Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2499–2502

Practical and highly enantioselective alkylation of aldehydes catalyzed by a titanium complex of 3-aryl H_8-BINOL

Toshiro Harada* and Takahiro Ukon

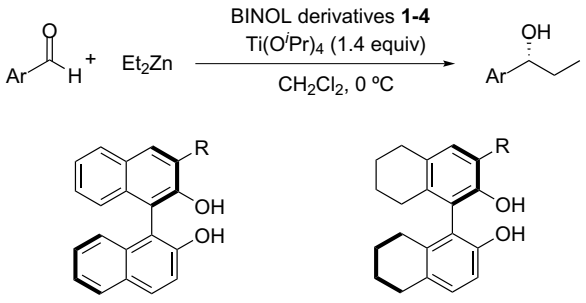
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

Received 1 September 2007; accepted 4 October 2007
Available online 5 November 2007

Abstract—A titanium complex derived from 3-(3,5-diphenylphenyl)-H_8-BINOL exhibits high catalytic activity and enantioselectivity in the alkylation of aldehydes. Enantioselectivities comparable to or higher than 20 mol % of the parent H_8-BINOL are obtained with 2 mol %-catalyst loadings. The reaction can be carried out without rigorous exclusion of water.

1. Introduction

The asymmetric addition of organometallic reagents to carbonyl compounds is a reaction of fundamental importance in modern synthetic organic chemistry.[1] There has been a continuing interest in developing 1,1′-bi-2-naphthol **1** (BINOL) based titanium(IV) catalysts for the asymmetric addition of diorganozincs to aldehydes (Scheme 1). Following the seminal discovery of Nakai[2] and Chan,[3] a variety of derivatives have been examined as chiral ligands to improve the enantioselectivity of the parent BINOL.[4] Of these derivatives, H_8-BINOL **3** is one of the best ligands for realizing excellent enantioselectivity in the reaction of aromatic aldehydes at 20 mol % catalyst loading.[5]



Scheme 1. Asymmetric alkylation of aldehydes catalyzed by titanium(IV) complexes of BINOL derivatives.

We recently reported that the titanium catalysts derived from 3-substituted unsymmetric BINOLs exhibit an enhanced activity, allowing the reduction of the catalyst amount.[6,7] By using less than 1 mol % of 3-(3,5-diphenyl)-phenyl-BINOL **2**, enantioselectivities comparable to or higher than 20 mol % of the parent BINOL were obtained. The remarkable effect of the 3,5-diphenylphenyl group prompted us to examine the corresponding H_8-BINOL derivatives **4** as a chiral ligand.

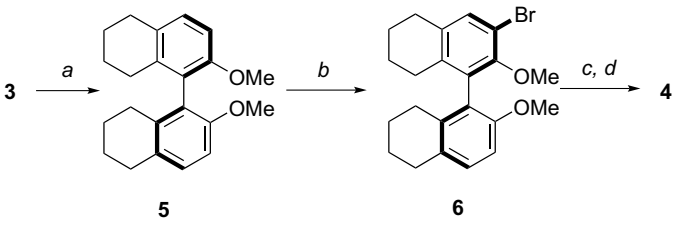
Herein we report a highly enantioselective alkylation of aldehydes catalyzed by titanium(IV) complex derived from 3-substituted H_8-BINOL **4**. The practicality of the reaction was demonstrated by excellent enantioselectivities (94–98% ee) at a low catalyst loading (2 mol %) and by the possible use of a commercial reagent and solvent as received without rigorous exclusion of water.

2. Results and discussion

Ligand (*R*)-**4** was prepared from H_8-BINOL (*R*)-**3** in four steps (Scheme 2). After protection of the phenolic oxygens with a methyl group,[8] treatment of the resulting dimethyl derivative **5** with bromine (1.0 equiv) at 0 °C gave monobromide **6**. A $Pd(PPh_3)_4$-catalyzed coupling of bromide **6** with 3,5-diphenylphenylboronic acid[9] followed by deprotection of the dimethyl derivative **6** with BBr_3 furnished (*R*)-**4**.

* Corresponding author. E-mail: harada@chem.kit.ac.jp

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.10.012



Scheme 2. Preparation of H_8-BINOL derivative (*R*)-**4**. Reagents and conditions: (a) MeI, K_2CO_3, acetone;[8] (b) Br_2 (1 equiv), CH_2Cl_2 (66%); (c) 3,4-$Ph_2C_6H_3B(OH)_2$, $Pd(PPh_3)_4$ (5 mol %), $Ba(OH)_2{\cdot}8H_2O$, aqueous dioxane (93%); (d) BBr_3,CH_2Cl_2 (100%).

