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SYNTHESIS OF CHIRAL CATALYSTS FOR THE ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO AROMATIC ALDEHYDES

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Abstract : The reaction of diethylzinc with aromatic aldehydes and (*S*)-porretine derived catalysts was investigated. The synthesis of new chiral catalysts is also described.

The enantioselective synthesis of chiral secondary alcohols which play an important role as intermediates in organic chemistry is a stimulating subject. Several methods for the asymmetric reduction of prochiral ketones using microbial processes[1], heterogenous metal

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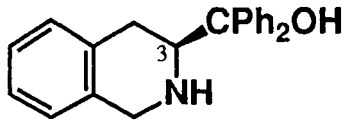
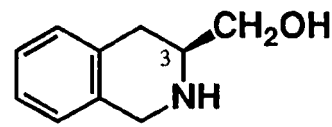


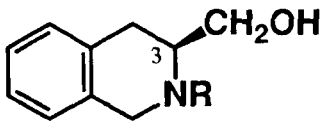
(*S*)-**1**

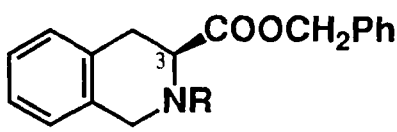


(*S*)-**2**

catalysts[2] or chirally modified hydride reagents[3] have been reported in recent years. The discovery that the relatively slow reaction of dialkylzinc reagents with aromatic aldehydes can be accelerated by chiral amino alcohols to produce secondary alcohols in high enantiomeric purity has stimulated a more detailed study of such reactions in a number of laboratories.[4] As a result several catalytic systems are now available which allow the synthesis of chiral secondary aryl alkyl carbinols from aromatic aldehydes. A variety of chiral auxiliaries are synthesized from amino acids.[5] Particularly with structurally rigid derivatives of cyclic amino acids great success was achieved.[6]

In continuation with our study on the preparation of new chiral auxiliaries prepared from proteinogenic and non proteinogenic amino acids[7] we report herein on new catalysts for the dialkylzinc-aldehyde addition having a sterically rigid *bicyclic* structure. The synthesis of (*S*)-α,α-diphenyl-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **1** and (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **2** from (*S*)-porretine[8] was described earlier.[9]





3 [R = CH_3]

4 [R = CHO]

5a [R = C_2H_3]

5b [R = $CH_2C(CH_3)_3$]

5c [R = $CH_2C_6H_5$]

6a [R = $COCH_3$]

6b [R = $COC(CH_3)_3$]

6c [R = COC_6H_5]

7 [R = H]

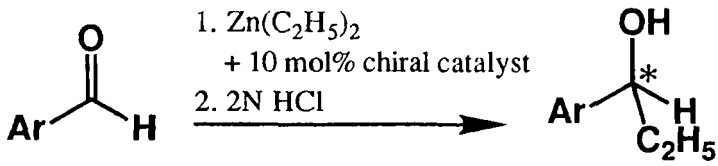
The chiral catalyst (*S*)-(+)-[(1,2,3,4-tetrahydro-2-methyl)isoquinolin-3-yl]methanol **3** was synthesized from **2** in two steps. Thus, the alcohol **2** is first formylated to give (*S*)-(+)-[(1,2,3,4-tetra-hydro-2-formyl)isoquinolin-3-yl]methanol **4**. The *N*-methyl derivative **3** is obtained from **4** by reduction with lithium aluminium hydride in 88% yield.

(*S*)-(–)-[(1,2,3,4-tetrahydro-2-ethyl)isoquinolin-3-yl]methanol **5a**, (*S*)-(+)-[1,2,3,4-tetrahydro-2-(2',2'-dimethylpropyl)isoquinolin-3-yl]methanol **5b**, and (*S*)-(–)-[(1,2,3,4-tetrahydro-2-benzyl)isoquinolin-3-yl]methanol **5c** were prepared by the reduction of the corresponding *N*-acyl esters **6a-c**. Benzyl (*S*)-(–)-1,2,3,4-tetrahydro-2-acetyl-isoquinoline-3-carboxylate **6a**, benzyl (*S*)-1,2,3,4-tetrahydro-2-pivaloyl-isoquinoline-3-carboxylate[10] **6b**, and benzyl (*S*)-(–)-1,2,3,4-tetrahydro-2-benzoyl-isoquinoline-3-carboxylate **6c** were obtained from the benzyl carboxylate[11] **7** by acylation with the corresponding acyl chlorides in toluene in the presence of triethylamine in 80-88% yield.

