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The Application of Chiral Aminonaphthols in the Enantioselective Addition of Diethylzinc to Aryl Aldehydes

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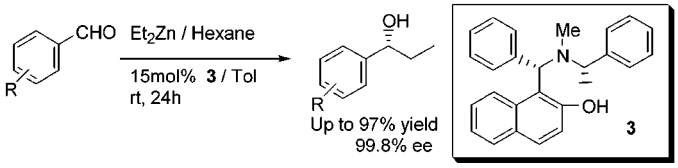
ABSTRACT



Optically active aminonaphthol 3 obtained by condensation of 2-naphthol, benzaldehyde, and (*S*)-methylbenzylamine followed by N-methylation was found to catalyze the enantioselective ethylation of aryl aldehydes to secondary alcohols with high enantioselectivities (up to 99.8%) at room temperature.

Catalytic asymmetric carbon−carbon bond formation is one of the most active research areas in organic synthesis.[1] In this field, asymmetric additions of diethyl zinc (Et_2Zn) to aldehydes using catalytic amount of chiral catalysts have attracted much attention.[2] Numerous efforts of using chiral ligands such as β-amino alcohols,[3] amino thiols,[4] pyridyl alcohols,[5] amines,[6] aminonaphthol,[7] *o*-hydroxylbenzylamines,[8] BINOL,[9] and metal complexes of them have been reported.[10] The racemic aminonaphthol synthesized from condensation of 2-naphthol with benzaldehyde and alkylamine must be resolved through its diastereoisomeric tartaric acid salts to obtain the optically active form.[7] A practical asymmetric synthesis of optically pure aminonaphthols is a challenging endeavor.

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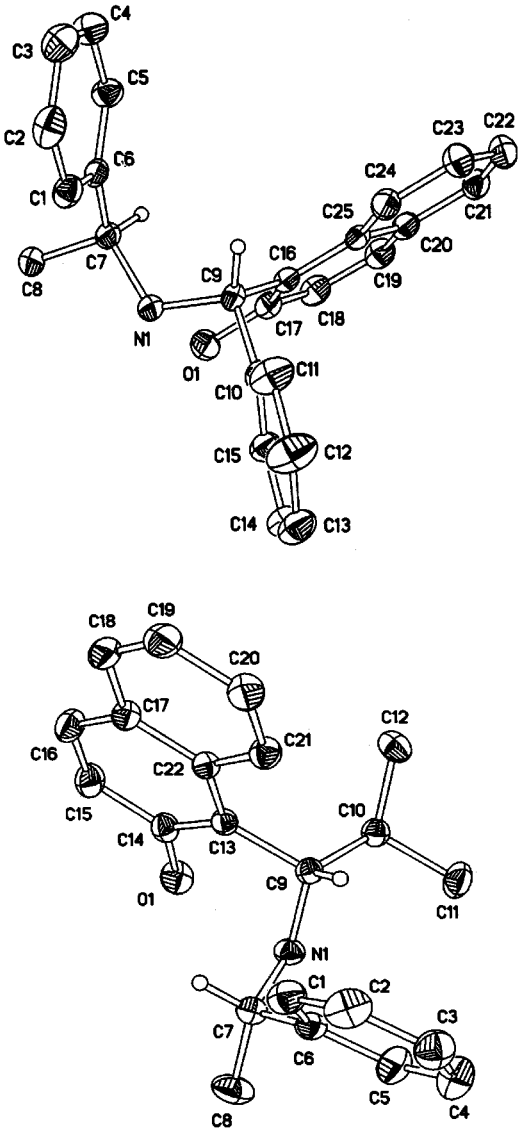
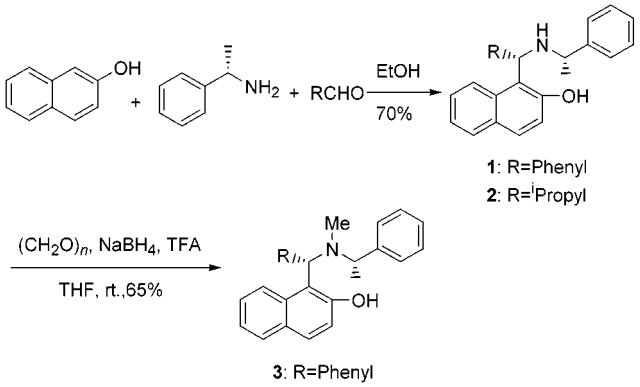


Figure 1.

