Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti(BINOL) complex

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Abstract: The enantioselective addition of diethylzinc to aldehydes was conveniently achieved by using a catalyst prepared *in situ* by mixing titanium tetraisopropoxide with S- or R-binaphthol. Optical yields as high as 95.6% were obtained. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Enantioselective carbon–carbon bond formation is one of the most interesting challenges in organic synthesis. In recent years the catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention because of its potential in the preparation of a variety of high value non-racemic chiral alcohols.[1]
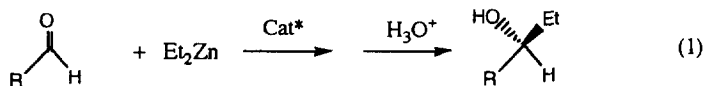

Previously most of the studies have focused on the use of β-aminoalcohols as chiral auxiliaries and excellent results have been reported.[2] More recently Seebach and co-workers developed a series of titanium tetra-aryldioxolanedimethanol complexes as catalysts and reported excellent results in the addition of dialkylzinc to aldehydes.[3] Other systems including the use of isoborneol-derived β-hydroxysulfides,[4] oxazaborolidines,[5] and N,N,N',N'-tetraalkyl-1,1'-bi-2-naphthol-3,3'-dicarboxamides[6] as chiral auxiliaries gave moderate to excellent enantioselectivities.

Recently, Cai *et al.* at Merck[7] 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% e.e. of the desired isomer. The S-BINOL was found to stay in the acetonitrile solution and gave the enantiomer in 99% yield and 99% e.e. 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).
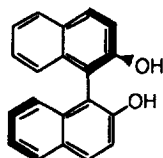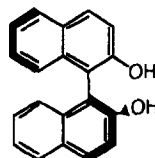
R-BINOL   S-BINOL

This new development offered an excellent opportunity for the exploitation of S-BINOL or R-BINOL 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 in asymmetric catalysis such

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Table 1. The effect of solvent on the enantioselectivity of the addition of diethylzinc to benzaldehyde

Entry	Solvent	Conversion (%)	e.e. (%)	Configuration
1	Toluene	99.5	88.3	S
2	Diethyl ether	98.8	88.6	S
3	Tetrahydrofuran	96.4	89.6	S
4	Dichloromethane	100	91.9	S

Benzaldehyde : S-BINOL : Ti(O^{i}Pr)$_4$: Et$_2$Zn = 1.0 : 0.2 : 1.4 : 3 (molar ratio);
reaction temperature = 0 °C; reaction time = 10 hours.

as the enantioselective addition of diethylzinc to aldehydes. With this background in mind we started a study of the diethylzinc addition with BINOL as a chiral auxiliary. A catalyst conveniently prepared by mixing small amounts of S- or R-BINOL with titanium tetraisopropoxide was found to be highly effective for the enantioselective addition of diethylzinc to a variety of aldehydes. In this paper we report the various aspects of the catalytic reaction.

Results and discussion

One of the purposes of this study is to develop a simple method for the preparation of chiral alcohols from aldehydes and diethylzinc. In this respect the preparation of the catalyst *in situ* from readily available starting materials is certainly most convenient. Chiral titanium alkoxide complexes are of particular interest because of the previous success in their application in enantioselective dialkylzinc addition reactions.[3] Since benzaldehyde has been most extensively studied previously, we focused our effort on the diethylzinc addition to benzaldehyde in our initial study so that the results can be easily compared with those from previous studies. Several common factors such as the choice of solvent, reaction temperature, ligand/metal molar ratio, etc., which are known to affect the enantioselectivity of the catalyst system, have been examined. The reaction was found to be quite clean and essentially no byproduct was observed. The solvent effect was detectable but not very significant. At 0°C, the use of toluene, ether, THF, and dichloromethane solvent gave a product with a e.e. range from 88.3 to 91.9% (Table 1).

Since dichloromethane gave the best rate and enantioselectivity, it was chosen to be the preferred solvent for the rest of the study.