Table 1 Enantioselective addition of diethylzinc to aromatic aldehydes at 22° C using 10 mol% of chiral amino alcohol catalysts.[a]

Educt **8**	Product **9**	Catalyst	Opt. yield[b] [%]
benzaldehyde	(*R*)-1-phenyl-1-propanol	(*S*)-**1**	27
benzaldehyde	(*R*)-1-phenyl-1-propanol	(*S*)-**2**	22
benzaldehyde	(*S*)-1-phenyl-1-propanol	(*S*)-**5c**	15
4-chlorobenzaldehyde	(*R*)-1-(4-chlorophenyl)-1-propanol	(*S*)-**1**	35
4-chlorobenzaldehyde	(*R*)-1-(4-chlorophenyl)-1-propanol	(*S*)-**2**	22
4-methylbenzaldehyde	(*R*)-1-(4-methylphenyl)-1-propanol	(*S*)-**1**	28

[a] The chemical yields of the chiral alcohols were > 80% in each case before distillation.– [b] Optical yields of chiral secondary alcohols obtained were calculated from optical rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = -45.45$ ($c = 5.15$, $CHCl_3$) for (*S*)-1-phenyl-1-propanol[12], $[\alpha]_D^{20} = -10.4$ ($c = 5$, benzene) for (*R*)-1-(4-chlorophenyl)-1-propanol in 44% *ee*[13], $[\alpha]_D^{20} = -39.2$ ($c = 5.1$, benzene) for (*S*)-1-(4-methylphenyl)-1-propanol.[14]



8 **9**

The reaction of diethylzinc and aromatic aldehydes **8** was examined in the presence of chiral catalysts **1**, **2**, and **5c** under a variety of reaction conditions.

The results are summarized in Table 1. In a typical procedure 36.5 ml of a 1.1 M solution of diethylzinc in abs. toluene was added in 10 min. to a solution of the catalyst **1** (2 mmol) in dry toluene at – 20° C. The mixture is allowed to reach the room temperature and treated within 10 min. with 2.12 g (20 mmol) benzaldehyde, then the resulting mixture was stirred for 24 h at the 22° C. The reaction was quenched with 2N hydrochloric acid, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were extracted with sodiumhydrogen sulfite solution, sodiumhydrogen carbonate solution and water, before drying. The solvent is evaporated under reduced pressure and the residue distilled under vacuum to afford (*R*)-1-phenylpropanol.

Further studies in order to improve the optical yields are still under progress.

Experimental Section

(*S*)-(–)-[(1,2,3,4-Tetrahydro-2-methyl)isoquinolin-3-yl]-methanol (3) : A mixture of **4** (18.0 g, 49 mmol) and $LiAlH_4$ (3.60 g, 94 mmol) in anhydrous THF was refluxed under Ar for 12 h. The reaction mixture was cooled to r.t. and quenched with a 5% aq. solution of potassium hydroxide (11 ml). The solid is filtered off and extracted with 3 x 150 ml THF at reflux temperature. The organic solution was dried over anhydrous $MgSO_4$. The solvent was eliminated under vacuum and the residue was treated with CH_2Cl_2/petroleum ether to give **3** as an off-white solid (2.05 g, 88%), mp.: 92 °C, $[\alpha]_D^{20} = -43.9$ (*c*= 1.27, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm= 2.40 (s, CH_3), 2.75-2.86 (m, 3H, H4, H3), 3.31 (s, 1H, OH), 3.56-3.70 (m, 2H, CH_2OH), 3.67 and 3.86 (2d, *J*=15.6 Hz, 2H, H1), 7.00-7.14 (m, 4H, Ar-H); MS (CI, *i*-butane): 178 (100) [MH^+], Anal. Calc. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 73.45; H, 8.93; N, 7.66.

