetric BINOLs **2**[5] exhibit an enhanced activity allowing the reduction of the catalyst amount. Enantioselectivities comparable to or higher than

(1) (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Mikami, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1995; Vol. 1, p 397. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (d) Mikami, K.; Nakai, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; John Wiley and Sons: New York, 2000; p 543.

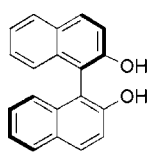
(2) (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233. (b) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585.

(3) (a) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (b) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528. (c) Shen, X.; Guo, H.; Ding, K. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321. (d) Lipshutz, B. H.; Shin, Y.-J. *Tetrahedron Lett.* **2000**, *41*, 9515. (e) Chen, Y.; Yekta, S.; Martyn, J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433. (f) Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (g) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57. (h) Jayaprakash, D.; Sasai, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2589. (i) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948. (j) Jiang, H.; Hu, A.; Lin, W. *J. Chem. Soc., Chem. Commun.* **2003**, 96. (k) Hua, J.; Lin, W. *Org. Lett.* **2004**, *6*, 861.

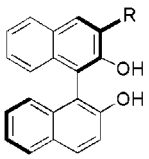
(4) For the enantioselective addition of dialkylzincs to aldehydes in general, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

10.1021/ol061407x CCC: $33.50 
**Published on Web 07/18/2006**

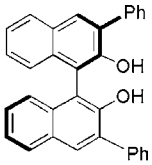
20 mol % of the parent BINOL can be achieved by using less than 1 mol % of the (3,5-diphenyl)phenyl derivative **2f**.




**1**




**2a**-**g** (see Table 1)




**3**

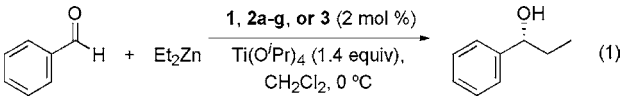
Asymmetric ethylation of benzaldehyde was examined at low catalyst loading (eq 1, Table 1). The reactions were carried out in the presence of (*R*)-BINOL derivatives **1**, **2a**−**g**, and **3** (2 mol %) with diethylzinc (3 equiv) and titanium tetraisopropoxide (1.4 equiv) in $CH_2Cl_2$ at 0 °C. Under these conditions, the reaction with the parent BINOL did not attain the full conversion after 5 h, affording (*R*)-1-phenylpropanol in lower enantioselectivity (85% ee) than reported for the reaction at 20 mol % catalyst loading (92% ee)[2b] (entry 1). The reaction with 3-substituted unsymmetric BINOLs **2a**−**d**, on the other hand, was completed within 5 h (entries 2−5). The conversion of benzaldehyde after 1 h revealed the following order in the reaction rate for the R group on the BINOL moiety: Ph > Me ≈ Br > PhC≡C > H, suggesting that BINOL derivatives with sterically more demanding substituents would afford a higher turnover frequency. Although the highly hindered 2,6-dimethylphenyl derivative **2g** did not show an anticipated reactivity (entry 8), the 3,5-dimethylphenyl derivative **2e** and 3,5-diphenylphenyl derivative **2f** were found to be highly efficient (entries 6 and 7). The reactions were accomplished within 3 and 1 h with **2e** and **2f**, respectively. In addition to the enhanced reaction rate, these unsymmetric BINOLs, **2f** in particular, exhibited an improved enantioselectivity. It should be noted that the enhanced activity was observed only for the monosubstituted unsymmetric derivatives. The reaction using 3,3′-diphenyl-BINOL **3** was sluggish and nonselective (entry 9).

A satisfactory reaction rate and high enantioselectivity were obtained even by using less than 2 mol % of the 3,5-diphenylphenyl derivative **2f** (Table 2). Reductions in the catalyst loading to 0.5 mol % were possible without lowering the enantioselectivity (entries 2 and 3). Decreased enantioselectivity upon further reduction (0.1 mol %, entry 4) is most probably attributed to a competing titanium tetraisopropoxide-promoted background reaction judging from its rate estimated from a control experiment (entry 5). By virtue of the rate enhancement, reactions could be carried out at −20 °C by using 1−2 mol % of **2f**, affording products with slightly higher ee's (entries 6 and 7). The higher activity of the catalyst derived from **2f** was again shown in comparing the conversion after 1 h with those of a parent BINOL and phenyl derivative **2d** (entry 6 vs entries 8 and 9).

