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Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by titanium–5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol complex

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Abstract: The use of Ti(H_8-BINOL) (H_8-BINOL=5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) as a catalyst for the diethylzinc addition to aldehydes has been studied, and high e.e.s (up to 98.5%) were obtained for the chiral alcohol products. The results were significantly better than those obtained with the corresponding Ti(BINOL) catalyst (BINOL=1,1′-bi-2-naphthol). © 1997 Elsevier Science Ltd

Introduction

Enantioselective carbon–carbon bond formation is one of the most extensively studied areas in catalytic asymmetric synthesis.[1] The catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention because of its simplicity and because of its usefulness in the preparation of a variety of high value chiral alcohols.[2] Many systems including β-aminoalcohols,[3] oxazaborolidines,[4] N,N,N′,N′-tetraakyl-1,1′-binaphthol-3,3′-dicarboxamides[5] as chiral auxiliaries, which gave moderate to excellent results, have been reported. The chiral titanium complexes (e.g. TADDOLs[6] and chiral sulfonamides[7]) have also been found to be highly effective in the addition of diethylzinc to aldehydes. In a recent publication we reported that Ti(BINOL) (BINOL=1,1′-bi-2-naphthol) was effective as a catalyst for the asymmetric addition of diethylzinc to aromatic aldehydes.[8] More recently we achieved success in establishing the first example of the asymmetric catalytic addition of trialkylaluminum to aldehydes. By using a Ti(H_8-BINOL) complex as a catalyst (H_8-BINOL=5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol), over 96% e.e. was obtained in the alkylation of benzaldehyde with triethylaluminum.[9] Interestingly, when the same reaction was carried out using Ti(BINOL) as a catalyst under otherwise identical conditions, only 81% e.e. was obtained for the alkylated product. These results revealed the advantage of the sterically more demanding H_8-BINOL and prompted us to re-examine the asymmetric addition of diethylzinc to aromatic aldehydes with Ti(H_8-BINOL) catalyst. It is of high scientific interest if we can establish the generality of this new finding. Since the BINOL can be easily prepared in large scale and high enantiomeric excess[10] and since H_8-BINOL can be readily derived from BINOL via hydrogenation,[11] the catalyst systems based on these ligands are expected to have excellent potential for practical applications. More importantly, since BINOL ligand has been extensively used in the preparation of chiral catalysts,[12] the establishment of the generality of the higher effectiveness of H_8-BINOL (as compared to BINOL) as a chiral ligand will create excellent opportunities for the improvement of many existing catalyst systems. Indeed, the diethylzinc addition to aldehydes catalyzed by Ti(H_8-BINOL) gave significantly better results than the same reactions catalyzed by Ti(BINOL). Herein we wish to report the results of the study.

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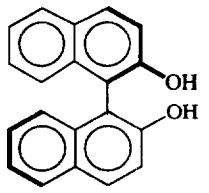
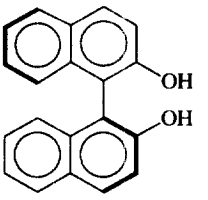


R-BINOL



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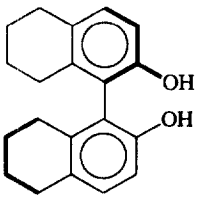
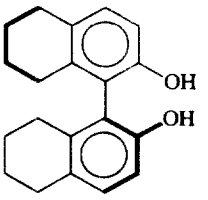


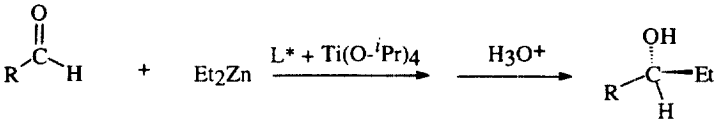
R-H8-BINOL



S-H8-BINOL

Results and discussion

By using the catalyst conveniently prepared *in situ* from Ti(O-^{i}Pr)$_4$ and (S)-H$_8$-BINOL, a variety of aromatic aldehydes were smoothly alkylated to the corresponding secondary alcohols in essentially quantitative yields.



