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Asymmetric hydrogenation catalyzed by CARAPHOS-rhodium

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Abstract

The enantiomers of CARAPHOS, the aminophosphine phosphinite derivative of the β-blocker Carazolol, have been prepared and investigated as ligands in the rhodium catalyzed asymmetric hydrogenation of non-proteinogenic amino acid precursors. In comparison with the similar catalysts PROPRAPHOS and PINDOPHOS the observed optical yields in the range of 85–87% ee were lower by about 6–8%. The resolution of racemic Carazolol into its optical antipodes is described.

Keywords: Chiral rhodium complexes; Aminophosphine phosphinites; Asymmetric hydrogenation; Carazolol

1. Introduction

Rhodium complexes of chiral aminophosphine phosphinites have been extensively studied as catalysts in asymmetric hydrogenations of amino acid precursors [1–4].

The origin of their chirality is mostly based on the natural amino acid pool bearing the stereogenic center on the N-bonded carbon atom. Systematic modification of the phosphorus residues opened the possibility to hydrogenate activated ketones [5–7]. During the last years our own interest in the field of aminophosphine phosphinites was focused on a new source of chiral 1,2-aminoalcohols well known as β-blockers and therefore commercially available. Now the stereogenic center is situated on the O-bonded carbon atom. The enantiomers of Propranolol [8] and Pindolol [9] were converted into the corresponding aminophosphine phosphinite rhodium complexes and used as catalysts in asymmetric hydrogenations of unusual amino acid precursors [10]. Both systems show very high activity and enantioselectivities up to 95% ee.

Here we like to report on a further catalyst of this type, based on Carazolol, and its use in asymmetric hydrogenations of *N*-Boc protected dehydroamino acid derivatives according to Scheme 1.

2. Results and discussion

2.1. Optical resolution of (R / S)-Carazolol

Racemic Carazolol, **I**, was dissolved in hot MeOH and a stoichiometric quantity of (+)-di-

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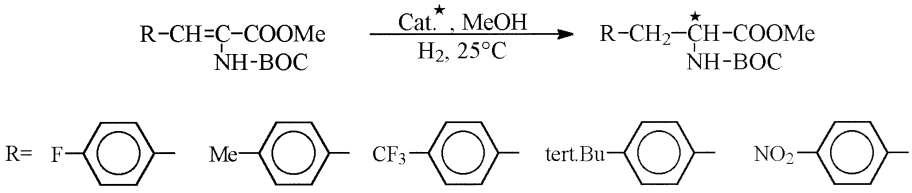
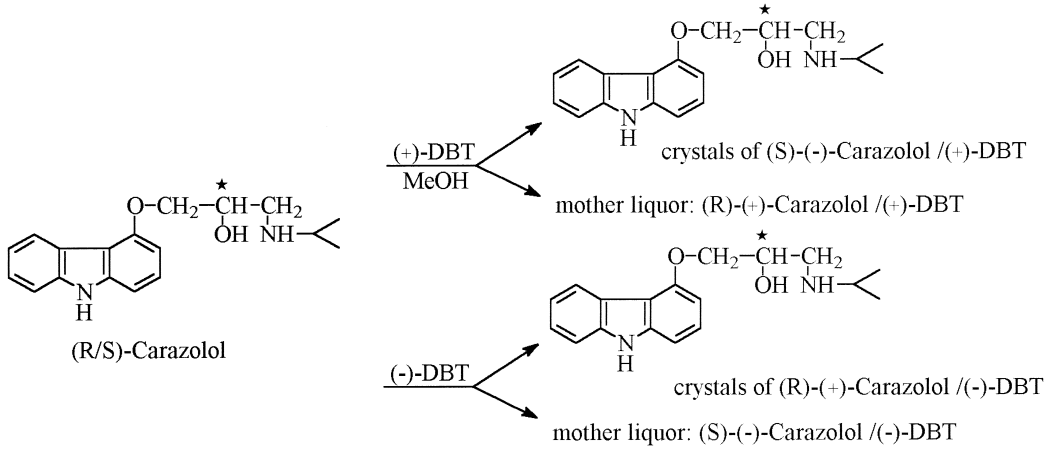


