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The synthesis of a novel non-C_2 symmetric H_4-BINOL ligand and its application to titanium-catalyzed enantioselective addition of diethylzinc to aldehydes

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Abstract

The synthesis of the novel non-C_2 symmetric ligand (*R*)-5,6,7,8-tetrahydro-1,1′-binaphthol has been achieved via partial reduction of 2,2′-bis(methoxymethoxy)-1,1′-binaphthyl with Raney Ni–Al alloy in dilute aqueous NaOH solution followed by hydrolysis with HCl. Its titanium complex was found to be an effective catalyst in the asymmetric addition of diethylzinc to a variety of aldehydes, leading to the formation of secondary alcohols in high yields with good to excellent enantioselectivities. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically active 1,1′-bi-2-naphthol (BINOL, **1**) and its derivatives have been successfully applied as chiral ligands of effective catalysts for many asymmetric reactions.[1] Very recent research has shown that the chiral catalysts derived from 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthyl ligands exhibited higher efficiency and enantioselectivity for many asymmetric reactions than those obtained from their parent ligands, due to the steric and electronic modulations in the binaphthyl backbone.[2] We have recently developed a convenient protocol for the preparation of octahydrobinaphthyls through the partial reduction of corresponding binaphthyls with Ni–Al alloy in dilute aqueous alkaline solution.[3] However, the reduction of enantiopure BINOL undergoes partial racemization and 91.8–97.5% enantiomeric excesses of H_8-BINOL **2** were obtained. In order to prevent the racemization in the course of the reduction, the OH groups of BINOL were protected with methoxymethyl chloride. However, the reduction of protected BINOL (2,2′-bis(methoxymethoxy)-1,1′-binaphthyl, MOM-BINOL, **4**) with Ni–Al alloy did not produce the octahydro-1,1′-binaphthyl derivative but resulted in the formation of

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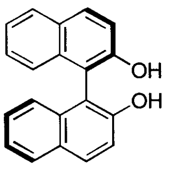
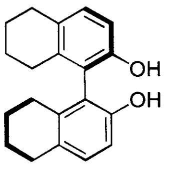
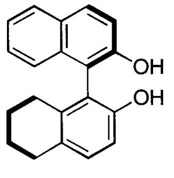
the 5,6,7,8-tetrahydro derivative of MOM-BINOL in high yield, which gave 5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (H_4-BINOL, **3**) upon hydrolysis with HCl without any racemization. In the present work, we report the details on the synthesis of this novel non-C_2 symmetric H_4-BINOL ligand and the enantioselective addition of diethylzinc to aldehydes with the catalysis of its titanium complex.



(*R*)--**BINOL 1**



(*R*)-H_8-**BINOL 2**

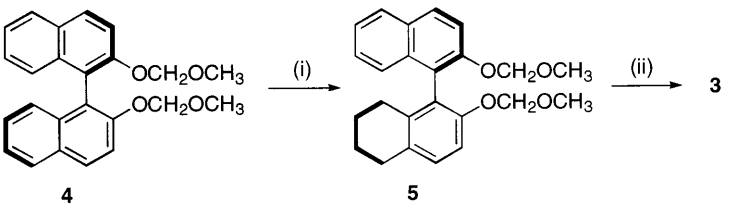


(*R*)-H_4-**BINOL 3**

2. Results and discussion

2.1. Synthesis of the H_4-BINOL 3

As described in the introduction, the reduction of BINOL (**1**) with Raney Ni–Al alloy in aqueous dilute alkaline solution proceeded with partial racemization, which was probably caused by the racemization of starting material under the basic conditions because ditetrallyl units are more configurationally stable than binaphthyl units.[4] Therefore the protection of acidic OH groups in the BINOL molecule should be a convenient way of avoiding the racemization process. As methoxymethyl is a good protecting group under alkaline conditions and is readily removed under acidic conditions, we investigated the possibility of the reduction of methoxymethyl derivative **4** of BINOL under the experimental conditions mentioned above. The MOM-protected BINOL **4** was prepared according to a literature procedure in 95% yield.[5] As shown in Scheme 1, the reduction of **4** was carried out in aqueous alkaline solution using Ni–Al alloy as reducing reagent. The addition of isopropanol to the reaction mixture enhances the solubility of **4** and as a result facilitates the conversion of starting material. Under the optimized reaction conditions, the conversion of starting material was completed in 24 h. Reduction product **5** was separated in 85% yield through column chromatographic purification using ethyl acetate/hexane (1:7) as eluent. Contrary to our expectations, the ^{1}H NMR spectrum of **5** showed that the ratio of aromatic protons to alkyl protons is 8:8 rather than the expected value of 4:16 for octahydrobinaphthyl derivatives. Meanwhile, two methoxymethyl groups obviously exhibited different chemical shifts, which demonstrated the non-C_2 symmetry of compound **5**. The molecular ion peak of 378 in the mass spectrum of **5** indicated that only one naphthyl ring was



