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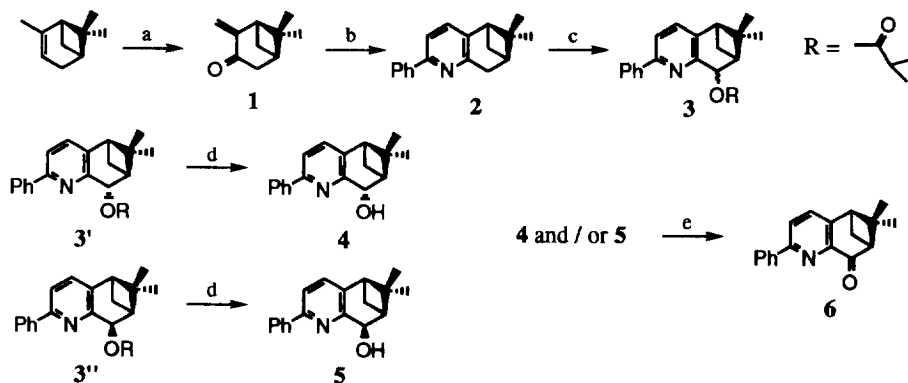
Synthesis of New Chiral Catalysts, Substituted 2-Phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-quinolines, for the Enantioselective Addition of Diethylzinc to Benzaldehyde

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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.^{1,2} 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.³ 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) $^1\text{O}_2$, Ac_2O , pyridine, 4-dimethylaminopyridine, meso-tetraphenylporphyrine, 20°C , 16h, 95%, Lit.⁴ b) phenacylpyridinium bromide⁵, NH_4OAc , HOAc , 100°C , 20h, 60%, Lit.⁶ c) i) HOOAc , HOAc , 70°C , 24 h; ii) isobutyric anhydride, 100°C , 8h, 65%, Lit.⁷ d) NaOH , methanol-water, reflux, 1h, 95%, Lit.⁷ e) chromic acid, acetone-water, 20°C , 7h, 80%, Lit.⁷

The pinocarvone **1** was obtained by $^1\text{O}_2$ oxidation of (-)- α -pinene in a quantitative yield.⁴ **1** reacts with phenacylpyridinium bromide⁵ to give 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethyl-5,7-methano-quinoline **2** in 60% yield.⁶ By oxidation of **2** to N-oxide with peracetic acid followed by Boelkeide-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.⁷ **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.⁷ The ee values of the ligands **4** and **5** were determined by ¹H 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).

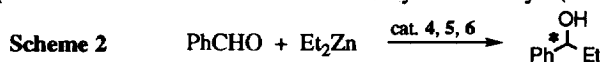


Table 1: Enantioselective addition of diethylzinc to benzaldehyde

Entry ^a	Ligand	Reac. temp. (°C)	Reac. time (h)	Yield (%) ^b	ee (%) ^b	Config. ^c
1	4	0	24	75	28	<i>S</i>
2	5	0	9	78	91	<i>R</i>
3	5	24	3	98	91	<i>R</i>
4	6	24	21	96	75	<i>R</i>
5 ^d	6	24	24	20 ^e	< 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 Na₂SO₄. 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.

References

- Hayoz, P.; von Zelewsky, A.; *Tetrahedron Lett.*, **1992**, *33*, 5165.
- Hayoz, P.; von Zelewsky, A.; *J. Am. Chem. Soc.*, **1993**, *115*, 5111.
- (a) Bolm, C.; Zehnder, M.; Bur, D.; *Angew. Chem.*, **1990**, *102*, 206; (b) Bolm, C.; Schlingloff, G.; Harms, K.; *Chem. Ber.*, **1992**, *125*, 1191; (c) Chelucci, G.; Socolini, F.; *Tetrahedron: Asymmetry*, **1992**, *3*, 1235; (d) Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O.; *Tetrahedron: Asymmetry*, **1994**, *5*, 411; (e) Ishizaki, M.; Hoshino, O.; *Tetrahedron: Asymmetry*, **1994**, *5*, 1901; (f) Macedo, E.; Moberg, C.; *Tetrahedron: Asymmetry*, **1995**, *6*, 549; (g) Nakano, H.; Kumagai, N.; Kabuto, C.; Matsuzaki, H.; Hongo, H.; *Tetrahedron: Asymmetry*, **1995**, *6*, 1233.
- Mihelich, E. D.; Eickhoff, D. J.; *J. Org. Chem.*, **1983**, *48*, 4135.
- Bamberger, E.; *Ber. Deutsch. Chem. Ges.*, **1887**, *20*, 3344.
- Kröhnke, F.; *Synthesis*, **1976**, 1.
- Reimann, E.; Reitz, R.; *Liebigs Ann. Chem.*, **1975**, 1081.