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Asymmetric Catalytic Alkylation of Aldehydes with Diethylzinc Using a Chiral Binaphthol-Titanium Complex

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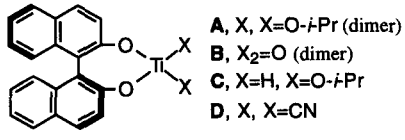
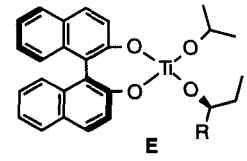
Abstract: *The asymmetric catalytic alkylation of aldehydes with diethylzinc using (R)-BINOL-Ti(O-i-Pr)$_2$ complex as an asymmetric precatalyst is shown to afford the corresponding secondary alcohols in a high enantioselectivity (up to 86% ee).*

In a continuing effort to develop asymmetric titanium catalysts based on (*R*)- or (*S*)-1,1'-di-2-naphthol (BINOL),[1] we are currently devoting our efforts to the development of asymmetric catalysis by using the chiral diisopropoxy complex **A** as an asymmetric *pre*catalyst that is easily accessible by mixing commercially available (*i*-PrO)$_4$Ti and (*S*)-BINOL. Reported so far are three different catalytic asymmetric processes, *i.e.*, the glyoxylate-ene reaction catalyzed by complex **B** prepared *via* hydrolysis of **A**,[2] the hydrosilylation of ketones with catalyzed complex **C** generated *in situ* from **A** and triethoxysilane,[3] and the cyanosilylation of aldehydes catalyzed by complex **D** generated *in situ* from **A** and trimethylsilyl cyanide.[4] Disclosed herein is a new asymmetric catalysis of the alkylation of aldehydes with diethylzinc using complex **A** as the asymmetric (pre)catalyst.[5,6] Of special interest here is whether the intermediary dichiral complex **E** might participate as *another* asymmetric precatalyst.[3]



A, X, X=O-*i*-Pr (dimer)
B, X_2=O (dimer)
C, X=H, X=O-*i*-Pr
D, X, X=CN



E

At the outset, we carried out the reaction of benzaldehyde with various equivalents of diethylzinc in toluene at -30 ℃ in the presence of complex **A** prepared *in situ* from (*S*)-BINOL and (*i*-PrO)$_4$Ti at 25 ℃ (eq 1). The results thus obtained reveal that the ratio of BINOL and (*i*-PrO)$_4$Ti is a key factor in dictating the enantioselectivity (Table 1). Notably, a large excess of (*i*-PrO)$_4$Ti (*vs.* BINOL) was required to render the reaction efficiently catalytic and an excess of Et_2Zn (*vs.* aldehyde) was needed to obtain a high chemical yield. Thus, the reaction was best carried out in toluene at -30-0 ℃ by using 10 mol% of (*S*)-BINOL, 1.2 equiv of (*i*-PrO)$_4$Ti, and 3.0 equiv of Et_2Zn to afford, after hydrolysis, the alcohol in 85% ee and >98% yield (entry 6).[7] Interestingly, when the four reactants were added successively *at no intervals*, the use of 1.6 equiv. of Et_2Zn gave a comparably high %ee and %yield (entry 8).

Next, the applicability of the present asymmetric catalysis to the reactions of aliphatic aldehydes was examined under similar conditions (eq 2, Table 2). Thus, a comparably high %ee was obtained with the saturated aldehydes at 0 ℃ (entries 2 and 4) and the unsaturated aldehydes at -30 ℃ (entries 6 and 10). Significantly, (*t*-butyldimethylsilyl)propynal provides a much higher %ee than the trimethylsilyl counterpart.

(1)

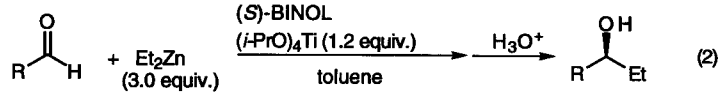
Table 1. The Asymmetric Catalytic Alkylation of Benzaldehyde Using Complex **A**.

entry	BINOL (equiv.)	$(i\text{-PrO})_4Ti$ (equiv.)	Et_2Zn (equiv.)	condition	% yield[a]	% ee[a](*config.*)[b]
1	0.2	0.8	1.8	-30 °C / 20 h	28	56 (*S*)
2	0.2	1.0	1.8	-30 °C / 20 h	36	77 (*S*)
3	0.2	1.2	1.8	-30 °C / 20 h	61	83 (*S*)
4	0.2	1.2	3.0	-30 °C / 20 h	89	85 (*S*)
5	0.2	1.2	3.0	0 °C / 1 h	97	85 (*S*)
6	0.1	1.2	3.0	0 °C / 1 h	> 98	85 (*S*)
7	0.06	1.2	3.0	0 °C / 1 h	> 98	80 (*S*)
8[c]	0.1	1.2	1.6	0 °C / 1 h	> 98	84 (*S*)

[a] Determined by chiral GLC analyses (CP-chiralsil-DEX OB).