(*S*)-(+)-[(1,2,3,4-Tetrahydro-2-formyl)isoquinolin-3-yl]-methanol (4) : (*S*)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol **2** (3.0 g, 18 mmol) is suspended in methyl formate (40 ml). The reaction mixture turns transparent after 3 h at r.t.. Stirring is continued for 2 d. Evaporation of the solvent afforded pure **4** (3.16 g, 92%) as colorless crystals. Mp.: 109 °C (from methanol/diethyl ether); $[\alpha]_D^{20} = +93.5$ (*c*=

1.55, MeOH); ^{1}H-NMR (DMSO-d_6): δ in ppm= 2.76 and 3.01 (2dd, $J_{3,4}$=6.3 and $J_{3,4}$= 1.8 Hz, $J_{geminal}$=16.4 Hz, 0.8x2H, H4), 2.80-2.93 (m, 0.2x2H, H4), 3.18-3.49 (m, 0.8x3H, CH_2OH), 3.95-4.03 (m, 0.2x3H, CH_2OH), 4.12 and 4.88 (2d, J=17.6 Hz, 0.8x2H, H1), 4.38 and 4.61 (2d, J=16.2 Hz, 0.2x2H, H1), 4.42-4.56 (m, 0.2x1H, H3), 4.87-4.98 (m, 0.8x1H, H3), 7.12-7.19 (m, 4H, Aromat), 8.16 (s, 0.8x1H, Formyl-H), 8.25 (s, 0.2x1H, Formyl-H); MS (CI, *i*-butane): 192 (100) [MH^+], 193 (14) [MH_2^+]. Anal. Calc. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.82; H, 6.89; N, 7.24.

(*S*)-(–)-[(1,2,3,4-Tetrahydro-2-ethyl)isoquinolin-3-yl]-methanol (5a): A mixture of the *N*-acetyl derivative **6a** (11.5 g, 37 mmol) and $LiAlH_4$ (11.3 g, 297 mmol) in anhydr. toluene (80 ml) and anhydr. THF (370 ml) was refluxed under Ar for 18 h. The reaction mixture was cooled to r.t. and quenched with a 5% aq. solution of potassium hydroxide (28 ml) and refluxed for 0.5 h. The solid is filtered off and extracted with 3 x 200 ml THF at reflux temperature. The organic solution was dried over anhydr. $MgSO_4$. The solvent was eliminated under vacuum and the residue was treated with 2N hydroxylic acid (120 ml). This solution is extracted with toluene (4 x 30 ml) and evaporated to dryness in vacuo. The resulting solid (5.06 g) is suspendet in dichloromethane (40 ml) and treated with triethylamine (2.0 g, 20 mmol). 2N sodium hydroxide solution (20 ml) was added and the resulting

solution extracted twice with dichloromethane (50 ml each). The combined organic layers were washed successively with sat. sodium chloride solution (40 ml) and water (50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent and bulb-to-bulb distillation afforded pure **5a** (3.98 g, 57%) as an.oil, $bp._{0.5\ mbar}$: 190-195 °C, $[\alpha]_D^{19} = -7.6$ (c= 3.90, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): δ in ppm= 1.11 (t, J= 7.1 Hz, 3H, CH_3), 2.52-2.64 (m, 3H, CH_2CH_3, H4), 2.84 (dd, $J_{3,4}$=5.9 and $J_{geminal}$=16.7 Hz, 1H, H4), 3.08 (m, 1H, H3), 3.33 (s, 1H, OH), 3.54 (d, J=6.8 Hz, 2H, CH_2OH), 3.67 and 3.90 (2d, J=16.2 Hz, 2H, H1), 6.95-7.18 (m, 4H, Ar-H); MS (CI, i-butane): 192 (MH^+, 100%), 193 (MH_2^+, 12%). Anal. Calc. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.45; H, 9.37; N, 7.34.