In this paper, we wish to report the application of optically active aminonaphthols **1**−**3** in enantioselective additions of diethylzinc to arylaldehydes. Optically active aminonaphthols **1** and **2** can be obtained by a simple and straightforward one-pot condensation of the corresponding benzaldehyde and isobutyric aldehyde with 2-naphthol and (*S*)-(−)-methylbenzylamine.[11] The S configuration of the α carbon is proved by X-ray single-crystal analysis (Figure 1). Ligand **3** was synthesized from the reaction of **1** with paraformaldehyde and $NaBH_4$ catalyzed by TFA.[12]

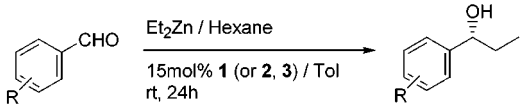
The relevant results of the enantioselective addition of Et_2Zn to aromatic aldehydes[13] in Table 1 showing the highest

Scheme 1



ee values (99.8%) were obtained with the tertiary aminonaphthol **3**.

Table 1. Diethyl Zinc Addition to Aldehydes in the Presence of Chiral Aminonaphthols



entry	cat.	R	yield (%)[a]	ee (%)[b]	config[c]
1	**1**	H	97	72	*R*
2	**1**	*p*-Me	90	92	*R*
3	**1**	*p*-OMe	87	80	*R*
4	**1**	*p*-Cl	88	87	*R*
5	**1**	*m*-Me	82	85	*R*
6	**1**	*o*-OMe	86	65	*R*
7	**1**	*m*-OMe	70	84	*R*
8	**2**	H	96	33	*R*
9	**2**	*p*-Me	91	46	*R*
10	**2**	*p*-OMe	89	46	*R*
11	**2**	*p*-Cl	86	28	*R*
12	**2**	*m*-Me	84	30	*R*
13	**2**	*o*-OMe	88	32	*R*
14	**2**	*m*-OMe	76	23	*R*
15	**3**	H	95[d]	99.4	*R*
16	**3**	*p*-Me	96[d]	99.8	*R*
17	**3**	*p*-OMe	97[d]	52	*R*
18	**3**	*p*-Cl	98[d]	96	*R*
19	**3**	*p*-NO_2	86[d]	99.8	*R*
20	**3**	*m*-Me	96[d]	91	*R*

[a] Isolated yields. [b] Determined by chiral HPLC (Chiralcel OD). [c] Configuration of the predominant enantiomer of the product. [d] Determined by HPLC analysis.

In summary, the main distinctive features of these aminonaphthols are represented by an economical and simple

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(11) **1-((*S*)-Phenyl(((1′*S*)-1′-phenylethyl)amino)methyl)-2-naphthol (1).** Benzaldehyde (1.11 g, 10 mmol) was added to a solution of 2-naphthol (1.00 g, 7.00 mmol) in 2 mL of ethanol. (*S*)-(−)-Methylbenzylamine (0.85 g, 7.00 mmol) was added dropwise to this solution with cooling to 0 °C. The mixture was stirred at room temperature for 6 days. The precipitate was recrystallized in methanol/acetone(3:1) after removal of ethanol in reduced pressure. A prism crystal was obtained (1.73 g, 70%, 98% ee

asymmetric synthesis, involving cheap starting materials, which merge to give a more complex compound without side-products.

