



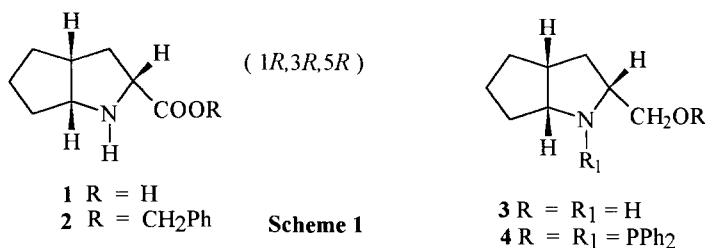
ENANTIOSELECTIVE HYDROGENATION USING A RIGID BICYCLIC AMINOPHOSPHINE PHOSPHINITE LIGAND.

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Abstract: Crystalline and in situ formed Rh-complexes from (1*R*,3*R*,5*R*)-O,N-bis-(diphenylphosphino)-3-hydroxymethyl-2-azabicyclo-[3.3.0.]octane and from the all (*S*)-enantiomer have been prepared and used in model asymmetric hydrogenations. The catalysts are highly active but the rigidity of their backbone does not contribute to an enhanced stereoselectivity. The ligand is readily available from an intermediate of the Ramipril synthesis the latter being a ACE inhibitor.

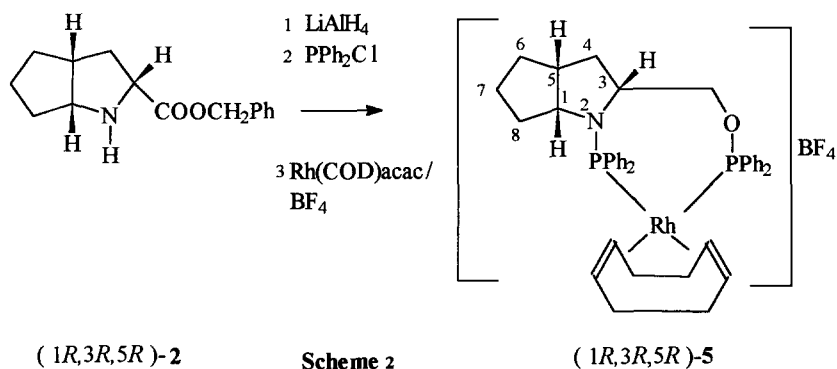
Introduction: Among the several amino alcohols and their derived aminophosphine phosphinites used in the enantioselective catalysis we are confined to amino alcohols readily available from pharmaceuticals or industrially produced intermediates¹. One building block of the ACE inhibitor Ramipril², the acid **1** (Scheme 1) seemed to be especially interesting because the well known derivatives of prolinol and hydroxyprolinol, ProNOP and E-ProNOP, with their cyclic backbone proved to be favourable ligands to afford high



stereoselectivity³.






The introduction of a condensed second ring, further enhancing the rigidity was expected to influence positively the stereocontrol. In order to check this thesis we prepared **4** and **5**.

Results and Discussion: Precatalyst synthesis is shown in Scheme 2. As follows from Table 1 the catalysts are highly active even in the hydrogenation of the heterocyclic amino acid precursors. The ligand **4** belongs to the "normal" series of aminophosphine phosphinites, the NP is bound to the stereogenic center and therefore a decreased enantioselectivity e.g. compared with those of Propaphos which belongs to the "iso" series has been anticipated. In comparison with ProNOP which rendered an enantiomeric excess of > 80 % applying the standard substrates, **5** affords only values lying between 50 - 70 % ee. Thus, the condensed "ProNOP" shows no advantage, on the contrary the second ring seems to influence the active conformation negatively. For characterization of the compounds **3** - **5** the ¹H and ¹³C NMR spectra were recorded. The NMR data are given in the experimental part. The assignment of the signals are ensured by recording the DEPT, ¹H/¹H-COSY, and ¹³C/¹H correlation spectra⁴.



The results of the asymmetric hydrogenation are summarized in Table 1.

Table 1. Asymmetric hydrogenation of dehydroamino acid derivatives $\text{RCH}=\text{C}(\text{NHCOR}_1)\text{COOR}_2$ catalyzed by (*S,S,S*)- and (*R,R,R*)-5

Cat*	Substrate			t/2 min	ee %	Conf. of product
	R	R ₁	R ₂			
(<i>S,S,S</i>)- 5	Ph	Me	Me	2	69	(<i>S</i>) ^a
(<i>S,S,S</i>)- 5	Ph	Ph	Me	3	72	(<i>S</i>)
(<i>S,S,S</i>)- 5	Ph	Me	H	< 1	57	(<i>S</i>) ^b
(<i>R,R,R</i>)- 5	Ph	Me	H	< 1	54	(<i>R</i>)
(<i>S,S,S</i>)- 5	Ph	Ph	H	< 1	62	(<i>S</i>)
(<i>R,R,R</i>)- 5	Ph	Ph	H	< 1	58	(<i>R</i>)
(<i>S,S,S</i>)- 5	Ph	Me	Me	< 1	70	(<i>S</i>)
(<i>R,R,R</i>)- 5	Ph	Me	Me	< 1	69	(<i>R</i>)
(<i>S,S,S</i>)- 5	Ph	Ph	Me	1	73	(<i>S</i>)
(<i>R,R,R</i>)- 5	Ph	Ph	Me	1	71	(<i>R</i>)
(<i>R,R,R</i>)- 5		Me	Me	1	64	(<i>R</i>)
(<i>R,R,R</i>)- 5		Me	Me	6	63	(<i>R</i>)
(<i>R,R,R</i>)- 5		Ph	Me	3	64	(<i>R</i>)
(<i>R,R,R</i>)- 5		Ph	Me	7	59	(<i>R</i>) ^c
(<i>R,R,R</i>)- 5		Ph	Me	7	59	(<i>R</i>) ^c