(*S*)-(+)-[(1,2,3,4-Tetrahydro-2-(2′,2′-dimethylpropyl)-isoquinolin-3-yl]methanol (5b): Prepared by $LiAlH_4$ reduction of the *N*-pivaloyl derivative **6b** as described for the synthesis of **5a**. Yield 84%, oil; $bp._{0.6\ mbar}$: 210-220 °C, $[\alpha]_D^{20} = +12.2$ (c= 3.24, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): δ in ppm= 0.92 (s, 9H, t-Bu), 2.28 and 2.38 (2d, J=13.9 Hz, 2H, $CH_2C(CH_3)_3$), 2.99-3.06 (m, 2H, H4), 3.11-3.19 (m, 1H, H3), 3.47 3.52 (m, 2H, CH_2OH), 3.63 and 4.03 (2d, J=17.1 Hz, 2H, H1), 6.98-7.19 (m, 4H, Aromat); MS (CI, i-butane): 234 (MH^+, 100%). Anal. Calc. for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.90; H, 9.73; N, 6.11.

(*S*)-(–)-[(1,2,3,4-Tetrahydro-2-benzyl)isoquinolin-3-yl]-methanol (5c): Prepared by $LiAlH_4$ reduction of **6c** as described for the synthesis of **5a**. Yield 80%, oil, bp. $_{0.5\ mbar}$: 215-220 °C, $[\alpha]_D^{20} = -5.6$ (c= 4.24, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): δ in ppm= 2.55 and 2.94 (2dd, $J_{3,4}$=5.7 and $J_{3,4}$=6.2 Hz, $J_{geminal}$=16.8 Hz, 2H, H4), 2.94 (s, 1H, OH), 3.18-3.27 (m, 1H, H3), 3.54-3.66 (m, 2H, CH_2OH), 3.58 and 3.85 (2d, J=16.5 Hz, 2H, H1), 3.70 (d, J=3.8 Hz, 2H, CH_2Ph), 6.93-7.16 (m, 9H, Ar-H); MS (CI, *i*-butane): 254 (MH^+, 100%), 255 (MH_2^+, 22%) . Anal. Calc. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.38; H, 7.89; N, 5.72.

Benzyl (*S*)-(–)-1,2,3,4-tetrahydro-2-acetyl-isoquinoline-3-carboxylate (6a): A mixture of the benzyl carboxylate **7** (13.0 g, 49 mmol) and triethylamine (5.41 g, 54 mmol) in anhydrous toluene was treated dropwise at 0°C (± 3°C) with acetyl chloride (4.20 g, 54 mmol) and allowed to stand at 20°C for 15 h. The reaction mixture is extracted successively with water (60 ml), 2N hydrochloric acid (60ml) and again with water (60 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded pure **6a** (12.8 g, 85%) as an oil. $[\alpha]_D^{20} = -6.5$ (c= 1.93, $CHCl_3$), ^{1}H-NMR ($CDCl_3$): δ in ppm= 2.07 (s, 0.4x3H, CH_3), 2.16 (s, 0.6x3H, CH_3), 3.12-3.26 (m, 2H, H4), 4.56 and 4.74 (2d, J=20.9 Hz, 0.4x 2H, H1), 4.62 and 4.75 (2d, J=15.7 Hz, 0.6x2H, H1), 5.02 (s, 0.6x2H, CH_2Ph), 5.04 (s, 0.4x2H, CH_2Ph),

5.19 (dd, $J_{3,4}$=3.0 and 5.3 Hz, 0.4x1H, H3), 5.25 (dd, $J_{3,4}$=3.9 and 5.8 Hz, 0.6x1H, H3), 7.07-7.30 (m, 9H, Ar-H); MS (CI, *i*-butane): 310 (100%) [MH^+], 311 (20%) [MH_2^+].Anal. Calc. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 72.25; H, 6.20; N, 4.48.

