Investigation of the Efficiency of Aminoalcohol Based Catalysts in the Addition of Diethylzinc to Aldehydes

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Summary: In this study, firstly, two amino alcohols, namely, (2S)-2-[Benzyl(2-hydroxyethyl)amino]-3-methyl-butan-1-ol (**1**) and (2R)-2-[Benzyl(2-hydroxyethyl)amino]butan-1-ol (**2**) were prepared in 89 and 94% yields, respectively, and their structures were elucidated by spectroscopic methods. Then, the catalytic activities of these amino alcohols in the reaction of diethylzinc addition to benzaldehyde and its derivatives were investigated. The catalytic activity of these amino alcohols in the diethylzinc addition reaction to benzaldehyde under the optimum conditions was determined as 96% conversion and 40% ee.

Keywords: Diethyl zinc, Catalysis, Amino alcohol, Chiral.

Introduction

The discipline of synthetic chemistry is very interested in finding new chiral ligands to employ in asymmetric catalysis [1-3]. With this technique, modest amounts of chiral catalyst can yield huge amounts of the desired chiral compounds. Reaction dependence, substrate dependence, and operational challenges in chiral ligand synthesis are some of the limits of chiral catalysts that have been established thus far. Thus, one of the most active research fields in synthetic organic chemistry is the design of novel effective chiral catalysts [4].

C-C bond formation, which involves enantioselective catalytic transformations, is probably one of the most fascinating subjects in the field of organic synthesis [5]. Thus, a significant number of chiral ligands such as diols [6], diamines [7], amino thiols [8], amino disulfides [9], and amino alcohols [10] have been successfully obtained by enantioselective addition of diethyl zinc to aldehydes. Dialkylzinc addition to pro-chiral aldehydes is a common reaction [11–12] because the corresponding chiral secondary alcohols are valuable building blocks for the synthesis of new drugs. As shown by Noyori and Kitamura [13], amino alcohols are important ligands for this reaction. However, despite these successful advances, it has not yet reached a sufficient and applicable level. For this reason, studies are required to investigate how chiral catalysts work and their catalytic types in the addition of diethyl zinc to aldehydes. On the other hand, natural amino acids and β-amino alcohols and their derivatives have been employed in numerous asymmetric processes. Among many organometallic nucleophiles, organozinc reagents tolerate the presence of many functional groups that are reactive toward organolithium and Grignard reagents. This property renders the organozinc species attractive useful alternatives to these highly active reagents [14].

The asymmetric addition of diethylzinc (Et_2Zn) to aldehydes has withdrawn a lot of interest in this area. Since uncoordinated organozinc species seldom ever react with the aldehyde, these reactions need a compound that coordinates the metal ion to increase the nucleophilicity of the organometallic reagent. Because of increased reactivity of the complex reagent, even a catalytic amount of the ligand can be utilized. The enantioselective addition of diethylzinc to aldehydes in the presence of catalytic quantities of chiral amino alcohols as efficient chiral ligands to yield the corresponding alcohols was initially investigated by Oguni *et al*. [15].

Then, in the presence of diethyl zinc, Noyori *et al*. performed a similar reaction with the terpene-based chiral ligand DAIB (N, N-dimethylamino isoborneol) and obtained the product with incredibly high enantioselectivity (up to 98%).

Subsequently, a variety of chiral amino alcohols obtained from terpenes have been investigated as chiral catalysts/promoters/ligands for these kinds of reactions [16].

In this study, firstly, two N-benzylated amino alcohols were synthesized and their structures were elucidated by spectroscopic methods. Then, the catalytic activities of these amino alcohols in the reaction of diethylzinc addition to benzaldehyde and its derivatives were studied.

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Experimental

Reagents and other starting materials were purchased at analytical grade from Merck, Aldrich, or Across. ^{1}H and ^{13}C NMR spectra were obtained with a BRUKER AV400 NMR device in the indicated solvents. Coupling constants (J) and chemical shift (δ) were calculated in Hertz and Parts per Million (ppm), respectively. Infrared spectra (IR) were recorded as KBr disks or from a Perkin Elmer 1605 FT-IR System Spectrum spectrophotometer with ATR probe. GALLENKAMP model melting point device was used to determine melting points.