Scheme 1. Synthesis of (*R*)-H_4-BINOL (**3**). (i) Raney Ni–Al alloy, NaOH, H_2O/^{i}PrOH, 80°C, 85% yield; (ii) HCl, MeOH, 99% yield

reduced and the ^{13}C NMR spectrum (16 aromatic carbons) further confirmed the non-C_2 symmetric structure of 2,2′-bis(methoxymethoxy)-5,6,7,8-tetrahydro-1,1′-binaphthyl **5**. Hydrolysis of **5** gave 5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (H_4-BINOL, **3**) in 99% yield with >99% enantiomeric excess. So far, a novel non-C_2 symmetric diol ligand **3** has been successfully prepared in 80% overall yield from **1**.

2.2. Asymmetric induction of H_4-BINOL in Ti complex catalyzed enantioselective addition of diethylzinc to aldehydes

Enantioselective addition of organozinc reagents to aldehydes constitutes one of the most important and fundamental asymmetric reactions.[6] Recently titanium complexes of BINOL and H_8-BINOL were reported to be effective catalysts for the enantioselective addition of diethylzinc to aldehydes by Chan et al. and Nakai et al., respectively.[7] With the novel non-C_2 symmetric H_4-BINOL ligand in hand, we then examined its asymmetric induction in titanium complex catalyzed enantioselective additions of diethylzinc to aldehydes. Benzaldehyde was taken as the substrate for optimizing the reaction conditions and comparing the asymmetric induction efficiency of **1** and **3**. As shown in Table 1, the molar ratio of **3**/$Ti(OR)_4$/$ZnEt_2$/benzaldehyde was set up to be 0.2:1.4:3:1. It was found that the reaction temperature has a slight influence on the enantioselectivity of the reaction but it affects the reactivity significantly (entries 1–3). The ee values of product obtained over a temperature range from 0 to −50°C varied from 90.7 to 91.5%. The enantioselectivity of the reaction with the catalysis of the H_4-BINOL–Ti complex is higher than that obtained using BINOL as a chiral inducer (entry 1 versus entry 4) under the same experiment conditions, but is slightly lower than the case using H_8-BINOL (entry 1 versus entry 5). The order of asymmetric induction efficiency (BINOL<H_4-BINOL<H_8-BINOL) may be attributed to the change of dihedral angle in the binaphthyl moiety after partial reduction,

Table 1
Optimization of reaction conditions for enantioselectivity of the addition of Et_2Zn to benzaldehyde[a]

Entry	Temp. (°C)	$Ti(OR)_4$	Time (h)	Ee (%)[b]	Yield (%)[c]
1	0	$Ti(OPr^i)_4$	5	90.7	96
2	−20	$Ti(OPr^i)_4$	7	90.9	90
3	−50	$Ti(OPr^i)_4$	8	91.5	60
4[d]	0	$Ti(OPr^i)_4$	5	86.8	92
5[e]	0	$Ti(OPr^i)_4$	5	93.2	93
6	0	$Ti(OBu^n)_4$	5	72.2	50
7	0	$Ti(OBu^t)_4$	5	81.5	89

[a] The reactions were carried out in dichloromethane/hexane mixed solvent at 0°C; (*R*)-H_4-BINOL/$Ti(O^iPr)_4$/$ZnEt_2$/benzaldehyde = 0.2:1.4:3:1.

[b] Determined by HPLC on a Chiralcel OD column. The absolute configuration of 1-phenyl-1-propanol is *R*.

[c] Isolated yield.

[d] (*R*)-BINOL was used instead of (*R*)-H_4-BINOL. Under the same experimental conditions, 91.9% ee of the 1-phenylpropanol was obtained by Chan.[7a] However, the best asymmetric induction with BINOL–Ti was reported to be 85% ee by Nakai.[7b]

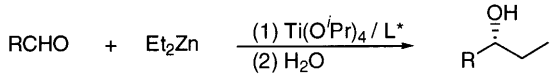
[e] (*R*)-H_8-BINOL was used instead of (*R*)-H_4-BINOL. Under the same experimental conditions, 97.6% ee of the 1-phenylpropanol was obtained by Chan.[7c]

which accordingly influence the bite angle of the Ti catalysts. Because a large excess of titanium tetraisopropoxide was required to render the reaction efficiently catalytic in such a reaction system,[7b] we investigated the effect of titanium alkoxide on the enantioselectivity and reactivity of the reaction. Among several titanium alkoxides investigated, titanium isopropoxide is the best in terms of both ee and yield of the product (entries 1, 6 and 7).

