Pergamon

*Tetrahedron: Asymmetry*, Vol. 7, No. 4, pp. 1011-1018, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00105-X

# ENANTIOSELECTIVE HYDROGENATION OF DEHYDRO-AMINO ACID DERIVATIVES USING PINDOPHOS-RHODIUM AS CHIRAL CATALYST

Hans-Jörn Kreuzfeld*, Ute Schmidt, Christian Döbler and Hans Walter Krause

Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstraße 5-6, D-18055 Rostock, Germany

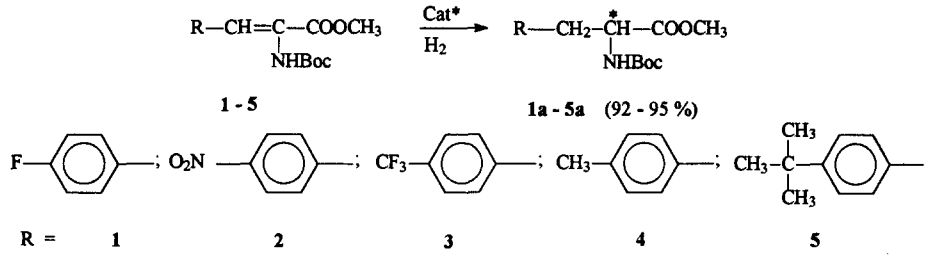
**Abstract:** The enantiomers of PINDOPHOS, the aminophosphine phosphinite derivative of the commercial ß-blocker Pindolol, were prepared and used as ligands in the rhodium catalyzed asymmetric hydrogenation of non-proteinogenic amino acid precursors. The isolated (R)- and (S)-configured rhodium complexes are highly active catalysts leading to (L)- or (D)-amino acids. Enantiomeric excesses between 92 and 95 % ee could be realized. The newly obtained amino acid derivatives were fully characterized by NMR spectroscopy.



## Introduction

During the last ten years a great variety of chiral aminophosphine phosphinites have been investigated and used as ligands for metal catalyzed asymmetric hydrogenations of amino acid precursors[1-4], activated ketones[5,6] and C-C-coupling reactions[7,8] as well as for the asymmetric hydroformylation[9]. Most of them are derived from the natural amino acid pool and therefore based on the chiral 1, 2-aminoalcohol moiety. ProNOP and AlaNOP are typical representatives of this type of chiral ligands, generated from prolinol and alaninol. The same fundamental structure can also be found among the pharmaceuticals well known as ß-adrenoreceptor antagonists (ß-blockers), but differing in the location of the stereogenic centre at the carbon atom bearing the alcohol function.

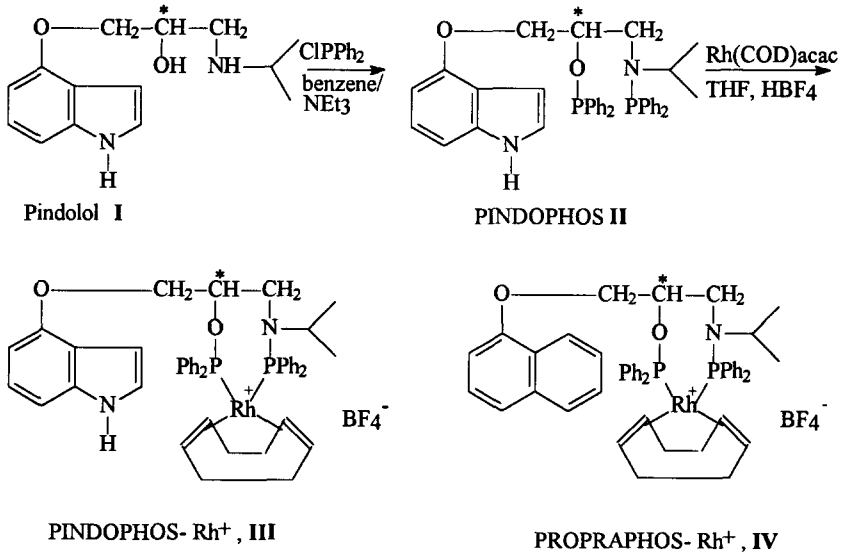
Some years ago we used this commercially available source for the modification of Propranolol to the chiral aminophosphine phosphinite ligand PROPRAPHOS[10]. The good experiences with PROPRAPHOS in rhodium catalyzed asymmetric hydrogenations of dehydroamino acid derivatives to synthesize non-proteinogenic amino acids[11] prompted us to look for a further 1.2-aminoalcohol in the series of ß-blockers. We selected Pindolol, **I**, which offers the possibility for derivatization at the nitrogen atom of the indole unit, a target to be investigated in future. In the present work we like to report on the preparation of the PINDOPHOS-Rh complex **III** in both the (S)- and (R)-configuration and its use in asymmetric hydrogenations of N-Boc protected dehydroamino acid derivatives 1-5 (Scheme 1).