Conditions: Substrate 1 mmol, Rh-complex 5 0.01 mmol, 25 °C, 0.1 MPa H₂-pressure, 15 ml MeOH.

^a in situ formed complex from ligand 4 and [Rh(COD)₂]₂BF₄, ^b crystalline complex 5,

^c addition of 1.5 mmol of HBF₄.

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Experimental: ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer BRUKER ARX 300. The calibration of the spectra was carried out by means of solvent peaks (CDCl_3 : δ ^1H = 7.25, δ ^{13}C = 77.0). The ^{31}P NMR spectra were recorded on a BRUKER AC 250 spectrometer (101.3 MHz). The ^{31}P chemical shifts are related to H_3PO_4 .

The hydrogenation was performed under normal pressure and 25 °C as described by Kagan⁵.

The solvents were purified and dried by usual methods, if necessary, under argon.

(1S, 3S, 5S) and (1R, 3R, 5R)-3-(Hydroxymethyl)-2-azabicyclo-[3.3.0]-octane x HCl 3

To a suspension of LiAlH_4 (0.84 g, 0.022 mol) in ether (30 ml) was added at 0 °C (*S,S,S*)-**2** respective (*R*)-**2** (5 g, 0.02 mol) with stirring which was continued at room temperature for 5 h. The calculated amount of water was added, the precipitate filtered off and washed several times with ether. After drying (MgSO_4) and removing the ether, to the remaining slightly yellowish coloured solution was given MeOH/HCl and the mixture concentrated under reduced pressure. Acetone was added and on standing for two days in a refrigerator the hydrochloride crystallized. It was filtered off and washed with a few ml of cold acetone. (*S,S,S*)-**3**, white crystals, yield 1.85 g (51 %), m.p. 157-9 °C. $[\alpha]_{\text{D}}^{25}$ 30.6 (c 1, EtOH). $\text{C}_8\text{H}_{15}\text{NO} \times \text{HCl}$ (177.7), calcd. C 54.08 H 9.08 N 7.88 Cl 19.96 found C 54.29 H 8.95 N 7.82 Cl 19.76. (*R,R,R*)-**3**, white crystals, yield 1.80 g (49 %), m.p. 155-6 °C. $[\alpha]_{\text{D}}^{25}$ -29.7 (c 1, EtOH). Found C 54.25 H 8.93 N 7.91 Cl 20.03. ^1H NMR (CDCl_3): δ 9.70 (1H, br, NH); 8.45 (1H, br, NH); 4.82 (1H, br, OH); 4.11 (1H, m, H-1); 3.92 (2H, m, CH_2O); 3.63 (1H, m, H-3); 2.83 (1H, m, H-5); 2.05-2.25 (2H, m, H-4, H-8); 1.92 (1H, m, H-7); 1.50-1.80 (5H, m, H-4, H-6, H-7, H-8). ^{13}C NMR (CDCl_3): δ 64.3 (C-1); 64.0 (C-3); 59.5 (CH_2O); 42.1 (C-5); 32.6 (C-4); 31.8 (C-6); 30.5 (C-8); 24.0 (C-7).

(1S, 3S, 5S) and (1R, 3R, 5R)-O,N-bis-(Diphenylphosphino)-3-hydroxymethyl-2-azabicyclo-[3.3.0]-octane 4