Because the materials used in all reactions were sensitive to moisture and air, the glassware and solvents were dried, and the reactions were conducted in a high-purity nitrogen environment using the conventional Schlenk procedure. The solvents such as THF, toluene were dried by distillation with sodium-benzophenone, while dichloromethane was dried with P_2O_5 (di-phosphorpentaoxide).

Synthesis and characterization of complexes

Synthesis of (S)-N-Benzyl-2-Amino-3-methyl-1-butanol (a)

L-Valine was reduced to L-valinol by the method reported by Yılmaz *et al* [17] Then, L-valinol (0.32 mol, 33 g), benzyl chloride (0.08 mol, 10.13 g), and anhydrous Na_2CO_3 (0.08 mol, 8.48 g) were placed in a 250 mL glass flask. This mixture was stirred at 110°C under inert atmosphere for 12 h. Then, this solution was cooled to RT, onto which $CHCl_3$ (150 mL) was added, followed by refluxing for 2 h. The solvent of the solution was removed by an evaporator and the precipitated solid was extracted with $CHCl_3$ (3 × 150 mL). Then, the obtained organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed by evaporating in vacuo. Yield 12 g (78%); E.n 110–112°C/0.8 mmHg, $[\alpha]_D^{20}$:−10.5 (c 1, MeOH). For element analysis $C_{12}H_{19}NO$ calculated: C 70.61; H 9.84; N 7.25; found: C 70.68; H 9.79; N 7.27. IR (KBr pellet cm^{-1}): 3397, 3095, 3070, 3024, 2960, 2877, 1612, 1503, 1464, 1406, 1375, 1162, 1060, 918, 874, 739. ^{1}H NMR (400 MHz, ppm, $CDCl_3$): δ 7.36-7.23 (m, 5H), 3.81-3.74 (m, 2H), 3.65-3.62 and 3.44-3.39 (m, 2H), 2.48-2.44 (m, 1H), 1.91-1.86 (m, 1H), 1.02-0.87 (m, 6H); ^{13}C NMR (100 MHz, ppm, $CDCl_3$): δ 140.97, 128.84, 127.42, 64.29, 60.98, 52.04, 29.09, 19.84, 18.86.

*Synthesis of (2S)-2-[Benzyl(2-hydroxyethyl)amino]-3-methyl-butan-1-ol (***1***)*

In a 250 mL flask was placed the solution of compound **a** (0.01 mol, 20 g) in 100 mL methyl alcohol and this solution was cooled to −20 °C. Subsequently, a solution of ethylene oxide (0.1 mol, 3.8 mL) in 10 mL of methyl alcohol was added drop wise from the equilibrium pressure dropping funnel at -20°C. After the dropping, the mixture was stirred at the same temperature for 12 h, at +4°C for 24 h, at room temperature for one day, and then the solvent was removed in an evaporator. Yield, 21 g (89%); E.n= 160–162°C/0.8 mmHg, $[\alpha]_D^{20}$: −14.9 (c 1, MeOH). For element analysis $C_{14}H_{23}NO_2$ calculated: C, 70.89; H, 9.70; N, 5.91, found: C, 70.94; H, 9.69; N, 5.88; IR (KBr pellet cm^{-1}): 3352, 3070, 3024, 2973, 1956, 1599, 1490, 1464, 1375, 1157, 1053, 913, 746, 701. ^{1}H NMR (400 MHz, ppm, $CDCl_3$): δ 7.36-7.20 (m, 5H), 3.91–3.87 (m, 2H), 3.69–3.63 and 3.55–3.44 (m, 4H), 2.92–2.80 (m, 2H), 2.56–2.50 (m, 1H), 1.91–1.85 (m, 1H), 1.07–0.86 (m, 6H); ^{13}C NMR (100 MHz, ppm, $CDCl_3$): δ 141.14, 129.23, 128.83, 127.44, 77.70, 77.38, 68.89, 61.14, 60.89, 55.90, 29.18, 22.45.