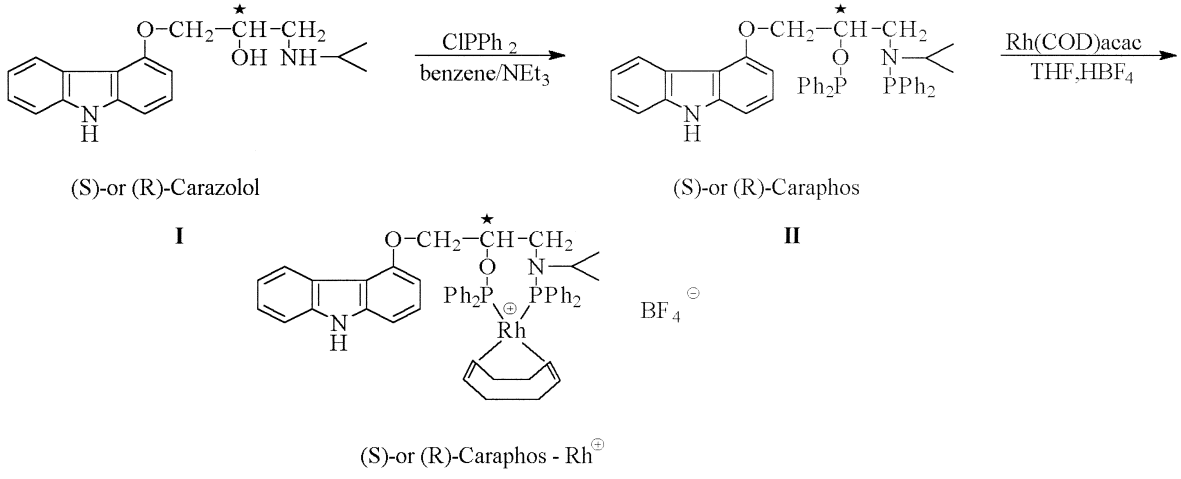
Scheme 1.

benzoyltartaric acid (abbreviated (+)-DBT) in hot methanol is added. (+)-DBT forms with (*S*)-(−)-Carazolol the less soluble diastereomer isolated after standing for 2 days at room temperature in about 71% optical purity showing $[\alpha]_D^{25}$ 55° for the diastereomer.

NaOH treatment of the diastereomer suspension in chloroform leads to the (*S*)-enantiomer,



Scheme 2. Resolution of racemic Carazolol.



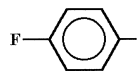
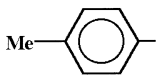
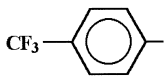
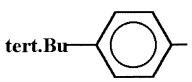
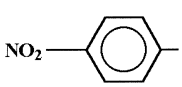
Scheme 3. Preparation of the catalyst.

$[\alpha]_D^{25}$ −17°. In a second resolution step the optical rotations change to 51.7 and −21.5° (89.6% o.p.), respectively. The more soluble diastereomer (*R*)-(+)-Carazolol/(+)-DBT was obtained after concentration of the mother liquor and showed an optical rotation of $[\alpha]_D^{25}$ 68° after the first step. Instead of a third resolution step we preferred alternatively the repeated crystallization of the enriched enantiomers from ethanol under HPLC control. As expected the use of (−)-DBT leads to the less soluble (*R*)-(+)-Carazolol/(−)-DBT diastereomer (−55°) and the enriched (*R*)-(+)-enantiomer (17°), Scheme 2.

Reaction of the pure enantiomers with P-chlorodiphenylphosphine leads to (*S*)- and (*R*)-CARAPHOS, **IIa**, **IIb**. The isolated viscous oils became solid powders after drying under reduced pressure. In a usual ligand exchange reaction with Rh(COD)acac and HBF_4 the cationic complexes are formed in pure solid state (Scheme 3). It is somewhat surprising that the mass spectrum registered the mol peak for the dimeric complex $Rh(CARAPHOS)_2$ (1435 Da/e). There is no hint in the ^{31}P NMR spectrum for this kind of coordination. It can be supposed that under mass spectrometric conditions COD leaves the coordination sphere and the dimeric complex is formed. On the other hand the very similar catalyst PINDOPHOS-Rh^+ (the difference exists in the indol unit instead of the carbazole part) does not show this behaviour.