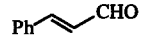
[b] Assigned by the sign of the optical rotation(*cf.* ref 5).

[c] BINOL, $(i\text{-PrO})_4Ti$, PhCHO, and Et_2Zn were added successively at no intervals.



(2)

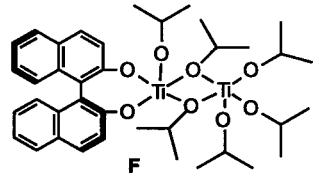
Table 2. The Asymmetric Catalytic Alkylations of Various Aldehydes.

entry	Aldehyde	BINOL(equiv.)	condition	% yield[a]	% ee[b](*config.*)[d]
1	$n\text{-}C_8H_{17}CHO$	0.2	0 °C / 3 h	90	81[b] (*S*)
2		0.2	-30 °C / 40 h	94	86 (*S*)
3	$c\text{-}C_6H_{13}CHO$	0.1	0 °C / 3 h	51	79[b] (*S*)
4		0.2	-30 °C / 40 h	75	85 (*S*)
5		0.1	0 °C / 1 h	>98	78[b] (*S*)
6		0.2	0 °C / 1 h	97	82 (*S*)
7		0.2	0 °C / 1 h	>98	56[c] (*S*)
8		0.2	-30 °C / 20 h	>98	26 (*S*)
9		0.1	0 °C / 1 h	>98	62[c] (*S*)
10		0.2	0 °C / 1 h	>98	79 (*S*)

[a] Isolated yield. [b] Determined by chiral GLC analyses as described above. [c] Determined by ^1H NMR assay of the MTPA esters. [d] Assigned by the sign of the optical rotations (*c.f.* ref 5).

In order to identify the actual catalytic species, the following NMR experiments were made on the catalyst solutions in toluene-d_8. (a) The ^{13}C NMR spectrum of complex **A** prepared from a 1:1 mixture of (±)-BINOL and $(i\text{-PrO})_4Ti$ showed two sets of peaks presumably due to the homochiral and heterochiral dimers,[8] while the spectrum of complex **F** prepared from a 1:6 mixture of (±)-BINOL and $(i\text{-PrO})_4Ti$ showed only a single set of different peaks. (b) The racemic complex **A** showed a different, more complicated ^1H NMR spectrum than that of the enantio-pure complex **A** derived from (*S*)-BINOL. By contrast, the racemic and enantio-pure complex **F** showed an identical and much simpler ^1H NMR spectrum than that of the enantio-pure complex **A**. These observations suggest that, under the reaction conditions, the dimeric complex **A** would readily react with an excess of $(i\text{-PrO})_4Ti$ to form a new monochiral species (probably identical with complex **F**) which might act as the actual asymmetric catalyst. Although the exact structure of the new complex **F** cannot be drawn at present,

the reported structures of related complexes[5,8] lead us to propose a dimeric structure having one BINOL ligand and six isopropoxy ligands as depicted below. The view that the asymmetric catalyst actually involved is not the dichiral complex **A** itself, but the monochiral complex **F** is supported by the independent observation that no significant level of the nonlinear effect between %ee of BINOL used and %ee of the product was observed in the present catalytic process as illustrated in Fig. 1. In addition, the initially thought involvement of the dichiral intermediary complex **E** as another asymmetric *pre*catalyst was totally excluded, since no appreciable change of %ee was observed throughout the reaction as shown in Fig. 2.[9]