Benzyl (*S*)-(–)-1,2,3,4-tetrahydro-2-benzoyl-isoquinoline-3-carboxylate (6c): Preparation similary from the benzyl carboxylate **7** and benzoyl chloride in 80% yield. Mp.: 91 °C (from dichloromethane/petroleum ether); $[\alpha]_D^{20}$ = – 43.0 (*c*= 1.64, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm = 3.17-3.30 (m, 2H, H4), 4.52 and 4.62 (2d, *J*=16.5 Hz, 2H, H1), 5.01-5.23 (m, 3H, H3, CH_2Ph), 7.09-7.44 (m, 14H, Ar-H); MS (CI, *i*-butane): 372 (MH^+, 100%], 373 ([MH_2^+, 28%) .

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References and Notes

1 Csuk, R.; Glänzer, B. I., *Chem. Rev.* **1991**, *91*, 49.

2 (a) Blystone, S. L.,*Chem. Rev.* **1989**, *89*, 1664. (b) Tungler, A.; Tarnai, T.; Máthé, T.; Petró, J., *J. Mol. Catal.* **1991**, *67*, 277.

3 Seyden-Penne, J., *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York, 1991.

4 (a) Oguni, N.; Omi, T., *Tetrahedron Lett.* **1984**, *25*, 2823. (b) Soai, K.; Ookawa, A.; Kaba, T., *J. Am. Chem. Soc.* **1987**, *109*, 7111. (c) Soai, K.; Niwa, S.; Watanaba, M.,*J. Chem. Soc. Perkin Trans.1*, **1989**, 109. (d) Soai, K.; Hori, H.; Kawahara, M., *Tetrahedron:Asymmetry* **1991**, *2*, 253. (e) Näslund, J.; Welch, C. J., *Tetrahedron: Asymmetry* **1991**, *2*, 1123. (f) Chaloner, A.; Langadianon, E.; Perera, S. A. R., *J. Chem. Soc. Perkin Trans.1*, **1991**, 2731. (g) Oppolzer, W.; Radinov, R. N., *Tetrahedron Lett.* **1988**, *29*, 5645. (h) Chelucci, G.; Falorni, M.; Giacomelli, G., *Tetrahedron:Asymmetry* **1990**, *1*, 843. (i) Hayashi, M.; Kaneko, T.; Oguni, N., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 25. (j) Asami, M.; Inoue, S., *Chem. Lett.* **1991**, 685. (k) Niwa, S.; Hatanaka, T.; Soai, K., *J. Chem. Soc. Perkin Trans.1*, **1991**, 2025.

5 Martens, J., *Top. Curr. Chem.* **1984**, *125*, 165.

6 (a) Martens, J., *Chem. Ztg.* **1986**, *110*, 169. (b) Drauz, K.; Kleemann, A.; Martens, J., *Angew. Chem.***1982**, *94*, 590; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 584.

7 (a) Martens, J.; Lübben, S., *Arch. Pharm. (Weinheim)* **1991**, *324*, 59.

(b) Martens, J.; Lübben, S., *Liebigs Ann. Chem.* **1990**, 949.

8 Hein, G. E.; Nieman, C., *J. Am. Chem. Soc.* **1962**, *84*, 4487.

9 Stingl, K.; Martens, J.; Wallbaum, S., *Tetrahedron: Asymmetry* **1992**, *3*, 223.

10 Huber, I.M.P.; Seebach, D., *Helv. Chim. Acta*, **1987**, *70*, 1944.

11 Hayashi, K.; Ozaki, Y.; Numani, K.; Yoneda, N., *Chem. Pharm. Bull.* **1983**, *31*, 312.

12 Pickard, R. H.; J. Kenyon, *J. Chem. Soc.* **1914**, *105*, 1115.

13 Capillon, J.; Guette, J.,*Tetrahedron* **1979**, *35*, 1817.

14 Chaloner, P.A.; Perera, S.A.R.,*Tetrahedron Lett.* **1987**, *28*, 3013.

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