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Supporting Information Available: Detail spectra and crystal data for ligands **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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determined by HPLC analysis using Chiralcel OD column): mp 147−148 °C; IR (KBr) 3311, 1621, 1236, 1095, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, 3H, $J = 6.7$ Hz), 1.53 (br s, 1H), 3.93 (q, 1H, $J = 6.7$ Hz), 5.49 (s, 1H), 7.24−7.79 (m, 16H); MS (M + 1) 354.12. **1-((*S*)-Propyl-(((1′*S*)-1′-phenylethyl)amino)methyl)-2-naphthol (2).** The use of isobutyric aldehyde with the same synthesis process as above produced a piece crystal (yield 71%, >99.8% ee): mp 134−135 °C; IR (KBr) 3336, 1619, 1235, 1101, 769, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (d, 3H, $J = 5$ Hz), 0.98 (d, 3H, $J = 6.7$ Hz), 1.49 (d, 3H, $J = 6.7$ Hz), 2.18 (senary, 1H, $J = 6.7$ Hz), 3.00 (t, 1H, $J = 6.7$ Hz), 2.50 (br s, 1H), 4.15 (d, 1H, $J = 6$ Hz), 7.05−7.70 (m, 11H), 13.01 (br s, 1H); MS (M + 1)320.16.

(12) **1-((*S*)-Phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl)-2-naphthol (3).** To a solution of **1** (445 mg, 1.258 mmol) in 10 mL of THF were added paraformaldehyde (377 mg, 12.58 mmol) and $NaBH_4$ (476 mg, 12.58 mmol). Then the solution of THA (5 mL) in 30 mL of THF was added dropwise (4 drops/min) under stirring acutely at room temperature; 351 mg (76% yield, >98% ee) was obtained after acid workup: mp 128−129 °C; IR(KBr) 3351, 1621, 1469, 1313 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, 3H, $J = 6.6$ Hz), 2.14 (s, 3H), 3.75 (q, 1H, $J = 6.6$ Hz), 5.35 (s, 1H), 7.21−7.81 (m, 16H), 13.82 (br s, 1H); MS (M + 1) 368.16.

(13) **Typical Procedure for the Asymmetric Addition of Et_2Zn to Benzaldehyde.** To a solution of optically active aminonaphthol (1) (50.3 mg, 0.142 mmol) in toluene (1.4 mL) was added dropwise a solution of Et_2Zn (2.84 mL, 1 M in hexane) at room temperature. After the mixture stirred for 1 h, benzaldehyde (100 mg, 0.947 mmol) was added at room temperature, and the reaction was stirred for 24 h at room temperature. Optically active 1-phenylpropan-1-ol (124 mg, 97%) was obtained after acid workup and purification by silica gel TLC.

(14) **Crystal data for 1:** $C_{25}H_{23}NO$, MW = 353.44, monoclinic, space group $P2_1/n$, $a = 14.494(3)$, $b = 17.802(3)$, $c = 16.530(3)$ Å; $\alpha = 90°$, $\beta = 113.136(4)°$, $\gamma = 90°$, $U = 3922.1$ $Å^3$, $T = 294$ K, $Z = 8$, $D_c = 1.197$ g cm^{-1}, $\mu = 0.072$ mm^{-1}, $\lambda = 0.9857-0.9787$ Å, $F(000)$ 1504, crystal size $0.30 \times 0.22 \times 0.20$ mm^3, 9055 independent reflections ($R_{int} = 0.0542$), 26195 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on $F^2 = 0.741$; final R indices [$I > 2\sigma(I)$] $R_1 = 0.0506$, $wR_2 = 0.1323$, SADABS. **Crystal data for 2:** $C_{22}H_{25}NO$, MW = 319.43, orthorhombic, space group $P212121$, $a = 9.7303(14)$, $b = 10.5655(15)$, $c = 35.924(5)$ Å; $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 3699.2(9)$ $Å^3$, $T = 294$ K, $Z = 8$, $D_c = 1.149$ g cm^{-1}, $\mu = 0.069$ mm^{-1}, $\lambda = 0.9849-0.9795$ Å, $F(000)$ 1376, crystal size $0.30 \times 0.22 \times 0.22$ mm^3, 8536 independent reflections ($R_{int} = 0.0513$), 25080 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on $F^2 = 0.739$; final R indices [$I > 2\sigma(I)$] $R_1 = 0.0460$, $_wR_2 = 0.1190$, SADABS (semiempirical).