Synthesis of (R)-(-)-N-Benzyl-2-amino-1-butanol **(b)**

(R)-(-)-2-amino-1-butanol (800 mmol, 71.2 g), benzyl chloride (200 mmol, 25.3 g), and Na_2CO_3 (180 mmol, 20.0 g) were mixed in a 250 mL flask, which was heated in an oil bath at 100 °C and stirred for 8 h under a nitrogen atmosphere. After the reaction finished, 150 mL $CHCl_3$ was added into this solution, which was subsequently refluxed for 1 hour. The $CHCl_3$ phase was separated by decanting. The salt was extracted three times with 25 mL $CHCl_3$ and the $CHCl_3$ phases were combined and dried with Na_2SO_4. After removal of $CHCl_3$ in the evaporator, the separated product was distilled at 98-100°C / 0.1 mmHg. Yield 33 g (94%) (yield calculated based on benzyl chloride as the limiting reagent), Mp: 71-72 °C, $[\alpha]_D^{20}$:-25.63 (c 0.08, EtOH). For element analysis $C_{11}H_{17}NO$ calculated: C 73.70; H 9.56; N 7.80; found: C 73.68; H 9.62; N 7.75. ^{1}H NMR (400 MHz, ppm, $CDCl_3$): δ 7.39-7.29 (m, 5H), 3.85-3.75 (m, 2H), 3.38-3.45 (m, 2H), 2.68-2.64 (m, 1H), 1.63-1.48 (m, 2H), 0.98 (t, 3H, J=7.5 Hz). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): δ 140.83, 128.86, 127.45, 63.05, 60.21, 51.48, 24.64, 10.73. IR (KBr pellet cm^{-1}): 1068, 1361,"1467, 2836, 2931, 3076, 3287.

(2R)-2-[Benzyl(2-hydroxyethyl)amino]butan-1-ol **(2)**

(R)-(-)-N-benzyl-2-amino-1-butanol (260 mmol, 47 g) was dissolved in 100 mL methyl alcohol, and then cooled to -20°C in a 250 mL flask. The solution of ethylene oxide (260 mmol, 11.52 g) in 50 mL methyl alcohol was added dropwise from the equilibrium pressure dropping funnel at -20°C. After completion of the addition, the solution was stirred for 12 h at -20°C, 24 hours at +4°C and one day at RT, and then the solvent was removed by an evaporator. The separated product was distilled at 155°C/ 0.1 mmHg. Yield 56 g (94%),

$[\alpha]_D^{20}$: -14.89 (c 0.08, EtOH). For element analysis $C_{13}H_{21}NO_2$ calculated: C 66.90; H 9.07; N 6.08; found: C 66.77; H 9.03; N 5.99.

^{1}H NMR (400 MHz, ppm, $CDCl_3$): δ 7.37–7.22 (m, 5H), 3.84–3.62 (m, 4H), 3.56–3.45 (m, 2H), 3.41 (t, 2H, J = 10.3 Hz), 2.85–2.71 (m, 2H), 2.64–2.59 (m, 1H), 1.67–1.60, (m, 1H), 1.29–1.22 (m, 1H), 0.93 (t, 3H, J = 7.5 Hz,). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): δ 140.52, 129.16, 128.76, 127.41, 63.41, 61.90, 60.52, 55.32, 51.87, 19.72, 12.23. IR (KBR pellet, cm^{-1}): 698, 729, 1054, 1115, 1372, 1453, 1494, 1602, 2876, 2957, 3026, 3061, 3085, 3368.

General Method for Enantioselective Diethylzinc Addition

Ligand **1** or **2** (0.2 mmol) was added to a Schlenk tube under an inert atmosphere. Freshly distilled dry solvent (5 ml) was added and stirred for 5 minutes at RT. $Ti(O^iPr)_4$ (1.4 mmol, 0.42 mL) for Ti-mediated reaction was added to this solution. 1 h later, the reaction mixture was cooled to the indicated temperature and a solution of diethylzinc in 1M hexane (2.7 mL, 3 mmol) was added. After 30 minutes, aldehyde (1 mmol) was added onto this mixture. The reaction was continued for different time periods. At the end of this time, the reaction was saturated with 1M HCl (20 mL). (WARNING! Exothermic reaction, gas formation), filtered, extracted with diethyl ether (3x15 ml). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The diethyl ether phase was concentrated by an evaporator. This phase was then purified by column chromatography (hexane–diethyl ether). Enantiomeric excess (ee%) of the obtained products was established by GC analysis.