As shown in Table 2, the catalyst derived from H_4-BINOL **3** was found to be effective for the ethylation of a variety of aldehydes including aromatic, α,β-unsaturated and aliphatic aldehydes. Up to 93.3% enantiomeric excess of product was obtained when α-naphthylaldehyde was used as the substrate (entry 7). Under the same experimental conditions, the H_4-BINOL–Ti complex showed higher enantioselectivities for all substrates than the BINOL–Ti complex. Therefore, the loss of the C_2 symmetry in **4** did not show any observed negative effect on the enantioselectivity of the reaction. The steric and electronic modulations in the binaphthyl backbone again proved to be key point for achieving better enantioselectivity of reaction.

In conclusion, a novel non-C_2 symmetric ligand (*R*)-5,6,7,8-tetrahydro-1,1′-binaphthol **3** has been synthesized through partial reduction of 2,2′-bis(methoxymethoxy)-1,1′-binaphthyl with Raney Ni–Al alloy in dilute aqueous NaOH solution followed by hydrolysis with HCl. Its titanium complex was found to be an effective catalyst in the asymmetric addition of diethylzinc to a variety of aldehydes, leading to the formation of secondary alcohols in high yields with good to excellent enantioselectivities.

Table 2
Asymmetric addition of diethylzinc to various aldehydes with the catalysis of the (*R*)-H_4-BINOL–Ti complex[a]



Entry	R	Ee (%)[b]	Yields (%)[d]	Configuration[e]
1	Phenyl	90.7 (86.8)	96 (94)	*R*
2	*o*-Anisyl	87.0 (80.0)	94 (92)	*R*
3	*m*-Anisyl	88.4 (81.4)	95 (95)	*R*
4	*p*-Anisyl	89.6 (81.3)	95 (96)	*R*
5	*m*-Tolyl	86.5 (78.6)	92 (92)	*R*
6	*p*-Chlorophenyl	91.1 (84.4)	96 (97)	*R*
7	α-Naphthyl	93.3 (88.0)	97 (96)	*R*
8	β-Naphthyl	75.4 (55.0)	92 (93)	*R*
9	Ferrocenyl	67.9 (58.5)	75 (78)	*R*
10	*trans*-Styryl	76.1 (70.3)	90 (90)	*R*
11	*n*-Hexyl	86.5[c] (82.9)	60 (75)	n.d.

[a] The reactions were carried out in dichloromethane/hexane mixed solvent at 0°C; (*R*)-H_4-BINOL/$Ti(O^iPr)_4$/$ZnEt_2$/substrate = 0.2:1.4:3:1.

[b] Determined by HPLC on Chiralcel OD, OD-H or OB-H columns. The ee values shown in parenthesis were obtained by the catalysis of (*R*)-BINOL–Ti complex.

[c] Determined by GC on a chiral B-PH capillary column.

[d] Isolated yields. The yields shown in parenthesis were obtained by the catalysis of (*R*)-BINOL–Ti complex.

[e] The configuration was determined on the basis of optical rotation.

3. Experimental

3.1. General considerations

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM 400 instrument. Chemical shifts were expressed in ppm with tetramethylsilane as an internal standard ($\delta=0$ ppm) for ^{1}H NMR and with the residual signal of $CDCl_3$ as an internal standard ($\delta=77.0$ ppm) for ^{13}C NMR. Optical rotation was measured with a PE 341 automatic polarimeter. Liquid chromatographic analyses were conducted on a Jasco 1580 system. Mass spectra were obtained on a HP5989A spectrometer. Elemental analysis was performed with an elemental Vario EL apparatus. All experiments which are sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Benzaldehyde was distilled before use. Dichloromethane and THF were freshly distilled from calcium hydride and sodium benzophenone ketyl, respectively. Racemic BINOL **1** was prepared and resolved according to the reported procedures[8] and its transformation to the methoxymethyl derivative **4** was carried out following the literature method.[5]

