Journal of Organometallic Chemistry, 344 (1988) 89–92
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Chiral bicyclic *O,N*-bis(diphenylphosphino)aminoalkanols as ligands for enantioselective metal complex hydrogenation catalysts

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(Received September 18th, 1987)

Abstract

The enantiomers of *O,N*-bis-(diphenylphosphino)-2-*exo*-hydroxy,3-*endo*-methylamino-norbornane have been prepared from the corresponding aminoalcohols and Ph_2PCl. These compounds have been used as ligands for Rh complexes and tested in asymmetric hydrogenation of α-acetamidocinnamic acid, methyl-α-acetamidocinnamate and acetamidoacrylic acid. Optical yields of up to 90% were obtained.

Introduction

During the past years several chiral bidentate ligands, derived from optically active β-aminoalcohols, have been synthesized and successfully tested as ligands for the control of enantioselectivity in metal complex-catalyzed asymmetric reactions [1–4].

We recently reported on the use of norbornene- and 7-oxanorbornane-based chiral bisphosphines as ligands for the rhodium-catalyzed asymmetric hydrogenation of C=C double bonds [5].

We now report the first results obtained with a ligand bearing *O*-diphenylphosphino and *N*-diphenylphosphino groups on the same rigid backbone. Starting from the pure enantiomers of *trans*-methylaminonorbornanol, the phosphinated derivatives *O,N*-bis-(diphenylphosphino)-2-*exo*-hydroxy,3-*endo*-methylamino-norbornanes have been prepared by reaction with Ph_2PCl (Scheme 1).

Experimental

Chemicals and apparatus

Benzene was distilled over sodium benzophenone ketyl, and Et_3N was distilled from sodium. All operations were carried out under argon. The optical rotations were measured by use of a Zeiss-Polamat A instrument. Enantiomers were separated

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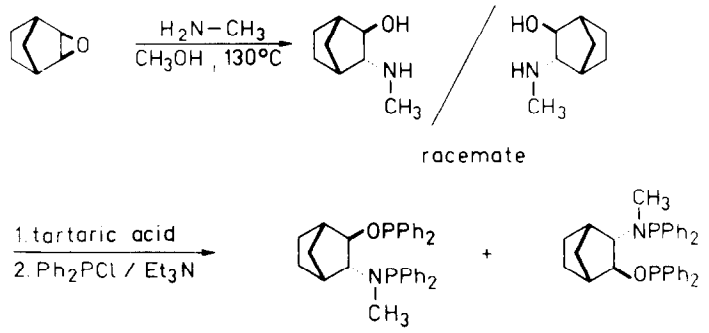


Scheme 1

on a fused silica capillary column containing *N*-stearoyl-valine-t-butylamide as chiral phase (6 m × 0.2 mm JD column at 125 °C isotherm for *N*-acetylalanine-methyl ester; 1 ml Ar/min; split 1 : 60). ^{31}P NMR spectra were recorded on a Varian-CFI-20 spectrometer.

Preparation of (±)-2-exo-hydroxy,3-endo-methylamino-norbornane (I)

A mixture of 17 g (0.15 mol) *exo*-norbornane epoxide [6] and 15 g (0.5 mol) of CH_3NH_2 was sealed in a pressure tube and heated at 130 °C for 170 h. The tube was cooled, opened and the reaction mixture evaporated to dryness. The residue was diluted with ether and the hydrochloride precipitated during treatment with HCl gas. The product was recrystallized from ethanol/acetone, m.p. 206–208 °C.

The methylaminonorbornanol hydrochloride was treated with KOH in ethanol, then filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from hexane, to leave 15 g (69%) of a white crystalline solid, m.p. 72–75 °C.

Anal. Found: C, 67.92; H, 10.87; N, 10.04. $C_8H_{15}NO$ calc: C, 68.04; H, 10.71; N, 9.92%.

Optical resolution of (±)-I

A solution of 16 g (0.113 mol) of I in 25 ml of ethanol was added to a heated solution of 17 g (0.113 mol) of (+)-tartaric acid in 10 ml H_2O. After 48 h the crystals which formed were separated from the mother liquor and washed with cold ethanol. Recrystallisation from ethanol yielded 16 g of the (+)-(+)-salt with $[\alpha]_D^{26} + 28°$ (*c* 1.0, EtOH) which was decomposed by a calculated amount of sodium ethoxide solution, and the insoluble material was filtered off. The solvent was removed under reduced pressure to give 6.5 g (81%) of (+)-2-*exo*-hydroxy,3-*endo*-methylamino-norbornane (Ia), which was recrystallized from hexane. m.p. 91–93 °C, $[\alpha]_D^{25} + 30°$ (*c* = 1, EtOH); $[\alpha]_D^{25} + 40.1°$ (*c* = 1, benzene). The mother liquor was concentrated under reduced pressure and 200 ml of acetone added to it. After 24 h at 0 °C the crystals were separated, desiccated and decomposed to leave 6.0 g (75%) (−)-2-*hexo*-hydroxy,3-*endo*-methylamino-norbornane $[\alpha]_D^{25} - 39{,}1°$ (c = 1,0, benzene).