The enantioselectivity of the reaction was found to be sensitive to the level of BINOL ligand used in the catalytic reaction. While keeping other conditions unchanged, the variation of the concentration of the chiral BINOL ligand in the catalyst system gave different rate and enantioselectivity. As expected, when the addition of diethylzinc to benzaldehyde was catalyzed by titanium tetraisopropoxide alone without the chiral auxiliary (BINOL), there was no enantioselectivity at all and the rate of reaction was slower than that with a proper combination of BINOL and titanium tetraisopropoxide as catalyst. The steady increase of the rate of reaction and the product e.e. with an increase of the BINOL level up to a certain point revealed that the enantioselective Ti(BINOL) catalyst which gave faster rate of reaction than titanium tetraisopropoxide was competing with the latter for the diethylzinc and benzaldehyde in the addition reaction. The detailed experimental data are summarized in Table 2.

It is of interest to note that the rate of reaction was substantially lower when the level of BINOL was close to the titanium tetraisopropoxide used (entry 6). This observation is consistent with previously reported data on similar reactions and the phenomena have been suggested to be due to the need of free titanium tetraisopropoxide (without BINOL) as a co-catalyst in the reaction.[8]

The temperature effect on the enantioselectivity of the reaction was detectable, albeit not very large. Like other diethylzinc addition reactions, at lower reaction temperature, the enantioselectivity of the

Table 2. The effect of the ratio of BINOL to Ti(O^{i}Pr)$_4$ on the enantioselectivity of the reaction

Entry	S-BINOL/Ti(O^{i}Pr)$_4$ (M/M)	Conv. (%)	e.e. (%)	Configuration
1	0	37.1	0	
2	1/70	89.1	69.1	S
3	1/28	98.6	87.6	S
4	1/14	98.9	89.3	S
5	1/7	100	91.9	S
6	1/1.4	17.1	91.8	S

Benzaldehyde : Ti(O^{i}Pr)$_4$: Et$_2$Zn = 1.0 : 1.4 : 3 (molar ratio); solvent = dichloromethane; reaction temperature = 0 °C; reaction time = 5 hours.

Table 3. The effect of reaction temperature on the enantioselectivity of the reaction

Entry	Temp (°C)	Reaction time (hours)	Conv. (%)	e.e. (%)	Configuration
1	-78	8	64.3	95.6	S
2	-40	8	80.2	94.7	S
3	-20	8	87.2	93.1	S
4	0	5	100	91.9	S
5	20	5	100	90.8	S
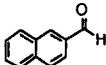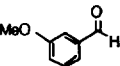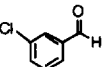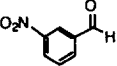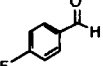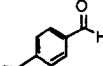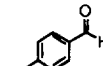
Benzaldehyde : S-BINOL : Ti(O^{i}Pr)$_4$: Et$_2$Zn = 1.0 : 0.2 : 1.4 : 3 (molar ratio); solvent = dichloromethane.

Ti(BINOL)-catalyzed reaction was found to increase. As expected, the rate of reaction decreased with the decrease of reaction temperature. Some typical results are summarized in Table 3.
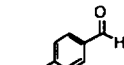