Method Used for Transfer Hydrogenation Reaction In Gas Chromatography

GC analysis was performed on a Shimadzu GC 2010 Plus model gas chromatography device fitted with a Cyclodex B (Agilent) capillary column (30m x 0.32mm I.D x 0.25 μm film thickness). The GC parameters utilized for the diethylzinc addition to benzaldehyde reaction are as follows:

Stage I: initial temperature: 50 °C; start time 1.1 min.; solvent retention 4.48 min; temperature increase 1.3 °C/min.; final temperature 150 °C;

Stage II: start time 2.2 min.; temperature increase 2.15 °C/min.; final temperature 250 °C;

Stage III: initial time 3.3 min.; final time 44.33 min.; injector port temperature 200 °C; detector temperature 200 °C; injection volume 2.0 μL.

Results and Discussion

Synthesis and structure elucidation of compounds **1** *and* **2**

α-Amino acids are chiral compounds that can be easily found in nature [18]. β-amino alcohols obtained by the reduction of α-amino acids are useful intermediates for the preparation of biologically active compounds [19] and are used as auxiliary substances and ligand groups in asymmetric synthesis [20]. Amino alcohols are important substances in contemporary synthetic chemistry due to their numerous synthetic uses as well as their biological characteristics [21]. Therefore, preparation of enantiomerically rich amino alcohols has been widely investigated. In this study, (2*S*)-2-[benzyl(2-hydroxyethyl)amino]-3-methyl-butan-1-ol (**1**) and (2*R*)-2-[benzyl(2-hydroxyethyl)amino]-butan-1-ol (**2**) were obtained in 89 and 94% yields, and their structures were elucidated by spectroscopic methods and given in detail in the synthesis section.

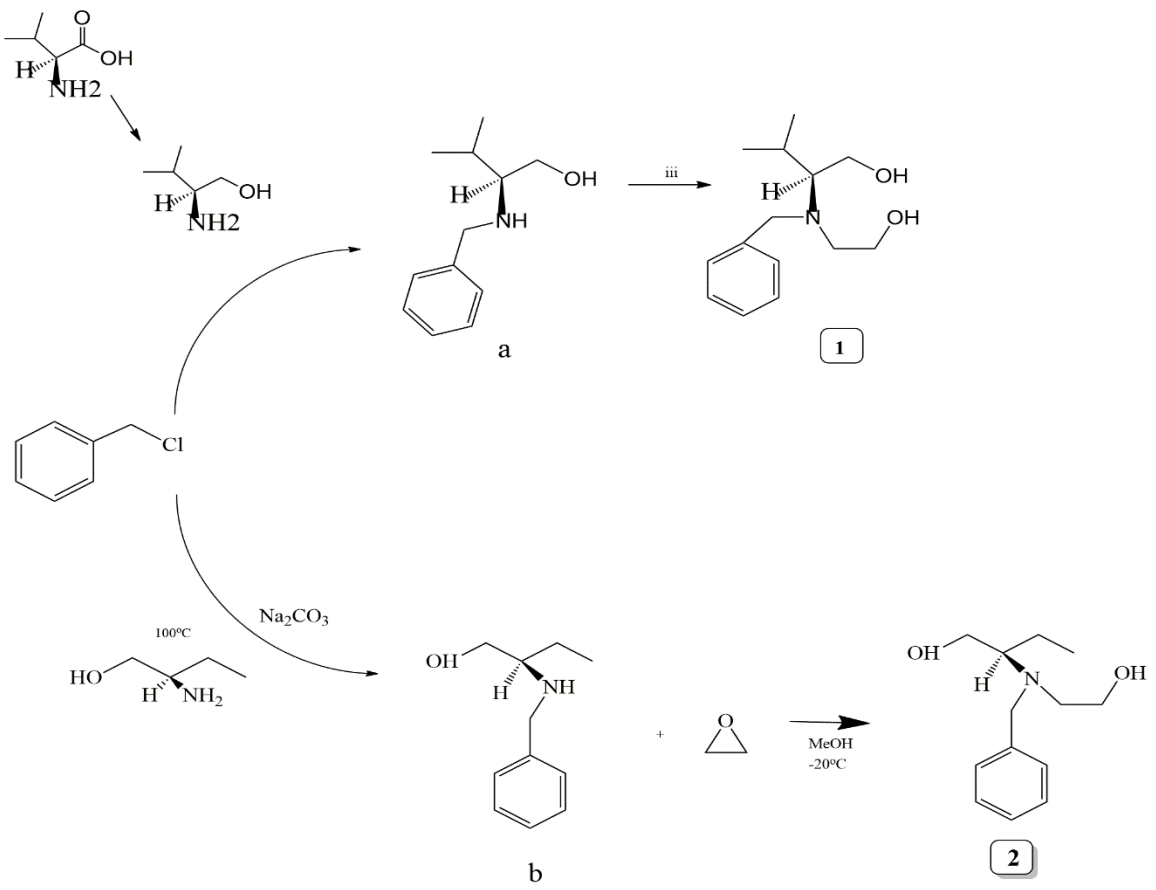
Catalytic Activities of the Chiral Alcohols in Enantioselective Diethylzinc Addition Reactions

