

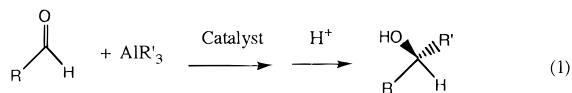
**Novel Asymmetric Alkylation of Aromatic Aldehydes with Triethylaluminum Catalyzed by Titanium·(1,1'-bi-2-naphthol) and Titanium·(5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol) Complexes**

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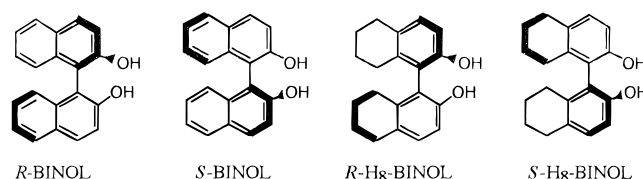
The catalytic asymmetric carbon–carbon bond formation is one of the most actively pursued areas of research in the field of asymmetric catalysis.<sup>1</sup> Over the past 10 years, the catalytic addition of diethylzinc to aldehydes as a route to chiral alcohols has attracted much attention.<sup>2</sup> Since many chiral alcohols are highly valuable intermediates for the manufacturing of chiral pharmaceuticals and agricultural products, the development of highly effective systems for the alkylation of aldehydes is not only of interest to the academic world but also of substantial interest to industrial scientists. Recently, several highly enantioselective catalysts for these reactions have been reported in the literature.<sup>3</sup> Similarly the catalytic asymmetric alkylation of aldehydes with alkylboranes, organotin compounds, and Grignard reagents also have attracted interest.<sup>2b,4</sup> From a broader perspective, the catalytic asymmetric alkylation of aldehydes with trialkylaluminum compounds should be of particularly high scientific and commercial interest.



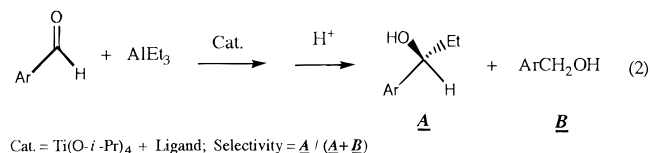
Trialkylaluminum compounds are economically prepared in industrial scale from aluminum hydride and olefins.<sup>5</sup> The successful alkylation of this type will certainly open up a new area for active research. Mukaiyama *et al.* found that when an aldehyde reacted with allyldialkylaluminum in the presence of stannous triflate and a chiral bidentate diamine, the aldehyde could be allylated and gave secondary homoallyl alcohols with up to 84% ee (enantiomeric excess).<sup>6</sup> In this paper, we report the first example of the enantioselective catalytic alkylation of aldehydes with triethylaluminum.

Since titanium chiral alkoxide complexes have been found to be highly enantioselective in the asymmetric addition of diethylzinc to aldehydes,<sup>7a</sup> our initial effort was focused on the use of this class of complexes as catalyst for the addition of

triethylaluminum to aldehydes. Recently, Cai *et al.* at Merck<sup>7</sup> found that binaphthol forms an inclusion complex with *N*-benzylcinchonidinium chloride in acetonitrile and the (*R*)-BINOL complex precipitated from the solution to give 99% yield and 96% ee of the desired isomer. The (*S*)-BINOL was found to stay in the acetonitrile solution and gave the enantiomer in 99% yield and 99% ee. The development of this finding is expected to provide excellent technology for the economic production of (*S*)- or (*R*)-1,1'-bi-2-naphthol ((*S*)- or (*R*)-BINOL) and consequently will provide an excellent opportunity for the exploitation of (*S*)- and (*R*)-BINOL and their derivatives as readily available and potentially low-cost chiral auxiliaries for asymmetric synthesis. In this respect, it is of great interest to examine the effect of (*S*)- or (*R*)-BINOL and their derivatives in asymmetric catalysis such as the enantioselective addition of triethylaluminum to aldehydes. With this background in mind, we started a study of the triethylaluminum addition with BINOL and 5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol<sup>8</sup> (H<sub>8</sub>-BINOL) as chiral auxiliaries.



The preliminary results were found to be highly encouraging. By using a catalyst conveniently prepared *in situ* from Ti(O-*i*-Pr)<sub>4</sub> and (*R*)-BINOL or (*S*)-H<sub>8</sub>-BINOL, a variety of arylaldehydes were smoothly alkylated to the corresponding alkylated alcohols. When suitable conditions are chosen, side reactions such as the reduction of the aldehydes to primary alcohols (which often took place in the diethylzinc addition reactions) could be reduced to minimum and quantitative yields of the alkylation products were frequently achieved.