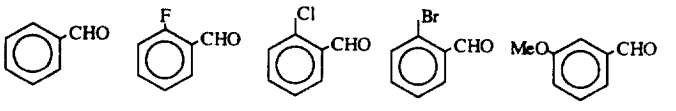
Since benzaldehyde has been most extensively studied previously, we focused our effort on the diethylzinc addition to benzaldehyde in our initial study. Some common factors such as the choice of solvent, reaction temperature, ligand/metal ratio, etc., which are known to affect the enantioselectivity of the reaction, have been examined. The enantioselectivities attained in the present study were found to be rather insensitive to the choice of solvents. For example, similar e.e.s were achieved in the diethylzinc addition to benzaldehyde in several different organic solvents within a period of 5 h: THF (89.1% conv., 96.7% e.e.); Et_2O (100% conv., 97.3% e.e.); toluene (99.5% conv., 96.4% e.e.); dichloromethane (100% conv., 97.7% e.e.). Likewise, reaction temperature variations had little effect on the selectivities of the reaction. The e.e.s varied from 97.5 to 98.5% over a temperature range from 20 to −40°C.

Since the temperature of 0°C was readily achieved in the laboratory and since dichloromethane gave the best rate and enantioselectivity, they were chosen to be the preferred conditions for the rest of the study.

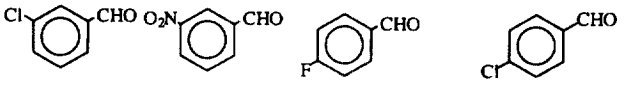
The molar ratio of chiral ligand to metal was found to be important in this addition reaction. When the addition of diethylzinc to benzaldehyde was catalyzed by either titanium tetraisopropoxide or (S)-H$_8$-BINOL alone, there was no enantioselectivity at all and the rate of reaction was at least 5 times slower than that with Ti(H$_8$-BINOL) as the catalyst. Similar to other catalyst systems of titanium complexes, the excess of Ti(O-^{i}Pr)$_4$ was essential in order to achieve the high reaction rate and excellent enantioselectivity.[6,8,9] In this study, the best ratio of (S)-H$_8$-BINOL to titanium tetraisopropoxide was found to be 1:7.

The addition of diethylzinc to a variety of aromatic aldehydes catalyzed by Ti(H$_8$-BINOL) have been studied and the results are summarized in Table 1. Similar to our observation in the catalytic addition of triethylaluminum to aldehydes,[9] it was clearly observed that the enantioselectivities of diethylzinc addition to aldehydes catalyzed by Ti(H$_8$-BINOL) were significantly higher than those from the same reactions catalyzed by Ti(BINOL).[8] A comparison of the experimental results from entries 1 and 3–5 (Table 1) revealed the detrimental effect on enantioselectivity of *ortho*-substituents on the aromatic aldehyde. 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. The electronic effects from the substrates were less significant as compared with the steric hindrance effect in influencing the enantioselectivity of the reaction, except that the strong electron-withdrawing group (–NO_2) at *meta*-position decreased the

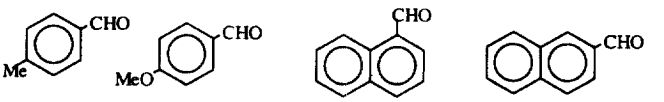
Table 1. Asymmetric addition of diethylzinc to aromatic aldehydes[a]



1 2 3 4 5



6 7 8 9



10 11 12 13

Entry	Aldehyde	Product	Conversion (%)[b]	% e.e.[c, d]	Config.[e]
1	1	1a	100	97.6 (91.9)	S
2[f]	1	1a	57.0	98.5 (94.7)	S
3	2	2a	100	93.7 (72.6)	S
4	3	3a	100	91.6 (68.6)	S
5	4	4a	98.2	85.4 (59.4)	S
6	5	5a	100	95.7[g] (94.0)	S
7	6	6a	99.2	96.2 (88.2)	S
8	7	7a	100	88.0[g] (70.0)	S
9	8	8a	100	96.9 (86.2)	S
10	9	9a	88.7	96.5 (88.1)	S
11	10	10a	100	91.3 (88.0)	S
12	11	11a	98.8	96.5 (79.0)	S
13	12	12a	100	98.2[g] (93.6)	S
14	13	13a	100	94.6[g] (81.0)	S