Catalytic enantioselective C-C bond formation reactions by adding organozinc compounds to aldehydes in the existence of a chiral ligand are one of the most basic and important research topics of enantioselective synthesis. The asymmetric and catalytic addition of diorganozinc to various aldehydes is an important technique used to prepare optically active chiral secondary alcohols [22]. Chiral secondary alcohols obtained by this method are important components in many commercially important pharmaceutical, fragrance, and pesticide fields.

Since it is a good Lewis acid and can chelate with ligands, element zinc is used most in the diethylzinc addition reaction. Diethylzinc is widely used in asymmetric reactions because it is not as strong a nucleophile as Grignard compounds [23].

Zinc complexes serve as catalysts and amino alcohols as ligands in a large number of systems that have been documented to date [24]. Very good results were obtained by using aminoalcohols in many asymmetric transformations [8].

The accepted mechanism for the chiral induced dialkylzinc additions to carbonyl compounds involves a dinuclear zinc chiral amino alkoxide intermediate 3 (see Fig. 1). This intermediate 3, acts as a Lewis acid to activate the carbonyl substrate, and enhances the nucleophilicity of the alkyl group on the neighbouring zinc reagent.



Scheme-1: Synthesis of chiral alcohols **(1**) and **(2).**

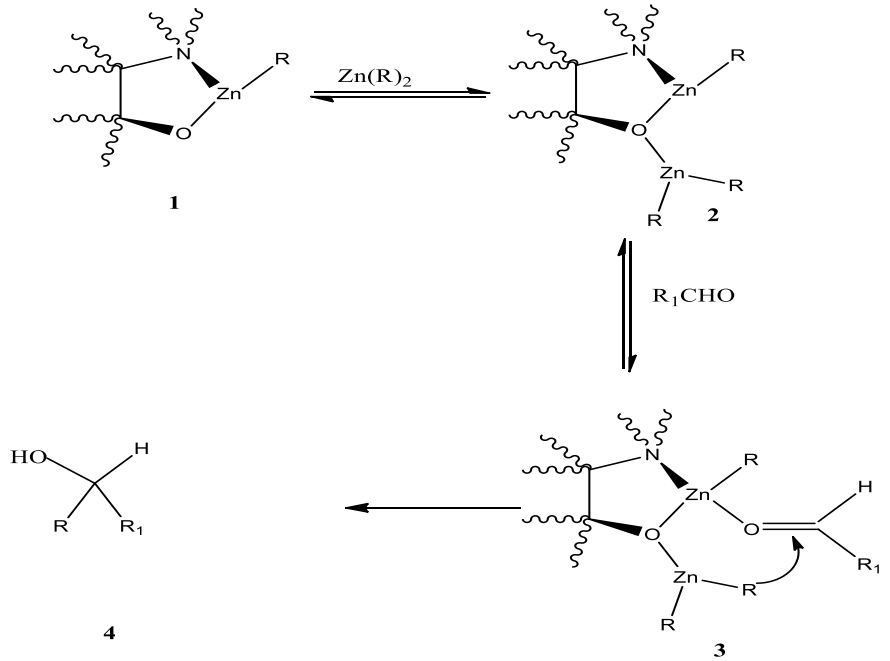


Fig. 1: Proposed mechanism for chiral induced dialkhyldizinc reactions [13].