(+)- and (−)-O,N-bis(diphenylphosphino)-2-exo-hydroxy,3-endo-methylamino-norbornane (IIa and IIb)

Table 1

Asymmetric hydrogenations of substrates **1–3** [a]

Catalyst	Solvent	Enantiomeric excess (%) in hydrogenation of		
		1	**2**	**3**
$[Rh(COD)Cl]_2$ + IIa	MeOH	85 (*R*)	87 (*R*)	89 (*R*)
$[Rh(COD)Cl]_2$ + IIb	MeOH	85 (*S*)	87 (*S*)	89 (*S*)
$[Rh(COD)_2]^+ BF_4^-$ + IIa	MeOH [b]	83 (*R*)	87 (*R*)	86 (*R*)

[a] Reaction conditions: 25 °C; 0.1 MPa H_2; 1 mmol substrate; 15 ml solvent; substrate/Rh = 100/1, conversion = 100%. Rh/ligand = 1/1 [b] Dioxane gave similar results.

To a magnetically stirred solution of 282 mg (2 mmol) Ia and Ib, respectively, and 0.79 ml (5.7 mmol) triethylamine in 8 ml dry benzene was added a solution of 0.72 ml (4 mmol) Ph_2PCl in benzene (6 ml) at 45–50 °C. The mixture was stirred for 1 h at this temperature and then for 2 h at room temperature. After filtration the solvent was removed under reduced pressure to yield 0.9 g (83%) (+)-*O*,*N*-bis(diphenylphosphino)-2-*exo*-hydroxy,3-*endo*-methylamino-norbornane (IIa) and the (−)-compound IIb, respectively. The products are colourless oils.

IIa. $[\alpha]_D^{25}$ +6.5° ($c = 1$, $CHCl_3$) $[\alpha]_D^{25}$ + 6.7° ($c = 1$, C_6H_6). Anal. Found: C, 75.36; H, 6.69; N, 2.50; P, 12.15. $C_{32}H_{33}NOP_2$ calc: C, 75.43; H, 6.53; N, 2.75; P, 12.15%.

IIb. $[\alpha]_D^{25}$ −6.2° ($c = 1$, $CHCl_3$) $[\alpha]_D^{25}$ −6.3° ($c = 1$, C_6H_6). Anal. Found: C, 75.30; H, 6.45; N, 2.55; P, 12.35%.

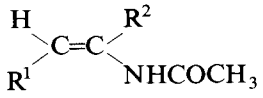
^{31}P NMR (vs. H_3PO_4 (ppm)): P (O) 107.3, 107.2; P(N) 52.7, 52.5.

Hydrogenation experiments

The hydrogenations were performed in a glass reactor. The catalysts were generated in situ from $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]^+BF_4^-$ and chiral ligand in degassed methanol and added at once to the substrate solution by syringe. The enantiomer ratio of the hydrogenation products was determined by GLC of the esters. The reaction conditions are given in Table 1.

Results and discussion

The optical resolution of the racemic *trans*-methylaminonorbornanol was successful and resulted in good yields when tartaric acid was used as described by Mousseron and Granger for *trans*-methylaminocyclohexanol [7]. After transformation with Ph_2PCl the enantiomers of the bidentate ligand with P–O–R–N–P structure (R = chiral bridge) were used for the asymmetric hydrogenation of the prochiral substrates **1–3**.



(**1**: R^1 = Ph, R^2 = COOH;
2: R^1 = Ph, R^2 = $COOCH_3$;
3: R^1 = H, R^2 = COOH)

The absolute configuration is not yet clear and can only be supposed by comparison with similar catalytically systems.

The results summarized in Table 1 show that the ligand gives high enantioselectivity. Both types of catalyst (cationic and neutral chloro complex) behave similarly with respect to optical yield and hydrogenation rate ($t/2$ in the range of 2 min). The (+)-ligand gives (*R*)-(−)-*N*-acetylphenylalanine and (−)-ligand yields (*S*)-(+)-*N*-acetylphenylalanine, the other hydrogenation products being the same. It should be noted that the methanolic solutions of the catalysts prepared in situ were stable for several days under argon. Thus solvolysis by MeOH of the N–P or O–P bond seems to be insignificant.

Acknowledgement

The authors thank Mrs. Chr. Fuhrmann, Mrs. E. Lampe and Mrs. R. Lilienthal for help in the experimental work.

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