



0957-4166(95)00381-9

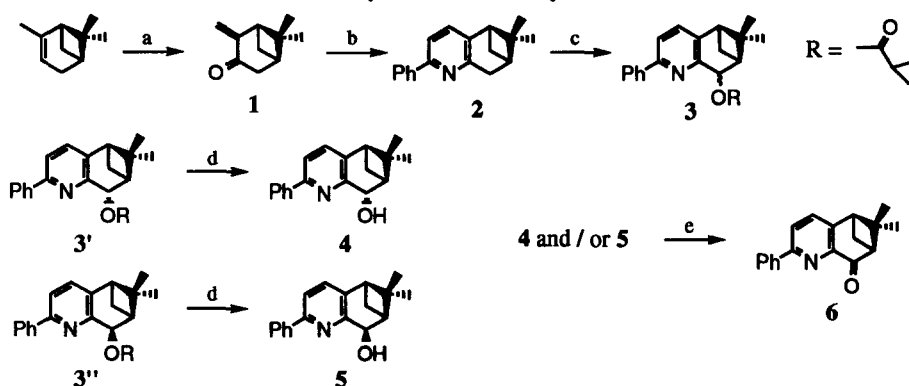
# Synthesis of New Chiral Catalysts, Substituted 2-Phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-quinolines, for the Enantioselective Addition of Diethylzinc to Benzaldehyde

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**Abstract:** New chiral ligands, substituted 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-quinolines, were prepared and the catalyzed reaction of diethylzinc with benzaldehyde was studied under various conditions to give 1-phenyl-1-propanol with up to 91% ee.

Pyridine derivatives designed as ligands for metal complexes with predetermined helical chirality have recently been synthesized.<sup>1,2</sup> The development of this synthetic method opens up the possibility to prepare a series of ligands that are useful in enantioselective catalysis. Many 2-(1-hydroxyalkyl)pyridines have proved to be efficient catalysts in the asymmetric addition of dialkylzinc to aldehydes.<sup>3</sup> We report here the preparation of new chiral ligands, 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-8-quinolinols **4**, **5** and 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-8-quinolinone **6** according to scheme 1. The three ligands have been used in the addition reaction of diethylzinc to benzaldehyde.

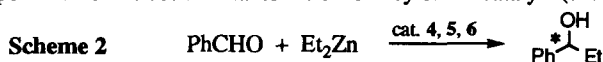


**Scheme 1:** a)  $^1\text{O}_2$ ,  $\text{Ac}_2\text{O}$ , pyridine, 4-dimethylaminopyridine, meso-tetraphenylporphyrine,  $20^\circ\text{C}$ , 16h, 95%, Lit.<sup>4</sup> b) phenacylpyridinium bromide<sup>5</sup>,  $\text{NH}_4\text{OAc}$ ,  $\text{HOAc}$ ,  $100^\circ\text{C}$ , 20h, 60%, Lit.<sup>6</sup> c) i)  $\text{HOOAc}$ ,  $\text{HOAc}$ ,  $70^\circ\text{C}$ , 24 h; ii) isobutyric anhydride,  $100^\circ\text{C}$ , 8h, 65%, Lit.<sup>7</sup> d)  $\text{NaOH}$ , methanol-water, reflux, 1h, 95%, Lit.<sup>7</sup> e) chromic acid, acetone-water,  $20^\circ\text{C}$ , 7h, 80%, Lit.<sup>7</sup>

The pinocarvone **1** was obtained by  $^1\text{O}_2$  oxidation of (-)- $\alpha$ -pinene in a quantitative yield.<sup>4</sup> **1** reacts with phenacylpyridinium bromide<sup>5</sup> to give 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-quinoline **2** in 60% yield.<sup>6</sup> By oxidation of **2** to N-oxide with peracetic acid followed by Boekelheide-rearrangement with isobutyric anhydride we obtained (2-Phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-8-quinolinyl) isobutyrate **3** as diastereomeric mixture of **3'** and **3''** in a 65 / 35 ratio.<sup>7</sup> **3'** could be isolated by recrystallisation in hexane and **3''** by column chromatography (silica gel, hexane-ethyl acetate (10:1)). The ligands **4** and **5** were

obtained by hydrolysis of **3'** or **3''**, respectively, and the ligand **6** by oxidation of **4** and / or **5** with chromic acid.<sup>7</sup> The ee values of the ligands **4** and **5** were determined by <sup>1</sup>H NMR of esters derived from (1*S*)-camphanoyl chloride.

Having prepared these ligands, we studied their properties as catalysts for the enantioselective addition of diethylzinc to benzaldehyde (Scheme 2 and Table 1). Ligand **5** proved to be the best catalyst in the series (entry 3). Ligand **4**, that differs from **5** only in the configuration on C8, induces the opposite enantiomer of 1-phenyl-1-propanol (*S*-enantiomer), but has a lower catalytic activity especially with regard to enantioselectivity (entry 1). At 24°C the reaction is faster than at 0°C but the temperature has no significant effect on the enantiomeric purity (entry 2, 3). The use of a polar solvent is detrimental to the efficiency of the catalyst (entry 5).



**Table 1:** Enantioselective addition of diethylzinc to benzaldehyde

Entry <sup>a</sup>	Ligand	Reac. temp. (°C)	Reac. time (h)	Yield (%) <sup>b</sup>	ee (%) <sup>b</sup>	Config. <sup>c</sup>
1	<b>4</b>	0	24	75	28	<i>S</i>
2	<b>5</b>	0	9	78	91	<i>R</i>
3	<b>5</b>	24	3	98	91	<i>R</i>
4	<b>6</b>	24	21	96	75	<i>R</i>
5 <sup>d</sup>	<b>6</b>	24	24	20 <sup>e</sup>	< 1	-

a) All reactions were carried out in toluene-hexane (1:1) if not otherwise indicated; b) Determined by GC analysis using a β-DEX™110 capillary column from the firm SUPELCO; c) Determined by comparison with the chromatograms of enantiomerically pure samples of *R*- and *S*-1-phenyl-1-propanol; d) THF instead of toluene was used; e) The reaction gave also 22% benzyl alcohol.

Representative procedure (entry 3): A dried 10-ml Schlenk flask was charged with 13.3 mg (0.05 mmol) of **5**, 2 ml of dry toluene and 1 mmol (106 mg) of benzaldehyde. To this stirred solution 2 ml of a 1 M solution of diethylzinc in hexane (2 mmol) was added dropwise over a 10-min period. After 3 h at 20°C the reaction was quenched with 5 ml of 1 M HCl. The reaction mixture was extracted with dichloromethane and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent the remaining oil was analyzed by GC to determine the conversion ratio of the benzaldehyde and the ee of the 1-phenyl-1-propanol. The full characterization of the ligands and an extended study of their catalytic activity are in progress.

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