Scheme 1

**Results and Discussion**

Racemic Pindolol, **I**, was resolved by use of di-O-p-toluyl-tartaric acid in methanolic solution. Both enantiomers, **Ia**, **Ib**, are available in sufficient yield and good enantiomeric excess after two steps. The following reaction with P-chlorodiphenylphosphine (Scheme 2) in the presence of triethylamine leads to the corresponding (S)- or (R)-PINDOPHOS, **IIa**, **IIb**. The isolated very viscous oils are not free of phosphorus containing impurities (traces) as indicated by the $^{31}P$ NMR spectra.




Scheme 2

Complex formation is accomplished by addition of Rh(COD)acac and $HBF_4$ in THF giving either the (S)- or the (R)-configured cationic rhodium complex, **IIIa**, **IIIb**, in a highly pure solid state.

The CD spectra of the enantiomeric complexes given in Figure 1 show the expected Cotton effects to be nearly identical with respect to the intensities and opposite sign. This finding is in good agreement with the catalytic behaviour leading to the same activity and stereoselectivity as shown below in the hydrogenation of dehydroamino acids.

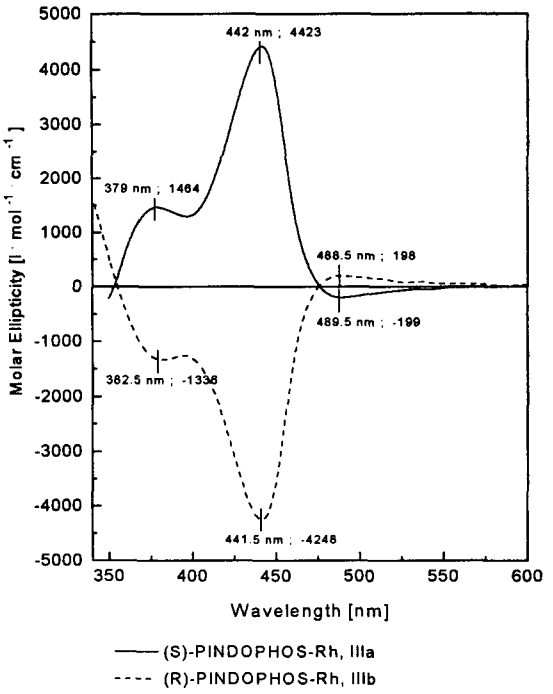



Figure 1. CD spectra of—(S)-PINDOPHOS-Rh, IIIa and --- (R)-PINDOPHOS-Rh, IIIb in methanol at 24°C

**Table 1**. Asymmetric hydrogenation of **1 - 5** catalyzed by PINDOPHOS - $Rh^+$, **III,** and PROPRAPHOS-$Rh^+$,**IV.**

| Catalyst | Substrate | t/2 min | ee % | Abs. Config. |
|---|---|---|---|---|
| (R)- **III** | **1** | 4 | 94 | (L) |
| (R)- **III** | **2** | 6 | 94 | (L) |
| (R)- **III** | **3** | 5 | 94 | (L) |
| (S)- **III** | **1** | 4 | 94 | (D) |
| (S)- **III** | **2** | 5 | 93 | (D) |
| (S)- **III** | **3** | 4 | 95 | (D) |
| (S)- **III** | **4** | 7 | 93 | (D) |
| (S)- **III** | **5** | 7 | 92 | (D) |
| (S)- **IV** | **1** | 9 | 92 | (D) |
| (S)- **IV** | **2** | 6 | 92 | (D) |
| (S)- **IV** | **3** | 6 | 93 | (D) |

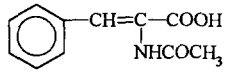
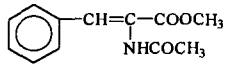
The hydrogenation experiments were performed in a standard apparatus. 1.0 mmol of substrate, 15 ml of methanol at 25 °C and 0.1 MPa $H_2$ - pressure, 0.01 mmol of catalyst. Rates < 5 minutes are diffusion controlled rather, than true reaction rates.enantiomeric excesses (ee %) were determined by HPLC analysis on chiral columns.

