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An Asymmetric Hydrogenation System Breeding Its Own Counter-configurated Ligand

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Abstract: A homogeneous catalytic system based on Ruthenium-Skewphos complexes is presented, which breeds enantioselectively a precursor for the synthesis of Skewphos. In contrast to the known 'self breeding' system of Prophos, this system generates the precursor for the opposite enantiomer of the ligand to enable access to both enantiomers of Skewphos after one and two cycles, respectively.

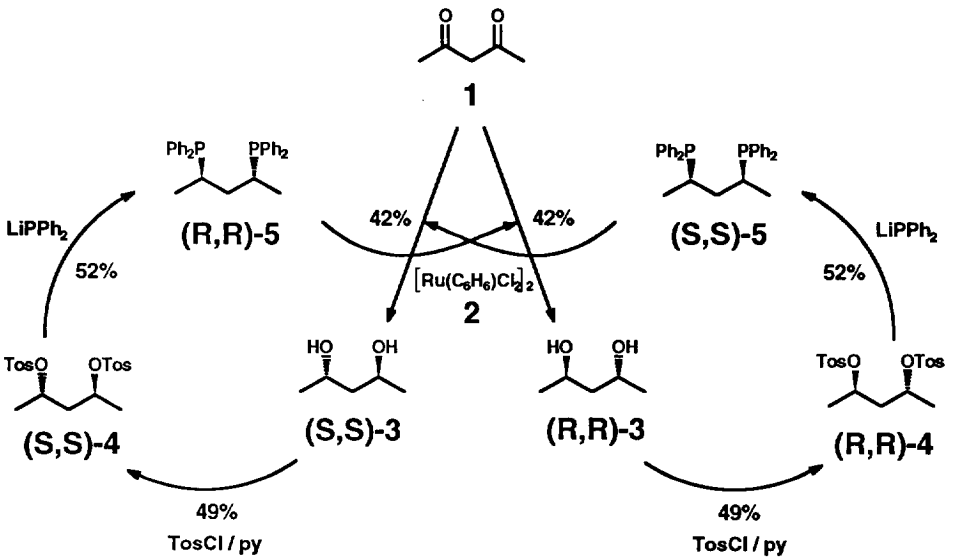
When Noyori et al. discovered the ability of Ruthenium(II)-BINAP complexes to hydrogenate substituted ketones with high enantioselectivities[2,3] it became clear that Ru-catalysts expanded significantly the area of double-bond containing substrates. Until today the highest enantioselectivities were obtained using BINAP or other atropisomeric phosphanes,[4,5] such as BIHEMP, while diarylalkyl phosphanes, which had proved their efficiency in Rhodium catalysts, were not very successful in Ruthenium catalysts up to now. In particular, the work of Genet proves the inferiority of these ligands compared to BINAP in the hydrogenation of carbonyl functions[6,7]. Surprisingly, Skewphos **5**[8] (BDPP[9]), a phosphane forming six-membered chelate rings, showed considerable efficacy as cocatalyst upon hydrogenation of substituted ketones in our hands. This led to the idea to hydrogenate 2,4-pentanedione **1** with a preformed but not isolated Ruthenium-(S,S)-Skewphos catalyst in analogy to the method described by Noyori.[10] The resulting 2,4-pentanediol **3** could be the starting material for a synthesis of Skewphos **5** itself,[11] provided one of the intermediates could be enriched to enantiopurity.

A process, in which a metal complex containing a chiral ligand catalyzes the formation of a product which can be converted into the chiral ligand of the catalyst, is called 'self breeding'. In the literature there is the self breeding Prophos system,[12] involving the asymmetric hydrogenation of 2-acetoxyacrylic acid with an *in situ* Rhodium-Prophos catalyst which gave an enantiomerically enriched lactic acid derivative. Transformation of these lactic acid derivatives yielded Prophos of the same configuration as used in the hydrogenation step.

The hydrogenation of 2,4-pentanedione **1** with a catalyst prepared from (S,S)-Skewphos **(S,S)-5** and $[Ru(C_6H_6)Cl_2]_2$ **2** in methanol (substrate/catalyst ratio = 1700) at 80°C under 80 bar of hydrogen resulted in quantitative formation of a mixture of the corresponding 2,4-pentanediols in a ratio of 73 (S,S) : 25 (R,S) : 2 (R,R) (the optical purity of the product was 71%). Thus, the enantioselectivity was 97%ee, whereas the diastereoselectivity reached only 50%de. This mixture could be easily enriched to enantiomeric purity by two

crystallizations from petroleum ether (bp 40 - 60°C) giving a 42% chemical yield of (2S,4S)-2,4-pentanediol **(S,S)-3** (Scheme 1).

Scheme 1:



If the reaction temperature was increased to 120°C, the optical yield fell to 67%, while at room temperature no reaction occurred. Substitution of methanol by dichloromethane suppressed the reaction at any temperature.