The addition of diethylzinc to other aldehydes was examined by using **2f** under condition A (1 mol % at 0 °C) and B (2 mol % at −20 °C) (Table 3). For aromatic aldehydes, the reactions were accomplished within 2 h even with the low catalyst loadings to give the corresponding ethylation products in high enantioselectivity (90−96% ee) (entries 1−10). Under condition A, **2f** exhibited enantioselectivities comparable to or higher than those reported for BINOL (20 mol % at 0 °C).[2b] A further albeit small improvement in enantioselectivity was observed by carrying out the reaction at −20 °C (condition B). Although an aliphatic aldehyde was less reactive and less enantioselective (entry 11), a high enantioselectivity as well as turnover efficiency was observed for an α,β-unsaturated aldehyde (entries 12 and 13).

In a recent study on the mechanism of asymmetric alkylation catalyzed by BINOL-derived titanium complexes,

**Table 1.** Asymmetric Ethylation of Benzaldehyde with BINOLs **1**, **2a**−**g**, and **3**[a]




(1)

| entry | ligand | R | conversion (%) after 1 h | conversion (%) after 5 h | ee (%) |
|---|---|---|---|---|---|
| 1 | **1** | H | 39 | 94 | 85 |
| 2 | **2a** | PhC≡C | 44 | >98 | 84 |
| 3 | **2b** | Br | 55 | >98 | 81 |
| 4 | **2c** | Me | 55 | >98 | 79 |
| 5 | **2d** | Ph | 65 | >98 | 87 |
| 6 | **2e** | 3,5-$Me_2C_6H_3$ | 91 | >98[b] | 90 |
| 7 | **2f** | 3,5-$Ph_2C_6H_3$ | >98 | | 93 |
| 8 | **2g** | 2,6-$Me_2C_6H_3$ | 32 | 83 | 83 |
| 9 | **3** | | < 5 | 94[c] | 9 |

[a] Unless otherwise noted, reactions were carried out in the presence of the (*R*)-BINOL derivatives (2 mol %) with $Et_2Zn$ (3 equiv) and $Ti(O^iPr)_4$ (1.4 equiv) in $CH_2Cl_2$ at 0 °C for 5 h. [b] After 3 h. [c] After 48 h.

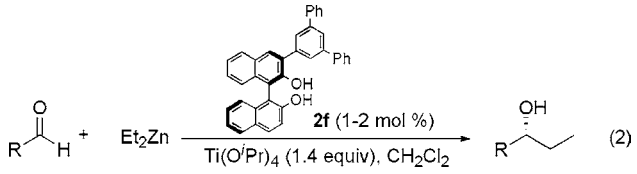
**Table 2.** Asymmetric Ethylation of Benzaldehyde with Unsymmetric BINOL **2f**[a]

| entry | mol % | temp (°C) | conversion (%) after 1 h | conversion (%) after 5 h | ee (%) |
|---|---|---|---|---|---|
| 1 | 2 | 0 | >95 | | 93 |
| 2 | 1 | 0 | 96 | >98[b] | 94 |
| 3 | 0.5 | 0 | 81 | >98 | 93 |
| 4 | 0.1 | 0 | 32 | 92 | 82 |
| 5 | 0 | 0 | <5 | 15 | 0 |
| 6 | 2 | −20 | 95 | >98[b] | 95 |
| 7 | 1 | −20 | 64 | >98 | 94 |
| 8[c] | 2 | −20 | 33 | 87 | 89 |
| 9[d] | 2 | −20 | 56 | >98 | 92 |

[a] Unless otherwise noted, reactions were carried out with **2f**, $Et_2Zn$ (3 equiv), and $Ti(O^iPr)_4$ (1.4 equiv) in $CH_2Cl_2$. [b] After 2 h. [c] BINOL **1** was used. [d] Ph-BINOL **2d** was used.

(5) For unsymmetrically substituted binaphthyl ligands in enantioselective catalysis, see: Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213.

**Table 3.** Asymmetric Ethylation of Aldehydes Catalyzed by a Titanium Complex Derived from Unsymmetric BINOL **2f**[a]




| entry | aldehydes | conditions[a] | yield (%)[b] | ee (%)[c,d] |
|---|---|---|---|---|
| 1 | *p*-$MeC_6H_4CHO$ | A | 94 | 92 (88) |
| 2 | | B | 89 | 94 |
| 3 | *m*-$MeOC_6H_4CHO$ | A | 91 | 94 (94) |
| 4 | | B | 94 | 95 |
| 5 | *o*-$ClC_6H_4CHO$ | A | 74 | 77 (69) |
| 6 | | B | 72 | 80 |
| 7 | 1-naphthylCHO | A | 95 | 95 (94) |
| 8 | | B | 82 | 96 |
| 9 | 2-naphthylCHO | A | 93 | 90 (81) |
| 10 | | B | 84 | 91 |
| 11[e] | $PhCH_2CH_2CHO$ | B | 53 | 85 |
| 12 | PhCH=CHCHO | A | 96 | 92 |
| 13 | | B | 92 | 93 |