The $^{31}P$ NMR spectrum of PINDOPHOS-$Rh^+$, **III**, unambiguously confirms the lack of any additional interaction between the indolyl nitrogen and rhodium. In comparison with PROPRAPHOS-$Rh^+$, **IV**, both complexes show the same phosphorus-phosphorus coupling constants, $J_{P,P}$, in the range of 26 to 27 Hz. In addition, a strong coordination of the nitrogen, connected with an increased coordination number, would inhibit the oxydative addition of hydrogen during the catalysis and is therefore incompatible with the high activity observed for PINDOPHOS-$Rh^+$, **III**. In fact, such a relationship has been reported by K. Achiwa et al.[12] for the cationic rhodium complex of the pyrrolidinobisphosphine PPM.

The results of the hydrogenation of **1-5** are summerized in Table 1.

To check the productivity of **III** the substrate: catalyst ratio was enlarged using the standard substrates (Z)-α-acetamidocinnamic acid and methyl (Z)-α-acetamidocinnamate. Table 2 shows the results based on 0.01 mmol of catalyst.

**Table 2** Asymmetric hydrogenation of standard substrates by variation of the substrate/catalyst ratio

| Substrate | Catalyst | Substrate/ Catalyst | t/2 (min) | rate (ml $H_2$ / min) | ee (%) | Conf. (D / L) |
|---|---|---|---|---|---|---|
|  | (R) **III** | 1000 | 3.5 | 31.0 | 91 | L |
| | | 2000 | 7.0 | 32.0 | 90 | L |
| | | 3000 | 16.0 | 22.5 | 90 | L |
| | (R) **IV** | 2000 | 5.5 | 40.0 | 86 | L |
| | | 3000 | 20.6 | 16.3 | 85 | L |
|  | (R) **III** | 1000 | 4.0 | 28.0 | 90 | L |
| | | 2000 | 3.7 | 30.0 | 89 | L |

Condition: see Table 1. Conversion 100 %

The crucial point and rate limiting factor of these experiments is the increasing oxygen sensitivity of the catalytic system. In spite of repeated careful evacuation last traces of air included in the crystalline powder of the substrates are difficult to remove. Up to a ratio of 3000:1 the enantioselectivity and conversion are not significant influenced. The hydrogenation rate is reduced to about 1 mmol $H_2$ per minute.

The results of the present investigation (Table 1 and 2) show that PINDOPHOS-$Rh^+$ is a very effective catalyst for asymmetric hydrogenations of unsaturated amino acid precursors, readily prepared from the commercially available Pindolol. In comparison with PROPRAPHOS-$Rh^+$ the PINDOPHOS system acts with a slightly increased enantioselectivity and a significant higher activity in most cases. The Boc protecting group is tolerated. It will be of interest to modify the electronic as well as the steric conditions around the

rhodium by substitution at the heterocyclic nitrogen atom and to investigate the consequences. These experiments are under work.

**Experimental**

Apparatus: Optical rotation was measured on a GYROMAT-HP polarimeter (Fa. Dr. Kernchen, Seelze). The enantiomeric excess (% ee) was determined by GLC on a Hewlett-Packard chromatograph 5880 A fitted with a 4.3 m capillary column XE-60 (N-L-valine-tert.butylamide), FID, split 1:60, 175 °C, for the acetyl-derivatives, by HPLC on a Hewlett-Packard 1090 chromatograph Series II fitted with 50 x 4.6 mm CHIRACEL OD and 250 x 4.6 mm CHIRACEL OD columns (eluent: n-hexane/isopropanol) for the Boc-derivatives. Melting points were determined on a Boetius microscope. CD spectra were recorded on a Jasco J-710 CD spectrometer. The $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra were recorded on a BRUKER spectrometer AC 250 ($^{1}H$: 250.1 MHz, $^{13}C$: 62.9 MHz, $^{31}P$: 101.3 MHz). The $^{1}H$ and $^{13}C$ chemical shifts are related to TMS. The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: $\delta$ $^{1}H$ = 7.25, $\delta$ $^{13}C$ = 77.0). The assignment of the $^{13}C$ signals was achieved by recording the DEPT spectra. The $^{31}P$ chemical shifts are related to $H_3PO_4$. The mass spectra were recorded on a AMD 402/3 spectrometer (Cl, isobutane, source temperature 200 °C). 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 ml of benzene and filtered on a small column of silica (Kieselgel 60, Fa. Merck) to remove the catalyst quantitatively. The benzene was evaporated to give a solid, sometimes an oily product. The described method to separate the catalyst fails, when amino acids were isolated instead of the esters.