The results of the catalytic measurements

Table 1
Asymmetric hydrogenation of amino acid precursors with CARAPHOS-Rh ⊕

Substrate	Catalyst **III a**		Catalyst **III b**	
	$t/_2$ (min)	% ee (config.)	$t/_2$ (min)	% ee (config.)
AMe	1	76(R)	1	78(S)
	8 (4)*	86(R) (94)*	8 (4)*	87(S) (94)*
	10 (7)*	84(R) (93)*	11	85(S)
	10	85(R)	10 (5)*	86(S) (94)*
	15 (7)*	85(R) (92)*	15	86(S)
	9 (5)*	85(R) (93)*	9 (6)*	85(S) (94)*

AMe = methyl(*Z*)-α-acetamidocinnamate.
The hydrogenation experiments were performed in a standard apparatus: 1.0 mmol of substrate, 15 ml of methanol, 25°C, and 0.1 MPa H_2 pressure, 0.01 mmol of catalyst. Enantiomeric excesses (% ee) were determined by HPLC analysis on chiral columns.
* Data obtained with PINDOPHOS-Rh^+ as catalyst [9]; $t/2$ is the time needed for 50% conversion, an usual parameter to compare the activity of catalysts.

using six selected substrates are summarized in Table 1. They are confirmed by the good agreement of the CD curves (Fig. 1). The high hydrogenation rate in case of the standard substrate methyl (*Z*)-α-acetamidocinnamate (AMe) is rather diffusion controlled than the true rate. In comparison with the catalyst PINDOPHOS-Rh^+ the complexes **III** (a,b) are less active by the factor 2 and the enantioselectivity is diminished by 6–8%.

Table 2 shows the ^{31}P NMR data of the complex **III** in comparison to the complexes of PINDOPHOS and PROPRAPHOS.

The chemical shifts as well as the coupling constants of the CARAPHOS-Rh^+ complexes (**IIIa**, **IIIb**) do not show significant differences in comparison with the structural similar complexes PINDOPHOS-Rh^+ and PROPRAPHOS-Rh^+. They cannot give arguments for the reduced catalytic efficiency of the complexes **IIIa** and **IIIb**. We suppose that the enlarged residue (carbazole) in the ligand exerts a negative steric influence on the coordination sphere during the catalytic process.

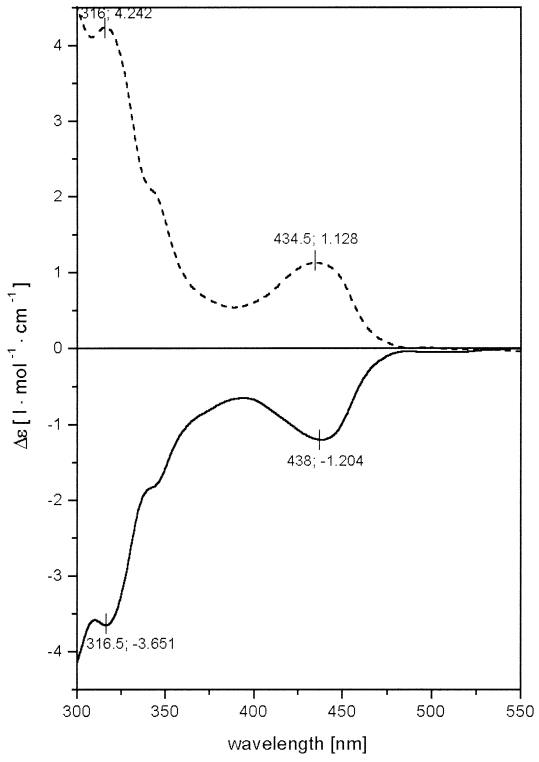


Fig. 1. Shows the CD spectra of the enantiomeric complexes **IIIa**, **IIIb** with the expected Cotton effects. ———— Rh-(*R*)-CARAPHOS(COD), **IIIb**; --- Rh-(*S*)-CARAPHOS(COD), **IIIa**.