[a] Unless otherwise noted, reactions were carried out for 1−2 h. Condition A: **2f** (1 mol %) at 0 °C. Condition B: **2f** (2 mol %) at −20 °C. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC; Chiralcel OB (entries 5 and 6) or Chiralcel OD (other entries). [d] Values in parentheses refer to the ee reported for the reaction using BINOL (20 mol %) under otherwise identical conditions.[2b] [e] The reaction was carried out for 5 h.

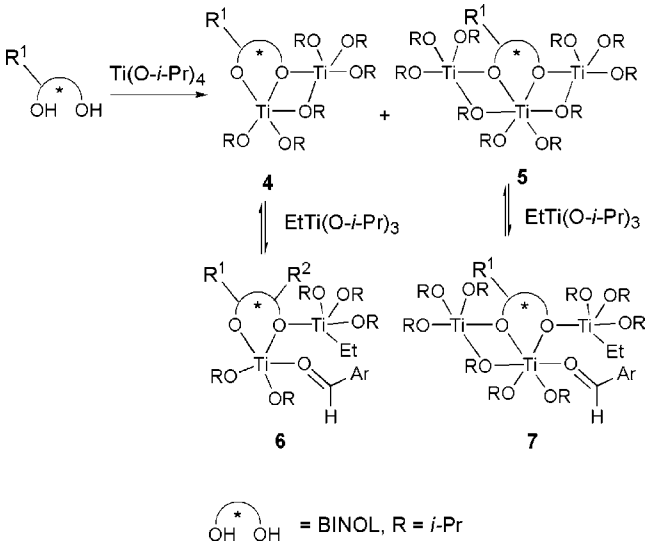
it was shown that the ethyltitanium species formed in equilibrium from diethylzinc and titanium tetraisopropoxide is an active alkylating agent.[6] A large excess of titanium tetraisopropoxide is required with respect to the ligand to obtain the sufficient concentration of the alkyltitanium species. At the low catalyst loading, BINOL and a large excess of titanium tetraisopropoxide most probably form a mixture of 1:1-aggregate **4** and 1:2-aggregate **5** (Scheme 1; $R^1$ = H).[7,8] If we assume that the asymmetric alkylation proceeds through complex **6**[6a] with a five-coordinate titanium center but not through six-coordinate titanium complex **7**, the presence of **5** diminishes the concentration of **4**, the

(6) (a) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336. (b) Waltz, K. M.; Carroll, P.; Walsh, P. J. *Organometallics* **2004**, *23*, 127.

(7) Aggregates **4** and **5** were characterized by X-ray crystallography.[6a]

(8) The solution mixture of BINOL and tetraisopropoxide was studied by NMR spectroscopy: Pescitelli, G.; Bari, L. D.; Salvadori, P. *Organometallics* **2004**, *23*, 4223. Although they did not observe the formation of aggregate **5** up to 10 metal equiv (corresponding to the reaction with 14 mol % of BINOL), it is plausible to assume such an aggregate in the reaction with lower catalyst loading (e.g., 70 metal equiv for 2 mol % reaction).

**Scheme 1**




precursor of the reactive intermediate **6**, to reduce the overall catalyst efficiency. The introduction of a substituent ($R^1$) at the 3-position of the naphtholate moiety may cause a destabilizing interaction in 1:2-aggregate **5**, thereby maintaining the sufficient concentration of **4** even at the lower catalyst loadings. The very low activity observed for 3,3′-diphenyl derivative **3** (Table 1, entry 9) is consistent with this rationale because aggregate **4**, as well as aggregate **6**, should be destabilized by the additional substituent ($R^2$) at the 3′-position. Judging from the rate of the background reaction, the enantioselectivity of BINOL derivatives **2** seems to be determined primarily by the extent of the background reaction and might not be influenced much by the structure of the substituents. The observation is also in accord with the catalytic reaction through **6** where substituent $R^1$ locates distal to the reaction site.

In summary, we have demonstrated that the titanium complexes derived from 3-substituted unsymmetric BINOLs **2** exhibit enhanced catalytic activity in the asymmetric alkylation of aldehydes. Less than 1 mol % of the 3,5-diphenylphenyl derivative **2f** is enough to obtain a comparable or higher enantioselectivity than reactions using 20 mol % of the parent BINOL.

**Supporting Information Available:** The preparation of ligands and a representative reaction procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061407X