The reaction of benzaldehyde with diethylzinc (3 equiv) was carried out in CH_2Cl_2 at 0 °C in the presence of (*R*)-**4** (2 mol %) and titanium tetraisopropoxide (1.4 equiv) (Table 1, entry 2). As we anticipated, the reaction proceeded rapidly under these conditions, and was complete within 3.5 h to give (*R*)-1-phenylpropanol in 98% ee. Under similar conditions, a control reaction using the parent H_8-BINOL **3** did not attain full conversion of the aldehyde after 5 h, affording the product in lower enantioselectivity (75% ee) than reported[5a] for the reaction at 20 mol % catalyst loading (98% ee) (entry 1). A slightly decreased, but still high, enantioselectivity (96% ee) was obtained in the reaction with 1 mol % of **4** (entry 3). Judging from conversions after 1 h, the turnover efficiency of the catalyst derived from **4** is significantly improved by the introduction of the 3,5-diphenylphenyl group, while being slightly inferior to a catalyst derived from 3-(3,5-diphenylphenyl)-BINOL **2** (entries 2,3 vs entries 4,5).

The addition of diethylzinc to other aldehydes was examined by using ligand **4** (2 mol %) (Table 2).[10] For all the aromatic aldehydes examined, the reactions were accomplished within 5 h and the corresponding ethylation products were obtained in excellent enantioselectivity (94–98% ee) (entries 1–8). In comparison with 3-(3,5-diphenylphenyl)-BINOL **2**,[6] **4** consistently showed enhanced enantioselectivity. The observed selectivities were comparable to or higher than those obtained with 20 mol % of the unsubstituted H_8-BINOL **3**.[5] Ligand **4** exhibited slightly lower, but acceptable selectivities in the reaction of an unsaturated aldehyde and an aliphatic aldehyde (entries 9 and 10).

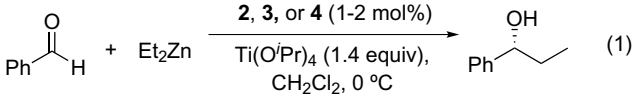
Another practical advantage of using ligand **4** is that the reaction can be carried out without rigorous exclusion of water. Reactions could be carried out with commercial titanium tetraisopropoxide and dichloromethane as received by using non-dried glassware to give products without a noticeable deterioration in enantioselectivity (entries 2 and 7).[11]

We have previously proposed[6] that the high catalytic activity of the titanium complex derived from BINOL derivative **2** can be attributed to the steric inhibition of the formation of six-coordinate titanium aggregates **8** and **10** based upon recent mechanistic studies[12] (Scheme 3; R′ = 3-(3,5-diphenyl)phenyl). It was assumed that the asymmetric alkylation proceeds through complex **9** with a five-coordinate titanium center, but not through six-coordinate titanium complex **10**. At low catalyst loading, a large excess of titanium tetraisopropoxide with respect to BINOL **1** (and H_8-BINOL **3**) might result in the formation of the 1:2-aggregate **8** (R′ = H), which can serve as a catalyst sink to reduce an overall catalyst activity. The introduction of the aryl group at the 3-position of BINOL **1** (and H_8-BINOL **3**) destabilizes **8** and **10** sterically, thereby maintaining the sufficient concentration of **7** and **9** even at the lower catalyst loading. The enhancement of catalytic activity observed for the complex derived from 3-substituted H_8-BINOL **4** provides additional support for our rationalization. The observation that the high enantioselectivity of the parent compound **3** (20 mol %) is retained in **4** (2 mol %) is inconsistent with the assumed activated complex **8**, where the R′ substituent locates far away from the reaction site.

3. Conclusion

In conclusion, we have shown the enhanced catalytic activity of the titanium complexes derived from the 3-substituted BINOL **4** in asymmetric alkylation of aldehydes. The low catalyst loading, the excellent enantioselectivities, and the ease of operation without the need for rigorous exclusion of water attest to its practicality.

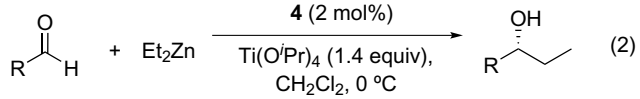
Table 1. Asymmetric ethylation of benzaldehyde with unsymmetric BINOL **4**[a]



Entry	Ligand	mol %	Conversion (%)		ee (%)
			After 1 h	After 5 h	
1	**3**	2	49	80	75
2	**4**	2	98	>98[b]	98
3	**4**	1	76	>98	96
4[6]	**2**	2	>98	—	93
5[6]	**2**	1	96	>98[c]	94

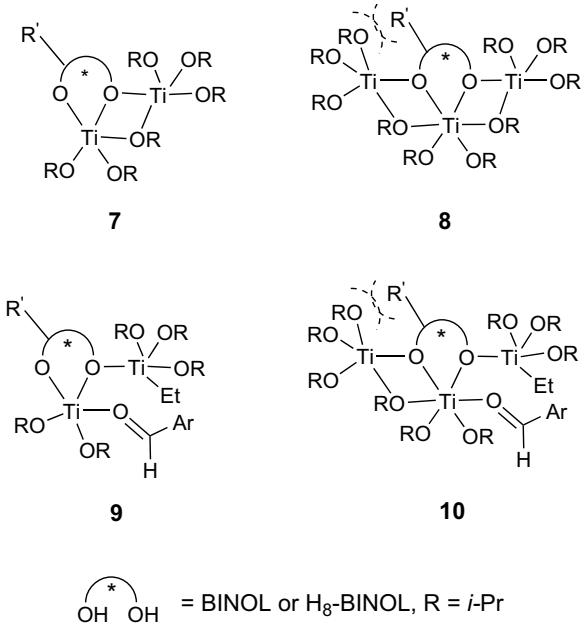
[a] Reactions were carried out with Et_2Zn (3 equiv) and Ti(O*i*-Pr)$_4$ (1.4 equiv) in CH_2Cl_2 at 0 °C.
[b] After 3.5 h.
[c] After 2 h.

