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A Convenient, One-Step Synthesis of Optically Active Tertiary Aminonaphthol and Its Applications in the Highly Enantioselective Alkenylations of Aldehydes

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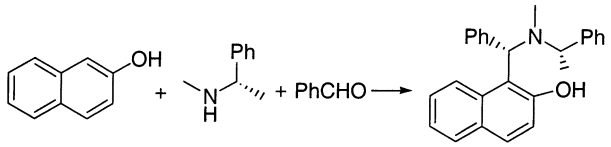
Abstract: Optically active tertiary aminonaphthol **1** was obtained by a new, convenient procedure and was found to catalyze the enantioselective alkenylation of various aldehydes with high ee values, which provides a practical method for the synthesis of chiral (*E*)- allyl alcohols.

Over the past two decades, great progress has been made in the catalytic asymmetric alkylation of aldehydes with use of chiral amino alcohols as ligands, and products with excellent enantiomeric excesses have been achieved for all types of substrates.[1] In contrast, the enantioselective alkenylation of aldehydes is substantially less developed despite its importance in organic synthesis.[1c] The asymmetric alkenylation of aldehydes affords very useful chiral allyl alcohols, which are key intermediates for a large number of natural products and biologically active compounds.[2]

Highly effective chiral ligands for the enantioselective alkenylation of aldehydes are relatively rare. Amino alcohols which were effective in the asymmetric dialkylzinc additions were studied in this reaction, but generally gave only moderate selectivities.[3] Oppolzer et al. found that the 3-*exo*-dimethylaminoisobornenol (DAIB) ligand[3a] gave high ee values in the alkenylation of certain aldehydes and Dahmen and Bräse reported that a ketimine ligand[4] which contains the [2,2]-paracyclophane backbone gave high ee values for para-substituted benzaldehydes and α-branched aliphatic aldehydes. The search for efficient chiral ligands to generate high enantioselectivities in the alkenylations of different types of aldehydes is an important challenge in this area.

SCHEME 1. One-Step Synthesis of Ligand 1



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On the other hand, of the approximately 600 chiral ligands in a recent review on organozinc additions by Pu and Yu,[1c] only a small number can be obtained via simple synthetic methods. For the practical applications of useful catalytic asymmetric synthesis, it is highly desirable to develop convenient methods for the preparation of effective chiral ligands.

In this paper, we wish to report a new, one-step procedure for the synthesis of optically active tertiary aminonaphthol **1** and the highly enantioselective alkenylations of various aliphatic and aromatic aldehydes promoted by ligand **1**.

Compound **1** had been previously prepared through a three-step synthesis.[5] In this study, we tried to use commercial (*S*)-(−)-*N*-α-dimethylbenzylamine as one component in the Mannich-type aminoalkylation of 2-naphthol and found that the direct condensation of benzadehyde with 2-naphthol and (*S*)-(−)-*N*-α-dimethylbenzylamine without any solvent (Scheme 1) proceeded smoothly to give a single diastereomer of the tertiary aminonaphthol exclusively either at room temperature or at high temperature (rt, 45 h, 70%; 95 °C, 30 h, 78%). This is the first example of a straightforward asymmetric synthesis of optically active tertiary aminonaphthol through a Mannich-type reaction. Optically pure **1** was easily obtained by simply adding methanol to the crude reaction mixture, and the precipitated product could be used directly in the asymmetric alkenylation of aldehydes without any further purification. The operational simplicity of this synthetic methodology makes it possible to synthesize chiral ligand **1** on a large scale.

Alkenylzinc reagents was prepared by using a method developed by Oppolzer et al. Hydroboration of terminal alkyne with freshly prepared dicyclohexylborane gave (*E*)-1-alkenylborane, which was directly treated with diethylzinc or dimethylzinc. In Oppolzer's procedure, the hydroborations of alkynes were carried out in hexane. To improve the solubility of substrates and the chiral ligand in the reaction system, we used toluene as the solvent for hydroboration. The reaction of 1.5 equiv of alkenylzinc reagent with benzaldehyde in the presence of 15 mol % of **1** was tested and the expected allyl alcohols were obtained in good yields. As shown in Table 1, the reaction gave better isolated yields and enantioselectivities in toluene than in hexane. Increasing the amount of alkenylzinc reagent improved the isolated yield to 91%. Lowering the reaction temperature to −30 °C gave a slightly higher ee. Both diethylzinc and dimethylzinc gave similar results in the reaction.

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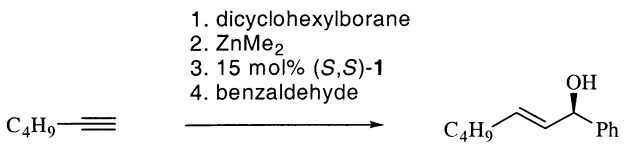
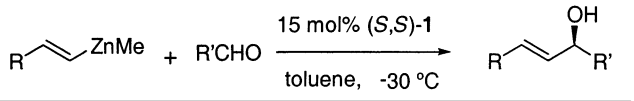
TABLE 1. Results for Alkenylzinc Addition to Benzaldehyde in the Presence of 1



entry	solvent	temp (°C)	time (h)	yield (%)	ee (%)[a]
1	hexane	0	5	79	90 (*R*)
2	hexane	−20	15	77	91 (*R*)
3	toluene	0	5	85	92 (*R*)
4	toluene	−20	15	80	95 (*R*)
5	toluene	−30	15	80	97 (*R*)
6[b]	toluene	−20	12	91	96 (*R*)
7[c]	toluene	−20	15	83	95 (*R*)

[a] Determined by HPLC (Chiralcel OD column). [b] 2 equiv of alkenylzinc reagent was used. [c] $ZnEt_2$ was used in transmetalation instead of $ZnMe_2$.