F

Fig.1

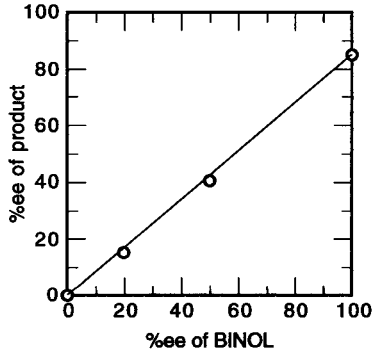
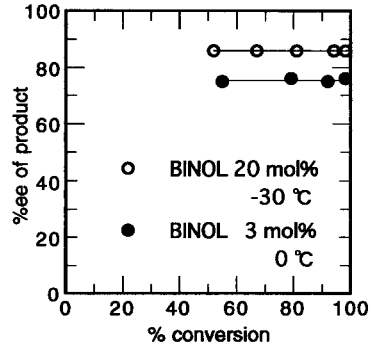
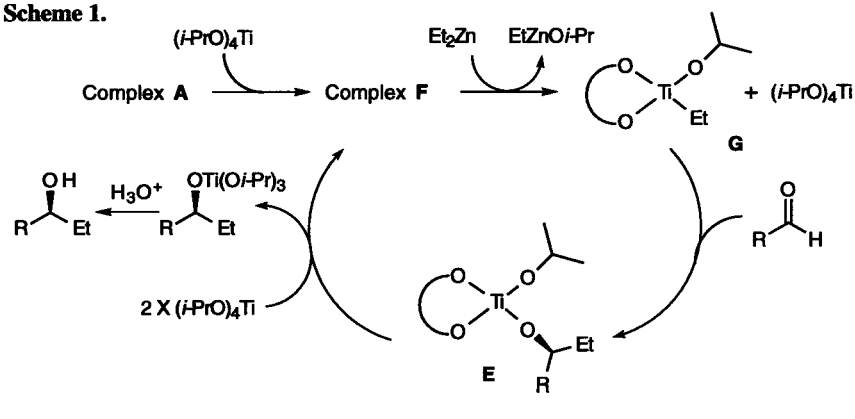


Fig. 2



Based on these findings, a plausible catalytic cycle for the present reaction is depicted in Scheme 1. The enantio-determining step is the addition of complex **G** once generated from complex **F** and Et_2Zn onto an aldehyde to form the dichiral complex **E** which then reacts with $(i\text{-PrO})_4Ti$ to give the titanium alkoxide product with the regeneration of complex **F**. Thus, this catalytic cycle accounts for why at least one equivalent of $(i\text{-PrO})_4Ti$ is required for rendering the catalytic reaction effective. Again, it should be noted that the third generation complex **E** does not participate as another asymmetric precatalyst. This observation is of mechanistic interest, since a complex similar to complex **E** has been proved to act as another asymmetric precatalyst, at least partially, in the complex **C**-catalyzed hydrosilylation of ketones with $(EtO)_3SiH$.[3]

Scheme 1.



In summary, we have developed an asymmetric catalysis of the alkylation of aldehydes with Et_2Zn using commercially available (*S*)-BINOL and $(i\text{-PrO})_4Ti$ as the catalyst precursors to afford the ethyl carbinols in high enantiomeric purity. Further work is underway to extend the present asymmetric catalysis to the reactions with other organozinc reagents and develop further new BINOL-based asymmetric catalysts.

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References and Notes

1. Reviews: (a) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255-265. (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press, Inc: London, 1995; 1, p 123-149.
2. Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861-1864.
3. Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, *12*, 1229-1230.
4. Mori, M.; Imma, H.; Nakai, T., the preceding paper.
5. For the asymmetric catalytic alkylations of aldehydes with organozinc reagents using chiral titanium catalysts in particular, see:(a) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363-4384. (b) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691-5700. (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*. 833-856. (d) Soai, K.; Hayase, T. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 138-150.
6. After this work was presented at the 70th Annual Meeting of the Chemical Society of Japan, March, 1996, Tokyo, Abstract 1J305, Chan and his co-workers have recently reported the addition reaction of diethylzinc to *aromatic aldehydes* catalyzed by essentially the same BINOL-Ti complex as reported herein: Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron:Asymm.* **1997**, *8*, 585-589. This publication prompted us to disclose our own results which include the reactions with *aliphatic aldehydes* and more detailed mechanistic aspects of this reaction.
7. The following procedure is representative. A solution of (*S*)-BINOL (0.2 mmol) and $Ti(Oi\text{-Pr})_4$ (1.2 mmol) in toluene (3 m*L*) was stirred at room temperature for 30 min. To the solution of Et_2Zn (3 m*L* of 1.0 *M* solution in hexane; 3 mmol) was added at -78 ℃. The resulting mixture was stirred for 30 min, and benzaldehyde (1 mmol) was added. The resulting mixture was gradually warmed to 0 ℃ and stirred for 1 h at that temperature. After hydrolysis with 2 m*L* of sat. NH_4Cl soln., the mixture was allowed to slowly warm up to room temperature and was then filtered through Celite to remove the solid formed. Usual workup followed by silica gel column chromatography afforded the corresponding alcohol. The enantiomeric purity was determined by GC on chiral column.
8. A dimeric structure has been reported for the crystal structure of complex **A**: Martin, C. A. Ph. D. Thesis, MIT, 1988. *Cf.* Imma, H. Master Thesis, Tokyo Institute of Technology, 1995.
9. The dichiral complex **E**, if it acts as a precatalyst, should provide a different %ee from that of the monochiral complex **F**, thus the overall %ee depending, more or less, on %conversion.

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