In this study, the catalytic activities of the two amino alcohols (**1-2**) in the addition reactions of diethylzinc to aldehydes were investigated. Optimization studies for the addition of diethylzinc to benzaldehyde are depicted in Tables 1 and 2. Diethylzinc addition reactions were performed for substituted benzaldehyde derivatives (2-chloro-, 2-NO_2-, 4-NO_2-, 4-chloro-, 4-methyl-, 2-methoxybanzaldehyde) and the results are given in Table 3. The asymmetric diethylzinc addition reaction to benzaldehyde is summarized in Table 1. These reactions were conducted under nitrogen gas and ligands **1** and **2** were used as catalysts to determine the optimum conditions. In the optimum studies using dry dichloromethane as the solvent, several parameters such as temperature, time, and the presence or absence of $Ti(O^iPr)_4$ were studied. Firstly, the reaction was carried out at two different temperatures, 0°C and 25°C, a better conversion was obtained at 0°C in the existence of $Ti(O^iPr)_4$. In another reaction performed under the same conditions except using $Ti(O^iPr)_4$, it was found that there was a higher conversion at 25 °C. It was observed that the change of the alkyl group (R: ethyl or isopropyl) in the ligands had little effect on the conversion and enantiomeric excess (ee) and that ligand **1** gave a slightly better result than ligand **2**. It was shown that the conversion rate increased when the reaction time was extended from 24 to 72 hours. Additionally, when $Ti(O^iPr)_4$ was not used, the enantiomeric excess (ee) ratio was at around 30% and the chiral alcohol formed was in the R form.

Table-1: Temperature test in the diethylzinc addition reaction of benzaldehyde catalyzed by ligands (1) and (2)[a].

Entry	Cat.	$Ti(O^iPr)_4$ (mmol)	Solvent	Temperature (°C)	Time (h)	% Con.[b]	% ee[c]	Conf.
	-	-	CH_2Cl_2	0	24 (72)	<10	-	-
	-	-	CH_2Cl_2	25	24 (72)	<10	-	-
	-	1.4	CH_2Cl_2	0	24 (72)	<10	-	-
	-	1.4	CH_2Cl_2	25	24 (72)	<10	-	-
1	1	1.4	CH_2Cl_2	0	24 (72)	58(60)	<5	*R*
2	2	1.4	CH_2Cl_2	0	24 (72)	55(56)	<5	*R*
3	1	1.4	CH_2Cl_2	25	24 (72)	25(35)	<5	*R*
4	2	1.4	CH_2Cl_2	25	24 (72)	23(33)	<5	*R*
5	1	-	CH_2Cl_2	0	24 (72)	10(10)	35(35)	*R*
6	2	-	CH_2Cl_2	0	24 (72)	10(10)	34(35)	*R*
7	1	-	CH_2Cl_2	25	24 (72)	62(80)	33(33)	*R*
8	2	-	CH_2Cl_2	25	24 (72)	60(78)	32(32)	*R*

Reaction conditions:
[a] Catalyst (0.2 mmol), substrate (1 mmol), diethylzinc (3 mmol), solvent (5 mL), $Ti(O^iPr)_4$ (1.4 mmol),
[b] The purity of the compounds was checked by ^1H NMR and GC (three independent catalytic experiments). % conversions were calculated based on unreacted benzaldehyde.
[c] GC analysis was determined using a chiral cyclodex B (Agilent) capillary column (30 m x 0.32 mm I. D. x 0.25 μm).

Table-2: Solvent tests in the diethylzinc addition reaction of benzaldehyde catalyzed by ligands (1) and (2)[a].

Entry	Cat.	Solvent	Temperature (°C)	Time (h)	% Con.[b]	% ee[c]	Conf.
1	1	CH_2Cl_2	25	24 (72)	62(80)	33(33)	*R*
2	1	Toluene	25	24 (48)	91(96)	37(37)	*R*
3	1	THF	25	24 (72)	16(35)	10(10)	*R*
4	1	Toluene/Hexane (1/1)	25	24 (72)	74(90)	40(40)	*R*
5	1	Ethanol	25	24 (72)	-	-	-
6	2	Toluene	25	24 (48)	89(94)	36(36)	*R*

Reaction conditions:
[a] Catalyst (0.2 mmol), substrate (1 mmol), diethylzinc (3 mmol), solvent (5 mL),
[b] The purity of the compounds was checked by ^1H NMR and GC (three independent catalytic experiments). % conversions were calculated based on unreacted benzaldehyde.
[c] Determined by GC analysis using chiral cyclodex B (Agilent) capillary column (30 m x 0.32 mm I.D. x 0.25 μm)

In the next stage, the effect of solvent on these reactions was investigated. Dry CH_2Cl_2, toluene, THF, toluene/hexane (1/1), and ethanol were chosen as solvents (Table 2). While 80% conversion and 33% ee were obtained in 72 hours when CH_2Cl_2 was used, 35% conversion and 10% ee were obtained in 72 hours with THF. While the toluene/hexane (1/1) mixture provided 90% conversion and 40% ee in 72 hours, no significant transformation was obtained in the reaction performed in ethanol until 72 hours. When toluene was used as the reaction solvent, 91% conversion in 24 hours, 96% conversion in 48 hours, and 37% ee were obtained. In addition, the shorter duration compared to other solvents was also considered an advantage. Since toluene was found to provide the highest conversion among these solvents, when the reaction in toluene was repeated with 2 ligands, 94% conversion and 36% ee were obtained in 48 hours.