[a] (S)-H_8-BINOL/Ti(O-^{i}Pr)$_4$/$ZnEt_2$/substrate = 0.2:1.4:3:1; dichloromethane as solvent; reaction temperature = 0°C; reaction time = 5.0 h. [b] Selectivity was quantitative in all cases (*i.e.* quantitative yield based on converted material was obtained in all cases). [c] Except as noted, the ee values were determined by chiral GLC with a Chrompack CD-Chirasil-DEX-CB capillary column [1a: t_R(min) = 8.5 (R) and 8.9 (S), oven temp. =130°C, column flow = 30 mL/min; 2a: t_R(min) = 12.1 (R) and 12.4 (S), oven temp. = 125°C, column flow = 30 mL/min; 3a: t_R(min) = 15.1 (R) and 16.2 (S), oven temp. = 140°C, column flow = 30 mL/min; 4a: t_R(min) = 7.3 (R) and 7.6 (S), oven temp. = 145°C, column flow = 35 mL/min; 6a: t_R(min) = 13.1 (R) and 13.7 (S), oven temp. = 145°C, column flow = 30 mL/min; 8a: t_R(min) = 8.5 (R) and 9.2 (S), oven temp. = 135°C, column flow = 30 mL/min; 9a: t_R(min) = 5.4 (R) and 5.6 (S), oven temp. = 170°C, column flow = 30 mL/min; 10a: t_R(min) = 9.0 (R) and 9.6 (S), oven temp. = 135°C, column flow = 30 mL/min; 11a: t_R(min) = 11.0 (R) and 11.4 (S), oven temp. = 150°C, column flow = 30 mL/min]. [d] Data in brackets are from experiments using S-BINOL as chiral ligand under otherwise identical conditions (ref. 8). [e] The sense of chirality was based on the comparison of the direction of optical rotation (or GLC and HPLC trace) of the products with known compounds of the same or similar structures. [f] Reaction temperature = -40° C; reaction time = 8.0 h. [g] Determined by HPLC with a Chiralcel-OD column from Daicel [1a: t_R(min) = 13.3 (S) and 17.9 (R), eluent, 2.5% 2-propanol in hexane, flow rate = 1.0 mL/min; 5a: t_R(min) = 28.1 (S) and 29.8 (R), eluent, 2.0% 2-propanol in hexane, flow rate = 1.0 mL/min; 7a: t_R(min) = 29.4 (S) and 31.2 (R), eluent, 2.0% 2-propanol in hexane, flow rate = 1.0 mL/min; 12a: t_R(min) = 14.4 (S) and 28.3 (R), eluent, 5.0% 2-propanol in hexane, flow rate = 1.0 mL/min; 13a: t_R(min) = 17.1 (S), 19.2 (R), eluent, 5.0% 2-propanol in hexane, flow rate = 1.0 mL/min]

enantioselectivity (entry 8). The excellent selectivities were also obtained in the addition of diethylzinc to naphthaldehydes (94.6–98.2% e.e.) catalyzed by Ti(H_8-BINOL) complex.

In summary, we have developed a new, easily prepared and highly efficient catalyst system for the production of chiral secondary alcohols from the diethylzinc addition to aldehydes. The high enantioselectivity of the Ti(H_8-BINOL) catalyst as compared with Ti(BINOL) gave support to the generality of the advantage of the sterically more demanding H_8-BINOL. Since the BINOL ligand

has been widely used in catalytic reactions,[12] the substantial improvement of the enantioselectivities by simply replacing BINOL with H_8-BINOL should offer excellent opportunities for upgrading many existing catalyst systems.

Experimental section

All experiments were carried out under a nitrogen atmosphere. Unless otherwise stated, commercial reagents were used as received without further purification. Benzaldehyde was distilled with calcium hydride and all solvents used were dried using standard, published methods and were distilled before use. The absolute configurations of the products were estimated based on the comparison of GLC (or HPLC) traces and/or the direction of optical rotation with known or similar compounds.

A typical procedure for the catalytic addition of diethyl zinc to benzaldehyde

Titanium tetraisopropoxide (60 μL, 0.175 mmol) was added to a solution of S-H_8-BINOL (7.4 mg, 0.025 mmol) in 1.0 mL dichloromethane at room temperature and stirred for 10 min followed by the addition of a solution of 1.0 M diethyl zinc (0.375 mL, 0.375 mmol) in hexane and continued stirring for 10 min. The solution was then cooled to 0°C, benzaldehyde (13.0 μL, 0.125 mmol) was added and the mixture was allowed to stir at 0°C for 5.0 h. The reaction was quenched with 2.0 mL 1.0 N hydrochloric acid solution and the product was extracted with 2.0 mL ethyl acetate and dried with Na_2SO_4. The conversion and enantioselectivity of the reaction were determined by GLC with a Chrompack CD-Chirasil-DEX-CB capillary column.

Acknowledgements

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