Table 2. Asymmetric ethylation of aldehydes catalyzed by titanium complex derived from H_8-BINOL derivative **4**[a]



Entry	Aldehyde	Yield[b] (%)	ee[c] (%)	**3**[d]	**2**[e]
1	PhCHO	77	98	98	94
2[f]		97	97		
3	*p*-MeC_6H_4CHO	80	98	92	92
4	*m*-$MeOC_6H_4CHO$	96	98	96	95
5	*o*-ClC_6H_4CHO	88	94	92	77
6	1-NaphthylCHO	73	99	98	95
7[f]		94	97		
8	2-NaphthylCHO	95	98	—	90
9	PhCH=CHCHO	97	94	—	92
10	$PhCH_2CH_2CHO$	80	90	—	85

[a] Reactions were carried out with Et_2Zn (3 equiv) and Ti(O*i*-Pr)$_4$ (1.4 equiv) in CH_2Cl_2 at 0 °C for 3–5 h.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC; Chiralcel OB (entry 5) or Chiralcel OD (other entries).
[d] Values refer to the ee reported for the reaction using H_8-BINOL **3** (20 mol %).[5a]
[e] Values refer to the ee reported for the reaction using BINOL derivative **2** (1 mol %) under otherwise identical conditions.[6]
[f] The reaction was carried out with commercial Ti(O*i*-Pr)$_4$ and CH_2Cl_2 as received by using a non-dried glassware.



Scheme 3. Plausible titanium aggregates.

Acknowledgments

Financial support from the Ministry of Education, Science, Sports and Culture of the Japanese Government [Grant-in-Aid for Scientific Research (No. 17550101)] is gratefully acknowledged.

References

1. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
2. Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233.
3. Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585.
4. (a) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528; (b) Shen, X.; Guo, H.; Ding, K. K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321; (c) Lipshutz, B. H.; Shin, Y.-J. *Tetrahedron Lett.* **2000**, *41*, 9515; (d) Chen, Y.; Yekta, S.; Martyn, J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433; (e) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321–4327; (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) Harada, T.; Hiraoka, Y.; Kusukawa, T.; Marutani, Y.; Matsui, S.; Nakatsugawa, M.; Kanda, K. *Org. Lett.* **2003**, *5*, 5059; (l) Hua, J.; Lin, W. *Org. Lett.* **2004**, *6*, 861; (m) Harada, T.; Kanda, K.; Hiraoka, Y.; Marutani, Y.; Nakatsugawa, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3879; (n) Harada, T.; Nakatsugawa, M. *Synlett* **2006**, 321.
5. (a) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651; (b) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080.
6. Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817.
7. For unsymmetrically substituted binaphthyl ligands in enantioselective catalysis, see: Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213.
8. Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409.
9. Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018.
10. *Representative procedure for asymmetric ethylation (Table 2, entries 6 and 7)*: Titanium tetraisopropoxide (0.413 mL, 1.4 mmol) was added to a solution of **4** (10.5 mg, 0.0200 mmol) in dry CH_2Cl_2 (8 mL) in a dry Schlenk flask at room temperature under an argon atmosphere. The resulting solution was stirred for 10 min at room temperature. To this was added diethylzinc (1 M in hexane, 3 mL, 3.0 mmol) and stirring was continued for 10 min. To the

resulting mixture was added 1-naphthaldehyde (0.156 g, 1.0 mmol) at 0 °C. After being stirred for 3 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted twice with ethyl acetate. The organic layers were washed with aqueous 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by a silica gel flash chromatography (5% ethyl acetate in toluene) to give 0.136 g (73% yield) of (*R*)-1-(1-naphthyl)-1-propanol (99% ee). The ee value as determined by HPLC analysis using a Chiralcel OD column (0.8 mL/min, 10% *i*-PrOH in hexane); 9.9 min [minor (*S*)-enantiomer] and 16.8 min [major (*R*)-enantiomer]. The absolute stereochemistry of the product was determined by comparing the retention time with that of an authentic sample prepared by asymmetric ethylation using (*R*)-BINOL as a ligand. The above reaction was carried out in a non-dried Schlenk flask with commercial titanium tetraisopropoxide and CH_2Cl_2 as received by following the same procedure except that, after addition of diethylzinc, the resulting mixture was stirred for 1 h at room temperature. The reaction gave 0.175 g (94% yield) of (*R*)-1-(1-naphthyl)-1-propanol (97% ee).

11. Under similar conditions, the reaction of 1-naphthaldehyde with **2** (1 mol %) gave the corresponding ethylation product in 94% ee and in 91% yield.
12. (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; (c) Pescitelli, G.; Bari, L. D.; Salvadori, P. *Organometallics* **2004**, *23*, 4223.