In THF solvent and at 0 °C, benzaldehyde was alkylated to give 1-phenyl-1-propanol quantitatively, and 81% ee was obtained when (*R*)-BINOL was used as the chiral ligand. When (*S*)-H<sub>8</sub>-BINOL was used as the chiral auxiliary, the enantioselectivity of the catalytic reaction improved. Under otherwise identical conditions, the ee for the 1-phenyl-1-propanol product was found to be 96.4% when a catalyst prepared *in situ* from Ti(O-*i*-Pr)<sub>4</sub> and (*S*)-H<sub>8</sub>-BINOL was used. This reaction was found to be general and of high yields for a variety of aromatic aldehydes. The aldehydes shown below (1–9) have been tested,

(1) For recent review, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) For recent reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 260–278. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(3) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321 and references therein. (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19. (c) Soai, K.; OoKawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (d) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343.

(4) (a) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151. (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umami-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

(5) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 4th ed.; Wiley: New York, 1980; p 342.

(6) Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K. *Chem. Lett.* **1986**, 97.

(7) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.

(8) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930.

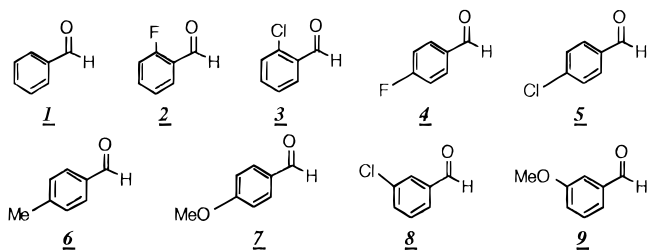
(9) A typical procedure for the experiment is as follows. Titanium tetraisopropoxide (60 μL, 0.175 mmol) was added to a solution of (*R*)-binaphthol (7.0 mg, 0.025 mmol) in 1.0 mL of THF at ambient temperature, and the solution was stirred with a magnetic stirrer for 10 min. A solution of triethylaluminum in toluene (0.375 mL of a 1.0 M solution, 0.375 mmol) was added to the catalyst solution, and the mixed solution continued to stir at ambient temperature for 30 min. The solution was cooled to 0 °C, and benzaldehyde (13 μL, 0.125 mmol) was added. The final solution was stirred at 0 °C for 5 h. The reaction was quenched sequentially with 1.0 mL of water and 0.5 mL of 2 N hydrochloric acid solution, and the product was extracted with 2.0 mL of ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and analyzed by GLC with a Chrompack CD-Chirasil-DEX-CB capillary column.

**Table 1.** Asymmetric Addition of Triethylaluminum to Arylaldehydes<sup>a-c</sup>

entry	aldehyde	ligand	convsn (%)	selectivity (%)	ee (%)	confign
1	<b>1</b>	( <i>R</i> )-BINOL	100	100	81	<i>R</i>
2	<b>1</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	100	100	96.4	<i>S</i>
3	<b>2</b>	( <i>R</i> )-BINOL	91.3	93.3	52	<i>R</i>
4	<b>2</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	95.8	100	91	<i>S</i>
5	<b>3</b>	( <i>R</i> )-BINOL	95.1	91.6	62	<i>R</i>
6	<b>3</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	95.8	100	90.6	<i>S</i>
7	<b>4</b>	( <i>R</i> )-BINOL	91.7	98.2	77.8	<i>R</i>
8	<b>4</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	97.6	100	94.4	<i>S</i>
9	<b>5</b>	( <i>R</i> )-BINOL	92.9	100	81	<i>R</i>
10	<b>5</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	59	100	90.1	<i>S</i>
11	<b>6</b>	( <i>R</i> )-BINOL	85.0	85.3	75.8	<i>R</i>
12	<b>6</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	92.1	100	93	<i>S</i>
13	<b>7</b>	( <i>R</i> )-BINOL	93	80.2	67 <sup>d</sup>	<i>R</i>
14	<b>7</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	97.9	100	92.8 <sup>d</sup>	<i>S</i>
15	<b>8</b>	( <i>R</i> )-BINOL	97.2	100	85.6	<i>R</i>
16	<b>8</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	97.6	100	94.4	<i>S</i>
17	<b>9</b>	( <i>R</i> )-BINOL	93.1	100	71.4 <sup>d</sup>	<i>R</i>
18	<b>9</b>	( <i>S</i> )-H <sub>8</sub> -BINOL	98.9	100	94.1 <sup>d</sup>	<i>S</i>