Chemicals: Pindolol, **I**, resolution with (S)- or (R)-di-O-p-toluyl-tartaric acid: (S,S)-salt: $[\alpha]_D^{25}$ -99 (c 1, MeOH), (R,R)-salt: $[\alpha]_D^{25}$ 97 (c 1, MeOH), (S)-Pindolol, **Ia**: m. p. 94-95 °C, $[\alpha]_D^{25}$ -4.8 (c 1, MeOH), -12.0 (c 1, EtOH) according to 99 % ee by HPLC*, (R)-Pindolol, **Ib**: $[\alpha]_D^{25}$ 11.7 (c 1, EtOH) according to 97 % ee by HPLC.

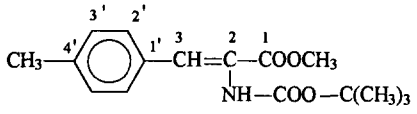
(S)-PINDOPHOS, **IIa**: To a solution of (S)-Pindolol (1.24 g, 5 mmol; $[\alpha]_D^{25}$ -12 (c 1, EtOH) in dry benzene (15 ml) and $NEt_3$ (4.2 ml, 30 mmol) P-chlorodiphenylphosphine (2 ml, 11 mmol) dissolved in benzene (10 ml) was added within 30 min. at 50 °C under argon with stirring. After heating under reflux for 4 h the mixture was kept under argon at room temperature over night. Filtration over Celite and evaporation under reduced pressure gave an oil, which dissolved in ether (3 ml) separated further crystals of $NEt_3$•HCl over night. After filtration and evaporation of the solvent the oily residue was kept under vacuo at 50 °C for 3 hours. Yield: 2.9 g (94 %), $[\alpha]_D^{25}$ 70.7 (c 0.74, benzene). $C_{38}H_{38}N_2O_2P_2$ (616.7), calcd. C 74.01 H 6.21 N 4.54 P 10.05; found C 73.98 H 6.41 N 4.58 P 10.05; $^{13}C$ NMR ($CDCl_3$): $\delta$ 79.3 (dd, $J_{P,C}$ = 18.1, $J_{P,C}$ = 3.0, CHO); 69.2 (d, $J_{P,C}$ = 4.8, $CH_2O$); 51.7 (d, $J_{P,C}$ = 13.8, CHN); 51.1 (dd, $J_{P,C}$ = 5.7, $J_{P,C}$ 5.7, $CH_2N$); 22.7 (d, $J_{P,C}$ = 18.4); $^{31}P$ NMR ($CDCl_3$) : $\delta$ 112.9 (P(O)); 49.8 (P(N)).

(R)-PINDOPHOS, **IIb**: Yield 2.85 g (92 %), $[\alpha]_D^{25}$ -67.2 (c 0.5, benzene), found C 73.85 H 6.26 N 4.50 P 10.16.

[(S)-PINDOPHOS-Rh(COD)]$BF_4$, **IIIa**: To a solution of **IIa** (2.77 g, 4.5 mmol) in dry THF (2.8 ml) was added with stirring under argon Rh(COD)acac (1.3 g, 4.5 mmol). Stirring was continued for 15 min. at room temperature and than $HBF_4$ (0.78 ml, 40 % aequous solution) was added. The complex crystallized rapidly on standing. In order to complete the crystallization the mixture was kept at 5 °C for several days. The yellow precipitate was filtered off, washed with THF/ether, and dried under vacuo ($H_2SO_4$). Yield: 2.1 g (50 %), m. p. 176-177 °C. $C_{46}H_{50}N_2O_2P_2BF_4Rh$ (914.6), calcd. C 60.41 H 5.50 N 3.06 P 6.77 Rh 11.25; found C 59.71 H 5.60 N 3.04 P 7.08 Rh 10.76. **IIIb**: Yield 2.4 g (58 %), m. p. 178-179 °C, found C 60.20 H 5.49 N 3.08 P 6.43 Rh 10.42. $^{31}P$ NMR (acetone-$D_6$): 126.7 (dd, $J_{P,Rh}$ 172.4; $J_{P,P}$ 26.1, P-O); 77.1 (dd, $J_{P,Rh}$ 157.4; $J_{P,P}$ 26.1, P-N).