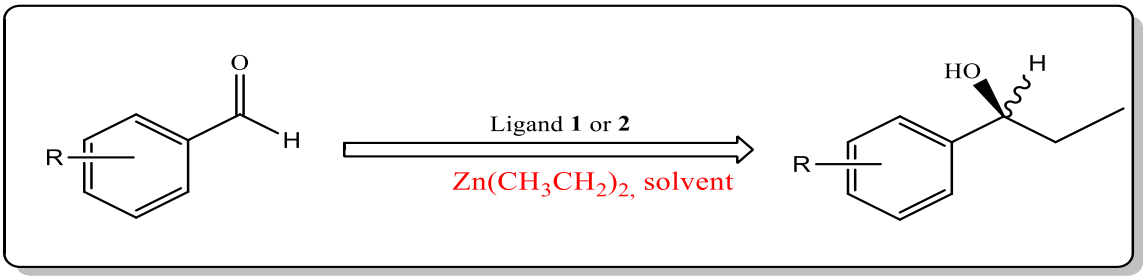
The results obtained by using two ligands (**1-2**) as catalysts in the asymmetric diethylzinc addition reactions of substituted benzaldehyde are summarized

in Table 3. An important finding obtained from the tables is that activity and enantioselectivity also depend on the position and electronic properties of the substituents attached to the phenyl group. As a result of the reaction catalyzed by ligand **1**, 93% conversion and 35% ee were obtained in 24 hours when 4-Cl was substituted to benzaldehyde, while 90% conversion and 32% ee were obtained when 2-Cl was substituted. The data obtained when 4-NO_2 and 2-NO_2 are substituted to benzaldehyde are shown in the table. When 4-Me was substituted to benzaldehyde, 80% conversion and 29% ee were obtained in 24 hours, while when 2-OMe was substituted, 70% conversion and 40% ee were obtained. As seen in the table, similar results were obtained in reactions catalyzed by two ligands.

Conclusions

In conclusion, the catalytic activities of the two amino alcohols (**1**-**2**) were investigated in the addition reactions of diethylzinc to aldehydes. For this purpose, benzaldehyde was first selected as the substrate for establishing the optimal conditions of the catalytic reaction. In the optimum studies using dry dichloromethane as the solvent, firstly the temperature, time, and the presence or absence of $Ti(O^iPr)_4$ were studied. The effectiveness of these amino alcohols in the diethylzinc addition reaction to benzaldehyde under the optimum conditions was determined as 96% conversion and 40% ee.

Table-3: Diethylzinc addition to substituted benzaldehydes catalyzed by ligands (1) and (2)[a].



Entry	R	Time	% Con.[b]	% ee[c]
Catalyst, **1**				
1	H	24 h	91	37
2	4-Cl	24 h	93	35
3	2-Cl	24 h	90	32
4	4-Me	24 h	80	29
5	2-MeO	24 h	75	24
6	4-NO_2	24 h	90	33
7	2-NO_2	24 h	70	40
Catalyst, **2**				
8	H	24 h	89	36
9	4-Cl	24 h	91	33
10	2-Cl	24 h	88	30
11	4-Me	24 h	78	29
12	2-MeO	24 h	72	26
13	4-NO_2	24 h	90	34
14	2-NO_2	24 h	68	38

Reaction conditions:
[a] Catalyst (0.2 mmol), substrate (1 mmol), diethylzinc (3 mmol), solvent (5 mL),
[b] The purity of the compounds was checked by ^{1}H NMR and GC (three independent catalytic experiments). % conversions were calculated based on unreacted benzaldehyde.
[c] Determined by GC analysis using chiral cyclodex B (Agilent) capillary column (30 m x 0.32 mm I.D. x 0.25 μm). The (R) configuration was obtained in all experiments.

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