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An efficient method for catalytic enantioselective addition of diethylzinc to aryl aldehydes by a C_2 -symmetric chiral imino alcohol

Peyman Salehi^{a,*}, Minoo Dabiri^{b,*}, Gholamreza Kozehgary^b, Mostafa Baghbanzadeh^b

^a Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran ^b Department of Chemistry, Faculty of Science, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran

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ABSTRACT

The enantioselective alkylation of aryl aldehydes with diethylzinc in the presence of a C_2 -symmetric chiral ligand derived from 2-hydroxy-3-pinanone was achieved at room temperature with high enantiomeric excesses.

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1. Introduction

In recent years, considerable attention has been devoted to the formation of chiral C–C bonds. Among the existing methods, the addition of dialkylzinc to aldehydes or ketones is one of the most convenient.¹

The chiral ligands for this purpose mainly include amino alcohol derivatives such as acyclic amine-based amino alcohols,^{2,3} cyclic amine-based amino alcohols,⁴ pyridyl alcohols,⁵ carbohydrate-based amino alcohols,⁶ ferrocene-based amino alcohols,⁷ and sulfonamide alcohols.⁸

Despite the great number of chiral amino alcohols used for the enantioselective addition of dialkylzinc to aldehydes, only a few examples have so far been reported for the application of chiral imino alcohol ligands in these reactions.⁹ Although some of these chiral imino alcohol ligands induce the addition of diethylzinc to different aldehydes with notable results, the enantiomeric excesses of the alcohols with non-Schiff base chiral imino alcohol ligands are consistently lower than their Schiff base counterparts.^{9a} Thus, a continuation of efforts in this area, aimed at narrowing the gap between these two forms, is fully warranted.

Herein, we report the application of a C_2 -symmetric chiral imino alcohol ligand derived from ethylenediamine and 2-hydroxy-3-pinanone in diethylzinc addition to aromatic aldehydes. A substantial advantage of this ligand is that it is inexpensive, stable in air and can be prepared in large quantities without any special precaution.

2. Results and discussion

Ligand **3** was synthesized by the reaction of 2-hydroxy-3-pinanone with ethylenediamine in the presence of 2 mol % of BF₃·Et₂O in dry toluene (Scheme 1).¹⁰

We examined the reaction of diethylzinc and benzaldehyde in the presence of catalytic amounts of chiral ligand **3** (Scheme 2). The results are summarized in Table 1.

The reaction was performed using 10 mol % of the chiral catalyst **3** in toluene at -10 °C with 120 mol % of Ti(OⁱPr)₄. The addition of titanium isopropoxide has been reported to increase the ee in many cases.⁹ However, in our experiments, treatment of **3** with titanium isopropoxide led to a significant decrease in the enantioselectivity (Table 1, entry 1). Therefore further reactions were carried out in



Scheme 1. Synthesis of chiral ligand 3.

* Corresponding authors. Fax: +98 21 22431783 (P.S.).

E-mail addresses: p-salehi@sbu.ac.ir (P. Salehi), m-dabiri@sbu.ac.ir (M. Dabiri).

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Scheme 2.

Table 1

Enantioselective addition of Et_2Zn to C_6H_5CHO catalyzed by chiral catalyst **3** under different conditions

Entry	Mol % of ligand	T (°C)	Time (h)	Yield ^a (%)	ee ^{b,c} (%)
1 ^d	10	-10	24	38	8
2	10	-10	24	67	99
3	5	-10	24	71	99
4	1	-10	24	12	0
5	5	+5	20	73	99
6	10	+5	20	73	99
7	5	rt	20	74	99

^a GC yield of the mixture of the two enantiomers.

^b ee was determined by GC using a chiral capillary column (HP-Chiral).

^c The absolute configuration of the major enantiomer was determined by comparison with an authentic sample. The major enantiomer in all cases had an (R)configuration.

^d With 120 mol % of Ti(OⁱPr)₄.

the absence of $Ti(O^iPr)_{4.}$ The amount of the catalyst and reaction temperature was optimized in subsequent reactions. As shown in Table 1, the best result (74% yield and 99% ee) was obtained when 5 mol % of **3** was used at room temperature (Table 1, entry 7).

After optimizing the best conditions for the reaction of diethylzinc with benzaldehyde, we applied the same conditions to other aromatic aldehydes. The results for the addition of diethylzinc in the presence of **3** are summarized in Table 2.

For the substituted aromatic aldehydes as shown in Table 2, high ees were obtained. In general, the introduction of substituents at the *ortho*-position led to a slight decrease in the enantioselectivity. The best enantioselectivity of up to 98% was obtained with *p*-fluorobenzaldehyde (Table 2, entry 1).