<sup>a</sup> A detailed experimental procedure is shown in ref 9. <sup>b</sup> Ligand/Ti(O-*i*-Pr)<sub>4</sub>/AlEt<sub>3</sub>/substrate = 0.2:1.4:3.0:1; solvent = THF; reaction temperature = 0 °C; reaction time = 5 h. <sup>c</sup> Except as noted, the ee values were determined by chiral GLC with a Chropack CD-Chirasil-DEX-CB capillary column, and the sense of chirality was based on the comparison of the direction of optical rotation (and GLC trace) of the products with known compounds of the same or similar structures. <sup>d</sup> Determined by HPLC with a Chiralcel-OD column from Daicel.

and the representative data of the addition reaction are summarized in Table 1.



These results clearly indicate the high potential of this new chemistry which, we believe, can be applied to the synthesis of a variety of chiral alcohols from low-cost raw materials.

Several interesting features can be noted from Table 1. While the (*R*)-BINOL/Ti(O-*i*-Pr)<sub>4</sub> system provided good yields of chiral alcohols in moderate to good ee values, the (*S*)-H<sub>8</sub>-BINOL/Ti(O-*i*-Pr)<sub>4</sub> system gave quantitative yields of the desired alcohols in excellent ee values (>90%) in the reaction from all of the aromatic aldehydes tested. A comparison of the experimental results from entries 1–6 (Table 1) revealed the detrimental effect on enantioselectivity by *ortho*-substituents on benzaldehyde. This was probably due to the strong steric hindrance effect of the *ortho*-substituent which significantly weakened the coordination of the aldehyde and consequently lowered the enantioselectivity of the reaction. In comparison,

*meta*- and *para*-substituents on the aromatic aldehydes had less effect on the enantioselectivity for the alcohol products. These results are consistent with the expectation that the electronic effects from the starting materials are less significant as compared with the steric hindrance effect in influencing the enantioselectivity of the reaction. An analysis of the results from entries 1, 7, 9, 11, and 13 indicated that, for the (*R*)-BINOL/Ti(O-*i*-Pr)<sub>4</sub> system, the electron withdrawing *para*-substituents had little influence on the enantioselectivity while electron-donating *para*-substituents had a small negative effect. For *meta*-substituted benzaldehydes, an electron-withdrawing substituent on the phenyl ring was found to increase the enantioselectivity while an electron-donating substituent was found to lower the enantioselectivity for the desired products (entries 1, 15, and 17). For the (*S*)-H<sub>8</sub>-BINOL/Ti(O-*i*-Pr)<sub>4</sub> system, the effects of the substituents were less significant, partly because all of the ee values were already quite high.

When trimethylaluminum was used as alkylating agent, the chemical selectivities were still quantitative and the expected 1-arylethanol products were obtained after hydrolysis. However, the ee values of the alcohols were found to be lower. For example, when benzaldehyde was allowed to react with trimethylaluminum under otherwise identical conditions as in entry 2 of Table 1, the *sec*-phenethyl alcohol product was found to be of 53% ee (91% conversion; 100% chemical selectivity). The ee values for the methylation of other aldehydes under identical conditions were as follows: *p*-fluorobenzaldehyde, 44.8% ee; *p*-chlorobenzaldehyde, 43.0% ee; *p*-fluorobenzaldehyde, 44.8% ee; *p*-methylbenzaldehyde, 42.1% ee; *p*-methoxybenzaldehyde, 42.7% ee (100% chemical yields were obtained in all of these cases). The lower ee values were probably due to the mismatch of the catalysts and the alkylating agent. Since there are many chiral catalysts available, as reported in the literature, further study of this reaction with other catalysts should be of significant interest. When triisobutylaluminum was allowed to react with arylaldehydes under these conditions, only reduction products were obtained. For example, the reaction of benzaldehyde with triisobutylaluminum gave benzyl alcohol exclusively. The use of triisobutylaluminum as a reducing agent is well established.<sup>10</sup> Further exploration of this new asymmetric alkylation reaction with other aluminum alkyls and other types of chiral catalyst is in progress.

In conclusion, we have developed a new, highly efficient method for the production of chiral alcohols from aldehydes and triethylaluminum using catalysts which can be conveniently prepared from commercially available or easily prepared reagents. This study opens up a new frontier for the development of more efficient synthetic methods. A more detailed study of this new class of reaction with different kinds of catalysts is underway.

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(10) Tolstikov, G. A.; Akbutina, F. A.; Adler, M. E.; Sidorov, N. N.; Kuchin, A. V.; Miftakhov, M. S. *Zh. Org. Khim.* **1988**, *24*, 2622.