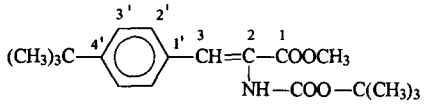
N-Boc-enamide derivatives: The precursors **1**, **2**, and **3** have been described[16]. The preparation of the substrates **4** and **5** follows the same procedure based on the general method reported by U. Schmidt et al.[13].

Methyl-(Z)-2-tert.butoxycarbonylamino-3-(4-methyl-phenyl)-propenoate **4**: Yield 81 %, m. p. 87-90 °C (light petroleum b. p. 80-100 °C), $C_{16}H_{21}NO_4$ (291.4), calcd. C 65.96 H 7.26 N 4.81; found C 65.77 H 7.13 N 4.87, MS: $[M + H]^+$: 292.



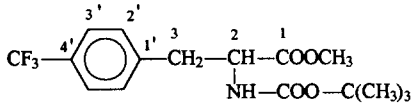

$^1H$ NMR: ($CDCl_3$): δ 7.44 (m, 2H, ph-2'); 7.23 (s, 1H, H-3); 7.15 (m, 2H, ph-3'); 6.07 (br, 1H, NH); 3.83 (s, 3H, $CH_3O$); 2.35 (s, 3H; $CH_3$-ph); 1.40 (s, 9H, $(CH_3)_3CO$); $^{13}C$ NMR: ($CDCl_3$): δ 166.1 (C-1); 152.9 (CONH); 139.4 (C-4'); 131.2 (C-1'); 130.7 (C-3); 129.8, 129.2 (C-2', C-3'); 123.9 (C-2); 80.7 ($(CH_3)_3\underline{C}O$); 52.3 ($CH_3O$); 28.1 ($(\underline{C}H_3)_3CO$); 21.3 ($CH_3$-ph).

Methyl-(Z)-2-tert.butyloxycarbonylamino-3-(4-tert.butyl-phenyl)-propenoate **5**: Yield 74 %, m. p. 88-91 °C (ether/hexane), $C_{19}H_{27}NO_4$ (333.4), calcd. C 68.44 H 8.16 N 4.20; found C 68.45 H 7.69 N 4.28, MS: $[M + H]^+$: 334,




$^1H$ NMR: ($CDCl_3$ : δ 7,48 ( m, 2H, ph-3'); 7.37 ( m, 2H, ph-2'); 7.23 ( s, 1H, H-3); 6.05 ( br, 1H, NH); 3.84 (s, 3H, $CH_3O$); 1.40 ( s, 9H, $(CH_3)_3CO$); 1.31 ( s, 9H, $(CH_3)_3C(ph)$); $^{13}C$ NMR: ($CDCl_3$) δ 166.1 (C-1); 153.0 (CONH); 152.6 (C-4'); 131.2 (C-1'); 130.6 (C-3); 129.6 (C-2'); 125.4 (C-3'); 124.2 (C-2); 80.8 ($(CH_3)_3\underline{C}O$); 52.4 ($CH_3O$); 34.7 ($(CH_3)_3\underline{C}(ph)$); 31.1 ($(CH_3)_3C(ph)$); 28.1 ($(\underline{C}H_3)_3CO$).

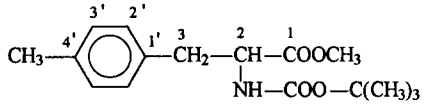
N-Boc-4-$CF_3$-D-PheOMe **3a**: $C_{16}H_{20}F_3NO_4$ (347.3), calcd. C 55.33 H 5.80 N 4.03; found C 55.40 H 5.60 N 4.10, m. p. 77-79 °C (pentane), $[\alpha]_D^{25}$ 8.1 (c 1, MeOH), $[\alpha]_D^{25}$ -44.3 (c 1, $CHCl_3$), 99 % ee by HPLC, MS: $[M + H]^+$: 348.



$^1$H NMR ($CDCl_3$): δ 7.54 (m, 2H, ph-3'); 7.24 (m, 2H, ph-2'); 4.99 (br, 2H, NH); 4.60 (br, 1H, CH); 3.71 (s, 3H, $CH_3O$); 3.19 (dd, 1H, $J_{3a,3b}$ = 13.8, $J_{3a,2}$ = 5.7, H-3a); 3.07 (dd, 1H, $J_{3a,3b}$ = 13.8, $J_{3b,2}$ = 6.3, H-3b); 1.39 (s, 9H, $((CH_3)_3CO$; $^{13}$C NMR ($CDCl_3$): δ 171.9 (C-1); 154.9 (NHCO); 140.4 (C-1'); 129.7 (C-2'); 129.3 (q, $J_{F,C}$ = 32.0; C-4'); 125.4 (q, $J_{F,C}$ = 3.7, C-3'); 124.2 (q, $J_{C,F}$ = 271.9, $CF_3$); 80.1 ($CH_3O$); 54.2 (C-2); 52.3 ($(CH_3)_3\underline{C}O$); 38.3 (C-3); 28.2 ($(CH_3)_3CO$).