3. Conclusion

In conclusion, we have shown that imino alcohol **3**, which is easily prepared from the reaction of 2-hydroxy-3-pinanone with ethylenediamine can be successfully used as a ligand in the high yield enantioselective addition of diethylzinc to aryl aldehydes. The method offers the use of a cheap and stable ligand in compar-

Table 2

Enantioselective addition of diethylzinc to aromatic aldehydes by chiral imino alcohol ${\bf 3}^{\rm a}$

Entry	Aldehyde	Yield ^b (%)	ee ^{c,d} (%)
1	p-FC ₆ H ₄ CHO	98	98
2 ^e	p-FC ₆ H ₄ CHO	98	94
3	p-ClC ₆ H ₄ CHO	100	92
4	p-BrC ₆ H ₄ CHO	98	93
5	p-MeC ₆ H ₄ CHO	100	95
6 ^e	p-MeC ₆ H ₄ CHO	100	92
7	p-MeOC ₆ H ₄ CHO	100	91
8	o-MeOC ₆ H ₄ CHO	94	72
9	o-ClC ₆ H ₄ CHO	81	71

^a Condition: rt, 20 h and 5 mol % of **3**.

^b Measured as conversion% by GC.

^c Determined by capillary chiral GC analysis using a chiral column (HP-chiral).

^d The absolute configuration was determined by comparing the sign of specific rotation.¹¹ The major enantiomer in all cases had an (*R*)-configuration.

^e With 10 mol % of **3**.

ison with previous imino alcohols⁹ that have been used for this purpose.

4. Experimental

4.1. General

Mass spectra were recorded on a FINNIGAN-MAT8430 mass spectrometer operating at an ionization-potential of 70 eV. Elemental analysis was performed using a Gmbh varioEL instrument. IR spectra were recorded on KBr pellets on a Nicolet Impact 400D spectrophotometer. Conversions were determined with a Hewlett– Packard HP-5890 GC instrument equipped with a flame ionization detector and a 30 m HP-1 capillary column, using nitrogen (2 mL/ min) as carrier gas. The enantiomeric ratios were determined with the aforementioned apparatus using a 30 m WCOT-fused silica capillary column (HP-chiral). ¹H and ¹³CNMR spectra were determined on a Bruker 300 DRX Avance instrument at 300.13 and 75.47 MHz, respectively.

4.2. (15,1'*S*,2*S*,2'*S*,3*E*,3'*E*,5*S*,5'*S*)-3,3'-(Ethane-1,2-diylbis(azan-1-yl-1-ylidene))bis(2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol) 3

To a solution of (15,25,55)-(-)-2-hydroxypinan-3-one (1.0 equiv)in dry toluene (20 mL) was added 2 mol % of BF₃·Et₂O and ethylenediamine (0.5 equiv). After heating at reflux for 18 h (TLC monitoring) with stirring, the solvent was distilled off under vacuum and the residue was purified by recrystallization from *n*-heptane to give 70% yield of the ligand **3** as a colorless solid. 70% Yield as colorless crystals; IR (KBr) 3340, 2909, 1647, 1390, cm⁻¹; Ms (EI) 361 (M⁺⁺1, 60), 343 (32), 289 (19), 195 (25), 71 (41), 43 (100); ¹H NMR (CDCl₃) δ 0.81 (6H, s), 1.28 (6H, s), 1.42 (6H, s), 1.52–1.56 (2H, m), 2.00– 2.02 (4H, m), 2.25–2.31 (2H, m), 2.55 (4H, s), 3.25 (2H, br s), 3.56 (4H, m); ¹³C NMR (CDCl₃) δ 176.4, 51.3, 50.4, 38.39, 38.32, 33.7, 28.2, 28.1, 27.3, 22.89, 22.82 (C₂₂H₃₆N₂O₂ requires: C, 73.3; H, 10.0; N, 7.7. Found: C, 73.6; H, 10.0; N, 7.7).

4.3. General procedure for the enantioselective addition of diethylzinc to aryl aldehydes

The ligand (0.055 mmol) was placed in a test tube and dissolved in dry toluene (2 mL). The solution was stirred for 5 min. A 1.0 M solution of diethylzinc in *n*-hexane (2.2 mmol, 2.2 mL) was then added, and after the mixture was stirred for 5 min, a solution of the aldehyde (1.11 mmol) in dry toluene (1 mL) was added by a syringe. The mixture was stirred at the appropriate temperature, for the time reported in Table 1. Saturated aqueous NH₄Cl was added (10 mL) and the mixture was extracted with ethyl acetate (3 × 20 mL). The collected organic phases were washed with water, dried over Na₂SO₄, and analyzed by GC, after suitable dilution.

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