To **3** (0.8 g, 4.5 mmol) in benzene (13.5 ml) Et_3N (3.8 ml, 27.5 mmol) was given and the mixture heated to 50 °C with stirring. Within 30 min. chlorodiphenylphosphine (1.77 ml, 9.5 mmol) in benzene (9 ml) was added dropwise and the mixture was then heated to 80 °C for 3 h. On standing over night $\text{Et}_3\text{N} \times \text{HCl}$ precipitates and was filtered off over Celite/glasswool. The solvent was removed under reduced pressure and to the remaining oil ether (3ml) was added. A second crop of $\text{Et}_3\text{N} \times \text{HCl}$ was filtered off as above, the ether removed and the oil heated for 3 h at 50 °C to remove traces of solvents and byproducts. (*S,S,S*)-**4**, yield 1.5 g (65 %) $[\alpha]_{\text{D}}^{25}$ -16.5 (c 1, benzene); $\text{C}_{32}\text{H}_{33}\text{NOP}_2$ (509.5) calcd. C 75.42 H 6.53 N 2.75 P 12.16; found C 75.54 H 6.74 N 2.87 P 12.28. (*R,R,R*)-**4**, yield 1.4 g (61 %) $[\alpha]_{\text{D}}^{25}$ 17.0 (c 1, benzene), found C 75.68 H 6.63 N 2.77 P 12.34. ^1H NMR (CDCl_3): δ 7.20-7.50 (20H, m, phenyl); 3.98 (1H, m, CH_2O); 3.78 (2H, m, CH_2O , H-3); 3.71 (1H, m, H-1); 2.53 (1H, m, H-5); 2.22 (1H, m, H-4); 1.40-1.60 (3H, m, H-4, H-6, H-7); 1.20-1.40 (2H, m, H-6, H-7); 1.00-1.20 (2H, m, H-8). ^{13}C NMR (CDCl_3): δ 73.5 (dd, $\text{J}_{\text{P-C}} \sim 17.1$, $\text{J}_{\text{P-C}} \sim 6.3$, CH_2O); 67.7 (C-1); 65.8 (dd, $\text{J}_{\text{P-C}} \sim 21.0$, $\text{J}_{\text{P-C}} \sim 8.8$, C-3); 43.5 (C-5); 36.9 (d, $\text{J}_{\text{P-C}} \sim 5.3$, C-4); 35.1 (C-8); 31.8 (C-6); 24.3 (C-7). ^{31}P NMR (CDCl_3): δ 114.1 (P-O); 49.1 (P-N).

(1S, 3S, 5S) and (1R, 3R, 5R)-O,N-bis-(Diphenylphosphino)-3-hydroxymethyl-2-azabicyclo-[3.3.0]-octane-rhodium-(1,5-cyclooctadiene)-tetrafluoroborate 5

4 (2.4 g, 4.7 mmol) was dissolved in THF (3 ml) with stirring and $\text{Rh}(\text{COD})\text{acac}$ (1.4 g, 4.5 mmol) added. After 15 min. a solution of HBF_4 (40 %, 0.84 ml) was added and stirring continued for 30 min. On standing in a refrigerator the complex crystallized. After 3 days it was filtered off under argon, washed with cold THF and dried over H_2SO_4 . Yield 1.7 g (45 %). (*S,S,S*)-**5** $\text{C}_{40}\text{H}_{45}\text{NOP}_2\text{RhBF}_4$ (807.5) calcd. C 59.50 H 5.62 N 1.73

P 7.67 Rh 12.75 found C 59.06 H 5.40 N 1.51 P 7.94 Rh 12.60. (*R,R,R*)-**5**, found C 59.30 H 5.58 N 1.72 P 6.44 Rh 12.50 ^1H NMR (CDCl_3): δ 7.93 (2H, m, phenyl); 7.83 (2H, m, phenyl); 7.37-7.65 (12H, m, phenyl); 7.29 (2H, m, phenyl); 7.00 (2H, m, phenyl); 5.33 (1H, br, COD); 4.88 (1H, br, H-3); 4.45 (1H, br, COD); 4.36 (1H, br, COD); 4.29 (1H, br, COD); 3.68 (1H, m, CH_2O); 3.50 (2H, m, CH_2O , H-5); 2.77 (1H, m, COD); 2.66 (2H, m, H-1, H-4); 2.48 (1H, m, COD); 2.05-2.35 (6H, m, COD); 1.60 (3H, m, H-6, H-7, H-8); 1.35 (3H, m, H-6, H-7, H-8); 1.00 (1H, m, H-4). ^{13}C NMR (CDCl_3): δ 106.1 (dd, $J \sim 8.7$, $J \sim 6.5$, COD); 102.0 (dd, $J \sim 7.7$, $J \sim 7.7$, COD); 100.8 (dd, $J \sim 10.9$, $J \sim 6.5$, COD); 96.7 (dd, $J \sim 12.1$, $J \sim 6.7$, COD); 72.0 (d, $J_{\text{P-C}} \sim 4.3$, CH_2O); 68.0 (d, $J_{\text{P-C}} \sim 6.1$, C-5); 65.1 (dd, $J_{\text{P-C}} \sim 13.8$; $J_{\text{P-C}} \sim 6.5$, C-3); 44.5 (d, $J_{\text{P-C}} \sim 3.2$, C-1); 34.7 (C-6); 34.5 (d, $J_{\text{P-C}} \sim 6.8$, C-4); 31.4 (d, $J \sim 2.9$, COD); 31.0 (d, $J \sim 2.9$, COD); 31.0 (C-8); 29.2 (dd, $J \sim 2.2$, $J \sim 2.2$, COD); 28.9 (dd, $J \sim 2.5$, $J \sim 2.5$, COD); 24.3 (C-7); ^{31}P NMR (CDCl_3): δ 123.0 (dd, $J_{\text{Rh-P}} \sim 172.4$, $J_{\text{P-P}} \sim 26.0$, P-O); 80.5 (dd, $J_{\text{Rh-P}} \sim 161.7$, $J_{\text{P-P}} \sim 26.0$, P-N).

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