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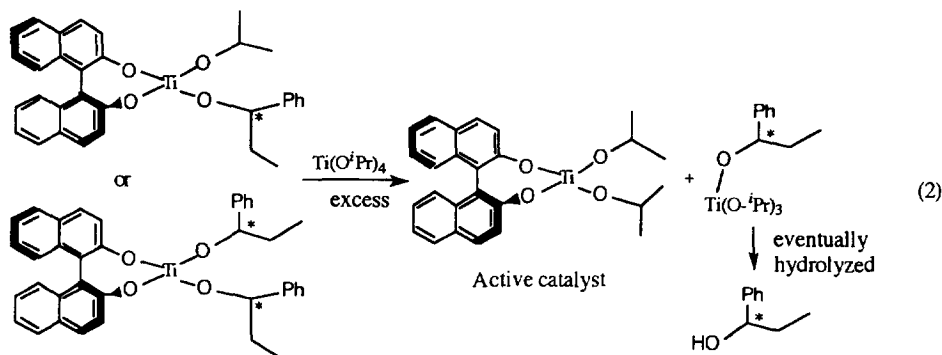
The catalyst system was found to be useful for the enantioselective addition of diethylzinc to a variety of aldehydes. A comparison of the structure of the starting materials versus the enantioselectivity for the products is summarized in Table 4. From this table it can be observed that the electronic effect from the substrate is substantially less important than the steric hindrance effect for the enantioselectivity of the reaction. For example, while *para*-substituted benzaldehydes gave products with only slightly lower e.e. than that from benzaldehyde, all of the *ortho*-substituted benzaldehydes gave products of significantly lower e.e.'s. This is probably due to the strong steric hindrance effect of the *ortho*-substituents which weaken the coordination of the substrate to the chiral catalyst and thus lower the influence of the chiral environment of the catalyst on the orientation of the substrate. Consequently lower enantioselectivity was observed for the alkylation of these aldehydes. For *meta*-substrate benzaldehydes, an electron-

Table 4. A comparison of the enantioselective addition of diethylzinc to different aldehydes[a]

Entry	Substrate	% Conv.	% e.e.	Configuration
1		100	91.9[b]	*S*
2		100	93.6[c]	*S*
3		100	81[c]	*S*
4		100	94[c]	*S*
5		98.7	88.2[b]	*S*
6		100	70.0[c]	*S*
7		100	86.2[b]	*S*
8		86.1	88.1[b]	*S*
9		99.1	88.0[b]	*S*
10		100	79.0[c]	*S*
11		100	72.6[b]	*S*
12		100	68.6[b]	*S*
13		99.2	59.4[b]	*S*

a) Substrate : S-BINOL : $Ti(O^iPr)_4$: $Et_2Zn = 1.0 : 0.2 : 1.4 : 3$ (molar ratio); solvent = dichloromethane; 0 °C; 5 hrs. b) e.e. determined by chiral GLC with a Chrompack CD-Chirasil-DEX-CB capillary column. c) e.e. determined by HPLC with a Chiralcel OD column.

donating substituent (e.g. a methoxy group) was found to increase the enantioselectivity while electron-withdrawing groups such as chloro and nitro group were found to decrease the enantioselectivity of the reaction. The steric effect on the enantioselectivity of the addition of diethylzinc to naphthaldehyde was found to be quite different from that of the substituted-benzaldehyde reactions. In the addition to naphthaldehyde the sterically more hindered 1-naphthaldehyde gave much higher enantioselectivity than that of the less hindered 2-naphthaldehyde. Obviously a thorough understanding of these effect requires more in-depth mechanistic studies.

Experimental

All experiments were carried out under dinitrogen atmosphere. Except as noted, commercial reagents were used as received without further purification. Benzaldehyde was distilled from calcium hydride and all solvents used were dried by 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 diethylzinc to benzaldehyde

A 10 mL pear-shape flask with a magnetic stirring bar was charged with 60 μL titanium tetraisopropoxide (0.175 mmol), 7.0 mg S-binaphthol (0.025 mmol), and 1.0 mL dichloromethane and the mixture was stirred at ambient temperature for 10 minutes. Into this solution was added 0.375 mL of a 1 M solution of diethylzinc in hexane (0.375 mmol) and the mixture was stirred for another 10 minutes. The solution was cooled to 0°C and 13 μL of benzaldehyde (0.125 mmol) was added to the solution and the final mixture was allowed to stirred at 0°C for 5 hours. The reaction was stopped by the addition of 2.0 mL of 1.0N hydrochloric acid and the product was extracted with 2.0 mL ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and the conversion and enantioselectivity of the reaction were determined by GLC with a Chrompack CD-Chirasil-DEX-CB capillary column and the absolution configuration was based on the comparison with the GLC trace of a known compound.

Acknowledgements

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