3. Experimental

3.1. General

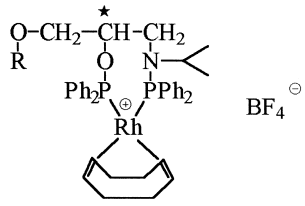
Optical rotation was measured on a Gyromat-HP polarimeter (Fa. Dr. Kernchen, Seelze). The optical purity of Carazolol was controlled by HPLC on a Hewlett-Packard 1090 chromatograph Series II fitted with 50×4.6 mm^2 Chiracell OF column (eluent: *n*-hexane/isopropanol/$NHEt_2$ = 60/40/0.2). The enantiomeric excess (% ee) of the hydrogenation products was determined by HPLC using a 250×4.6 mm^2 Chiracell OD column (eluent: *n*-hexane/isopropanol). Melting points were determined on a Boetius microscope. CD spectra were recorded on a Jasco J-170 CD spectrometer. The ^{31}P NMR spectra were recorded on Bruker AC 250 and ARX 400 spectrometers. The ^{31}P chemical shifts are related to H_3PO_4. The mass spectra were recorded on a Micro Mass Quattro II, ESI^+ and AMD 402/3 (Cl, isobutane, source temperature 200°C) spectrometers.

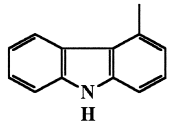
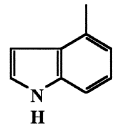
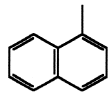
The hydrogenation was carried out in a standard apparatus. Work up: In general the methanol solution from the hydrogenation was freed from the solvent under reduced pressure. The resulting oily or solid products were dissolved in some milliliter of benzene and filtered on a small column of silica (Kieselgel 60, Fa. Merck) to remove the catalyst. The benzene was evaporated to give solid sometimes oily compounds.

3.2. Chemicals

The *N*-Boc-enamides and their hydrogenation products have been described in earlier

Table 2
^{31}P NMR chemical shifts δ (ppm) and ^{103}Rh–^{31}P and ^{31}P–^{31}P coupling constant J of CARAPHOS-Rh in comparison with PINDOPHOS-Rh and PROPRAPHOS-Rh



R	$\delta_{P(O)}$	$\delta_{P(N)}$	coordination chemical shift $\Delta^{a)}$		Ref.
			$\delta_{P(O)}$	$\delta_{P(N)}$	
	126.2 dd (173;27.5)	78.6 dd (158;27.6)	14.0	29.4	
	126.7 dd (172.4;26.1)	77.1 dd (157.4;26.1)	13.8	27.3	9
	126.4 dd (173;26)	80.7 dd (159;26)	13.9	31.7	12

publications [9,11]. (*S*)-Carazolol, **Ia**, first step: To 1.49 g (5 mmol) of the racemic Carazolol dissolved in 7.5 ml of hot methanol was added the hot solution of 1.79 g (5 mmol) (+)-DBT in 7.5 ml methanol. After standing for 2 days at room temperature the crystals were collected, washed with a small amount of cold methanol and dried. Yield: 1.65 g of the diastereomeric salt (−)-(*S*)-Carazolol × (+)-DBT, $[\alpha]_D^{25}$ 55.0 (c 0.5, MeOH). To a stirred suspension of 6.5 g of (−)-(+)-salt in chloroform (200 ml) was added 0.5 N NaOH (50 ml) in small portions. After the salt was completely dissolved the organic layer was separated, washed twice with 25 ml of water, dried with Na_2SO_4 and evaporated. Yield: 2.54 g (85%), $[\alpha]_D^{25}$ −17 (c 1.0, CH_3COOH). The mother liquor contains 1.63 g of the (+)-(+)-diastereomer, $[\alpha]_D^{25}$ between 65 and 67 (c 0.5, MeOH). Treatment with NaOH as described leads to (*R*)-enantiomer with $[\alpha]_D^{25}$ 16.5 (c 1.0, CH_3COOH). Second step: 1.49 g of (−)-Carazolol (−17.1) and 1.79 g of (+)-DBT were reacted in 15 ml of methanol. After 20 h the crystals were separated. Yield: 2.86 g (87%), $[\alpha]_D^{25}$ 51.7 (c 0.5, MeOH), leading to 1.16 g (90%) of the (−)-enantiomer with $[\alpha]_D^{25}$ −21.5 (c 1.0, CH_3COOH) according to 88.5% optical purity. For further purification four crystallizations from EtOH were needed as follows: 5.53 g of the enriched enantiomer (−21.1°, 86.8% o.p.), were recrystallized from 20 ml of EtOH to give 4.69 g (85%, 92.2% o.p.) after standing for 24 h at room temperature. 4.69 g, 17 ml of EtOH, gave 4.08 g (87%, 95.2% o.p.), 4.08 g, 16 ml of EtOH, gave 3.56 g (87%, 97.8% o.p.), 3.56 g, 14 ml of EtOH, gave 3.03 g (85%, > 99% o.p.), $[\alpha]_D^{25}$ −24.1 (c 1.0, CH_3COOH), m.p. 153–155°C; $C_{18}H_{22}N_2O_2$ (298.3), calcd. C, 72.46; H, 7.43; N 9.39, found: C, 72.13; H, 7.35; N 9.32.