The enantiomerically pure (2S,4S)-2,4-pentanediol **(S,S)-3** was activated by tosylation with 4-$CH_3C_6H_4SO_2Cl$/pyridine and transformed to the bisphosphane (R,R)-Skewphos **(R,R)-5** upon treatment with $LiPPh_2$ with an overall yield of 25%. Since this product got the opposite configuration compared to the ligand used in the hydrogenation step, it is not correct to speak of a self breeding process. We prefer to talk about 'cross breeding' in analogy to the cross catalysis of certain kinetic systems. In Scheme 1 this fact becomes visible at the point, where the cocatalyst pathways cross each other. Each cycle of this system results in the production of a 150 to 200-fold amount of the other enantiomer of Skewphos compared to that used in the hydrogenation step. To obtain Skewphos with the original configuration, a second run through this breeding cycle has to be performed.

Experimental part

The analytical data of all the described substances were identical to those in the literature[11], if not otherwise stated.

(2S,4S)-2,4-Pentanediol (S,S)-3

50.0 mg of $[Ru(C_6H_6)Cl_2]_2$ **2** (100 μmol) and 92.4 mg of (S,S)-Skewphos **(S,S)-5** (210 μmol) were dissolved in 3.5 ml of dry DMF under exclusion of air in a Schlenk tube and heated for 15 min at 100°C. The solvent was evaporated at ambient temperature in a high vacuum and the remaining red residue was taken up in 40 ml of MeOH. 8 ml of this solution/suspension were added under N_2 to a deaerated mixture of 7.0 ml of 2,4-pentanedione **1** (6.8 g, 68 mmol) and 2 ml of MeOH to be hydrogenated at 80°C and 80 bar H_2 for 16 h. After distillation of the reaction mixture the crude (2S,4S)-2,4-pentanediol **(S,S)-3** (optical purity 71%) was recrystallized twice from petroleum ether (bp 40 - 60°C) to obtain the enantiomerically pure product in form of white crystals (3.0 g, 42%).

The (R,R)-configurated product **(R,R)-3** was obtained analogously by using (R,R)-Skewphos **(R,R)-5** as a ligand.

(2S,4S)-2,4-Bis(toluene-4'-sulfonyloxy)pentane (S,S)-4

The product **(S,S)-4** was obtained from **(S,S)-3** according to ref. 11 in 49% yield. $[\alpha]_D^{22}$ (c 3, $CHCl_3$): 5.6 (lit.: 90% yield, $[\alpha]_D^{22}$ (c 3, $CHCl_3$): 6.5). The deviation of the optical rotation seems to be due to traces of MeOH, the solvent used for recrystallisation. The presence of even small amounts of this solvent increases the optical rotation significantly.

(2R,4R)-2,4-Bis(diphenylphosphino)pentane ((R,R)-Skewphos) (R,R)-5

A solution of 10.3 g of **(S,S)-4** (25.0 mmol) in 100 ml of THF was added under vigorous stirring to 60 ml of a 1 M solution of $LiPPh_2$ (60 mmol, prepared by reaction of 6.0 g of Li and 53 ml of $ClPPh_2$ in 280 ml of THF) maintaining a temperature of -10 to -5°C. Precipitation of Li-tosylate occuring after half of the addition rendered stirring more difficult. The reaction mixture was allowed to warm up to room temperature over night and was hydrolyzed with 50 ml of deoxygenated H_2O. After removal of the THF the residue was extracted with petroleum ether. The organic phase was concentrated and brought onto a chromatographic column (45 x 340 mm) prepared with petroleum ether. The product was eluted with a solvent gradient (1%, 2%, 5%, and 10% ethyl acetate in petroleum ether), separated from the forerunning impurities (Ph_2PH and Ph_2PPPh_2) and concentrated to dryness. The product was obtained as an air-sensitive, colorless oil (5.7 g, 52%), which solidified upon cooling to -30°C.

The (S,S)-configurated product has been obtained in a similar manner starting from **(R,R)-4**.

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References

[1] H. Brunner, C. Henrichs, *Tetrahedron: Asymmetry*, in print.

[2] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **109** (1987) 5856.

[3] Review: H. Takaya, T. Ohta, R. Noyori, "Asymmetric Hydrogenation" in I. Ojima (Ed.) "Catalytic Asymmetric Synthesis", VCH, New York 1993, p.1.

[4] R. Schmid, M. Cereghetti, B. Heiser, P. Schönholzer, H.-J. Hansen, *Helv. Chim. Acta* **71** (1988) 897.

[5] R. Schmid, J. Foricher, M. Cereghetti, P. Schönholzer, *Helv. Chim. Acta* **74** (1991) 370.

[6] J. P. Genet, X. Pfister, V. Ratovelomanana-Vidal, C. Pinel, J. A. Laffitte, *Tetrahedron Lett.* **35** (1994) 4559.

[7] J. P. Genet, V. Ratovelomanana-Vidal, C. Pinel, *Synlett* (1993) 478.

[8] P. A. MacNeil, N. K. Roberts, B. Bosnich, *J. Am. Chem. Soc.* **103** (1981) 2273.

[9] J. Bakos, I. Tóth, L. Markó, *J. Org. Chem.* **46** (1981) 5427.

[10] M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **32** (1991) 4163.

[11] J. Bakos, I. Tóth, B. Heil, L. Markó, *J. Organomet. Chem.* **279** (1985) 23.

[12] M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **100** (1978) 5491.

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