TABLE 2. Results for Alkenylzinc Additions to a Variety of Aldehydes in the Presence of 1



entry	R	R′	yield (%)	ee (%)[a]
1	$Ph(CH_2)_2$	*c*-C_6H_{11}	93	95 (*S*)
2[b]	$Ph(CH_2)_2$	*c*-C_6H_{11}	95	95 (*S*)
3	$Ph(CH_2)_2$	*i*-Pr	94	94 (*S*)
4	*n*-C_4H_9	phenyl	90	97 (*R*)
5	*n*-C_4H_9	*p*-Br-phenyl	89	94 (*R*)
6	*n*-C_4H_9	*p*-NO_2-phenyl	79	95 (*R*)
7	*n*-C_4H_9	*o*-NO_2-phenyl	77	98 (*R*)
8	*n*-C_4H_9	*o*-Cl-phenyl	90	>99 (*R*)
9	*n*-C_4H_9	*o*-Br-phenyl	87	98 (*R*)
10[b]	*n*-C_4H_9	*o*-Br-phenyl	84	96 (*R*)
11	*n*-C_4H_9	*m*-OMe-phenyl	91	94 (*R*)
12	*n*-C_4H_9	*m*-Br-phenyl	92	94 (*R*)

[a] Determined by HPLC (Chiralcel OD column used for entries 1−4 and 8−11; Chiralcel AD column used for entries 5−7 and 12). The absolute configuration was assigned by comparison of the optical rotation with the reported values of known compounds (ref 3f, entries 4 and 11) and with the expectation of similar reaction pathways for all other substrates. [b] $ZnEt_2$ was used in transmetalation instead of $ZnMe_2$.

The results of asymmetric alkenylation of various aldehydes in the presence of chiral ligand **1** are summarized in Table 2. High ee values and isolated yields were obtained in almost all cases. Aliphatic aldehydes gave somewhat higher yields than aromatic aldehydes. Nitro-substituted benzaldehydes provided lower yields than other substrates. The electron-rich *m*-methoxybenzaldehyde and the electron-poor *m*-bromobenzaldehyde provided similar product ee values, while the para- and meta-subtituted benzaldehydes gave products with slightly lower ee values than those from ortho-substituted benzaldehydes. To our knowledge, these are the best ee values in the catalytic asymmetric alkenylation of ortho-substituted benzaldehydes.

In conclusion, we have developed a highly efficient and practical method for the preparation of chiral tertiary aminonaphthol **1**, which provides a good opportunity for large-scale applications. A successful application of chiral ligand **1** in the enantioselective alkenylation of aldehydes was demonstrated and a variety of (*E*)-allyl alcohols were obtained in high yields with excellent ee values.

Experimental Section

General. All reactions were conducted under a nitrogen atmosphere. All chemicals and solvents were used as received unless otherwise stated. THF (Na, benzophenone), CH_2Cl_2 (CaH_2), methanol (Mg), and toluene (Na) were distilled from the drying agents indicated. Column chromatography was performed on silica gel (230−400 mesh).

1-((*S*)-Phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl)-2-naphthol (1). A mixture of benzaldehyde (2.0 mL, 20 mmol), (*S*)-(−)-*N*,α-dimethylbenzylamine (2.60 g, 19 mmol), and 2-naphthol (2.43 g, 16 mmol) was stirred at 95 °C for 30 h. Methanol (5 mL) was added and the precipitated product was collected and washed with methanol (5 mL). White crystals of tertiary aminonaphthol **1** (4.58 g, 78%) were obtained. ^1H NMR (500 MHz, $CDCl_3$) δ 14.01 (br s, 1H), 7.88−7.18 (m, 16H), 5.33 (s, 1H), 4.21 (br m, 1H), 2.10 (m, 3H), 1.51 (s, 3H); de >98%. No other stereoisomer was observed.

Typical Procedure for Alkenylzinc Addition to Aldehydes. To a stirred solution of dicyclohexylboran (1 mmol) in toluene (0.5 mL) was added 1-hexyne (114 μL, 1 mmol). The mixture was stirred for 1 h at room temperature, then was cooled to −78 °C, and a solution of dimethylzinc (600 μL, 1.2 mmol, 2 M in toluene) was added slowly. After 1 h at −78 °C, a solution of ligand **1** (0.075 mmol) in toluene (2 mL) was added. Then the temperature was increased to −30 °C over a period of 0.5 h and the aldehyde (0.5 mmol) was added and the final mixture was allowed to stir for 15 h at −30 °C. The reaction was quenched with water and the mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4 and solvent was removed in vacuo. The purification of the residue by flash chromatography yielded the allyl alcohol.

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Supporting Information Available: Characterizations for the addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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