In the same manner (*R*)-(+)-Carazolol, **Ib**, was obtained: o.p. > 99% ee, $[\alpha]_D^{25}$ 24.2 (c 1.0, CH_3COOH), m.p. 154–155°C; found C 72.20 H 7.33 N 9.30. The data of an original sample (Boehringer Mannheim) were found to be $[\alpha]_D^{25}$ 24.3 (c 1.0, CH_3COOH) according to 99.7% ee by HPLC, m.p. 151–153°C.

(*S*)-CARAPHOS, **IIa**: To a solution of (*S*)-Carazolol (0.74 g, 2.5 mmol, 99% ee) in dry benzene (20 ml) and NEt_3 (2.1 ml, 15 mmol) *P*-chlorodiphenylphosphine (0.98 ml, 5 mmol) dissolved in benzene (5 ml) was added within 60 min at 50°C under argon with stirring. After heating at 80°C for 6 h the mixture was kept under argon at room temperature over night. Filtration over Celite (1.5×10 cm^2), washing with dry benzene (3×20 ml) and evaporation under reduced pressure gave an oil, containing impurities of $NEt_3 \times HCl$ and phosphine oxide. The crude product was dissolved in dry ether (5 ml) and filtered over a column (1.5×10 cm) of basic Al_2O_3. After washing the column with ether (3×20 ml) and evaporation of the solvent the oily product was kept under vacuo at 50°C for 4 h to remove last traces of solvents. Yield: 1.2 g (72%), $[\alpha]_D^{25}$ 31.4 (c 0.5, benzene), m.p. 53–61°C. $C_{42}H_{40}N_2O_2P_2$ (666.7), calcd. C, 75.66; H, 6.05; N, 4.20; P 9.29; found: C, 76.09; H, 6.00; N, 4.10; P, 8.74; ^{31}P NMR ($CDCl_3$): δ 112.2 ppm (P(O)), 49.2 ppm (P(N)). MS: 666 (M^+), 500 ($M^+ -$ carazole), 185 (PPh_2).

(*R*)-CARAPHOS, **IIb**: Yield: 1.16 g (69.6%), $[\alpha]_D^{25}$ −30.7 (c 0.5, benzene), m.p. 50–57°C; found C 76.06 H 6.25 N 3.74 P 9.52; ^{31}P NMR ($CDCl_3$): δ 112.2 ppm (P(O)), 49.2 ppm (P(N)).

[Rh(COD)(*S*)-CARAPHOS]$^+BF_4^-$, **IIIa**: To a solution of **IIa** (0.75 g, 1.12 mmol) in dry THF (2.5 ml) under argon was added with stirring Rh(COD)acac (341 mg, 1.10 mmol). After 15 min HBF_4 (0.15 ml, 40% aqueous solution) and dry ether (15 ml) were added to precipitate the complex. To complete the precipitation the mixture was kept for 3 days at 5°C. The complex was filtered off, washed with dry ether and dried. Yield: 627 mg (58%), $C_{50}H_{52}N_2O_2P_2BF_4Rh$ (964.6), calcd. C, 62.26; H, 5.43; N, 2.90; P, 6.42; Rh, 10.67, found: C, 61.48; H, 5.27; N, 2.91; P, 6.14; Rh, 9.32. ^{31}P NMR (acetone-d_6): 126.2 ppm, δ P–O (dd, 173; 27.5 Hz); 78.6 ppm, δ P–N (dd, 158; 27.6 Hz); MS: 877 ($M - BF_4$), 500 ($M - (BF_4$, Rh(COD), carbazole)), 1435 (RhL_2).

[Rh(COD)(*R*)-CARAPHOS]$^+BF_4^-$, **IIIb**: Yield: 600 mg (55%), found C 61.18 H 5.25 N 2.57 P 6.33 Rh 11.10.

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