3.2. Synthesis of 2,2′-bis(methoxymethoxy)-5,6,7,8-tetrahydro-1,1′-binaphthyl **5**

A 500 mL flask was charged with Ni–Al alloy (3.5 g), water (130 mL), and **4** (0.37 g) in 70 mL of isopropanol, to which aqueous NaOH solution (1%, 200 mL) was gradually added over 4 h with continuous stirring at 80°C. The reaction process was monitored by TLC. After stirring at 80°C for 24 h, the reaction mixture was cooled to room temperature. The insoluble materials were filtered off through Celite and the solids were washed with ethyl acetate. The filtrate was extracted with ethyl acetate (3×80 mL) and the organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was submitted to column chromatographic separation on silica gel with hexane/ethyl acetate (7:1) as eluent to give (*R*)-H_4-BINOL-MOM (318 mg, 85% yield) as a colorless oil with >99% ee (determined by HPLC on an AD column with hexane/isopropanol (100:2) as eluent, 0.7 mL min^{-1}, $t_S=10.49$ min, $t_R=11.72$ min). $[\alpha]_D^{25}=+64.3$ ($c=0.99$, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.80 (m, 2H), 7.50 (d, 1H, $J=9.1$ Hz), 7.35–7.24 (m, 3H), 7.13 (d, 1H, $J=8.4$ Hz), 7.03 (d, 1H, $J=8.5$ Hz), 5.16 (d, 1H, $J=6.7$ Hz), 5.07 (d, 1H, $J=6.7$ Hz), 4.91 (d, 1H, $J=6.6$ Hz), 4.82 (d, 1H, $J=6.6$ Hz), 3.33 (s, 3H), 3.07 (s, 3H), 2.81 (t, 2H, $J=6.3$ Hz), 2.33–2.26 (m, 1H), 2.09–2.02 (m, 1H), 1.73–1.69 (m, 2H), 1.61–1.53 (m, 2H). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ 153.0, 151.8, 138.0, 134.0, 133.4, 131.0, 130.0, 129.6, 128.9, 128.0, 127.8, 126.5, 125.1, 124.0, 117.3, 113.0, 95.4, 94.8, 56.0, 55.6, 29.5, 27.2, 23.2, 23.1. EIMS (m/z): 378 (M^+, 31%), 302 (base peak).

3.3. Synthesis of (R)-5,6,7,8-tetrahydro-1,1′-binaphthol **3**

To a solution of (*R*)-H_4-BINOL-MOM (**5**) (165 mg) in 10 mL of CH_3OH, several drops of concentrated HCl (aq.) were added and the mixture was heated with stirring at 40°C for 30 min. After removing the solvent, the resulting residue was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica gel with hexane/EtOAc (4:1) to give (*R*)-H_4-BINOL **3** as a white solid (126 mg, 99% yield) with >99% ee (determined by HPLC on a Chiralcel AS column with

95:5 *n*-hexane/isopropanol as eluent, 0.7 mL min^{-1}, $t_S = 10.76$ min, $t_R = 12.03$ min). Mp 131–133°C; $[\alpha]_D^{25} = +40.4$ (*c* = 0.98, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 2H), 7.29–7.15 (m, 4H), 7.04 (m, 1H, *J* = 8.4 Hz), 6.79 (d, 1H, *J* = 8.3 Hz), 5.11 (s, 1H), 4.45 (s, 1H), 2.70 (t, 2H, *J* = 6.2 Hz), 2.22–2.14 (m, 1H), 2.04–2.00 (m, 1H), 1.67–1.50 (m, 4H). ^{13}C NMR (100.6 Hz, $CDCl_3$) δ 152.3, 151.9, 138.4, 131.5, 131.4, 131.0, 130.9, 130.3, 129.4, 128.4, 127.5, 127.4, 123.9, 123.8, 117.6, 113.3, 29.3, 27.1, 23.0, 22.9. EIMS (m/z): 290 ([M]$^+$, 100%). Anal. calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25%. Found: C, 82.78; H, 6.41%.

3.4. A typical procedure for the asymmetric addition of diethylzinc to benzaldehyde

Titanium tetraisopropoxide (60 μL, 0.175 mmol) was added to a solution of (*R*)-H_4-BINOL (**3**) (7.2 mg, 0.025 mmol) in 1 mL of dichloromethane at room temperature and was stirred for 15 min followed by the addition of diethylzinc (1.0 M, 0.375 mL) in hexane with continued stirring for 15 min. The solution was cooled to 0°C and benzaldehyde (13 μL, 0.125 mmol) was introduced with a microsyringe. The reaction mixture was stirred at 0°C for 5 h. The reaction was quenched with 2 mL of saturated NH_4Cl solution, the mixture was then filtered through Celite to remove the insoluble material and the filtrate was extracted with 3×20 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to solvent free. The residue was purified by column chromatography on silica gel affording 1-phenyl-1-propanol as a colorless liquid. The enantiomeric excess of product was determined by HPLC on a Chiralcel OD column or by GC on a B-PH capillary column.

Acknowledgements

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