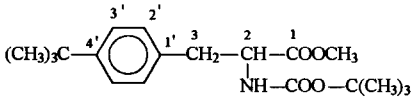
N-Boc-4-$CF_3$-D-PheOH, prepared by saponification of **3a**. Yield 82 %, $C_{15}H_{18}F_3NO_4$ (333.3), calcd. C 54.05 H 5.44 N 4.20; found C 54.15 H 5.56 N 4.32, m. p. 132-135 °C (light petroleum b. p. 80 - 100 °C), $[\alpha]_D^{25}$ -12.2 (c 1, EtOH), 97 % ee by HPLC. Prepared by direct asymmetric hydrogenation: m. p. 132 - 134 °C, $[\alpha]_D^{24}$ -12.3 (c 1, EtOH), $[\alpha]_D^{24}$ -5.0 (c 1, MeOH), 98 % ee by HPLC, found C 54.14 H 5.56 N 4.32; ref.[14]: m. p. 117-118 °C, $[\alpha]_D^{25}$ -4.8 (c 1, MeOH), ref.[15]: m. p. 132 °C, $[\alpha]_D^{25}$ 2.0 (c 1, EtOH) for the L-enantiomer. MS: $[M + H]^+$: 334.

N-Boc-4-$CH_3$-L-PheOMe **4a**: . Oil, which crystallized after days. In some cases crystallization from pentane at -15 °C could be realized. M. p. 27 - 29 °C, $[\alpha]_D^{24}$ 52.1 (c 1, $CHCl_3$), 98.4 % by HPLC. Racemate: m. p. 73 - 83 °C, $C_{16}H_{23}NO_4$ (293.4), calcd. C 65.51 H 7.90 N. 4.77; found C 65.38 H 7.89 N 4.81, MS: $[M + H]^+$: 294.



$^1$H NMR ($CDCl_3$): δ 7.08 (m, 2H, ph-3'); 7.00 (m, 2H, ph-2'); 4.92 (br, 1H, NH); 4.52 (br, 1H, CH); 3.70 (s, 3H, $CH_3O$); 3.06 (dd, 1H, $J_{3a,3b}$ = 14.0, $J_{3a,2}$ = 6.0, H-3a); 2.98 (dd, 1H, $J_{3a,3b}$ =14.0, $J_{3b,2}$ = 6.0, H-3b); 2.30 (s, 3H, $CH_3$ph); 1.40 (s, 9H, $(CH_3)_3CO$). $^{13}$C NMR ($CDCl_3$): δ 172.3 (C-1); 155.0 (NHCO); 136.5 (C-4'); 132.8 (C-1'); 129.2, 129.1 (C-2', C-3'); 79.8 ($CH_3O$); 54.4 (C-2); 52.0 ($(CH_3)_3\underline{C}O$); 37.8 (C-3); 28.2 ($(\underline{C}H_3)_3CO$); 20.9 ($CH_3$-ph).

N-Boc-4-tert.Bu-D-PheOMe **5a**: Oil. $[\alpha]_D^{24}$ -43.0 (c 1, $CHCl_3$), 99 % by HPLC, enriched by fractionated crystallization from pentane solution at low temperature. $C_{19}H_{29}NO_4$ (335.4), calcd. C 68.03 H 8.71 N 4.18, found C 67.88 H 8.54 N 4.00, MS: $[M + H]^+$: 336. Racemate: m. p. 52 - 56 °C.



$^1$H NMR ($CDCl_3$): δ 7.30 (m, 2H, ph-3'); 7.05 (m, 2H, ph-2'); 4.90 (br, 1H, NH); 4.58 (br, 1H, CH); 3.71 (s, 3H, $CH_3O$); 3.07 (dd, 1H, $J_{3a,3b}$ = 13.8, $J_{3a,2}$ = 5.5, H-3a) 2.98 (dd, 1H, $J_{3a,3b}$ = 13.8, $J_{3b,2}$ = 6.0, H-3b); 1.40 (s, 9H, $(CH_3)_3CO$); 1.29 (s, 9H, $(CH_3)_3C$(ph)); $^{13}$C NMR ($CDCl_3$): δ 172.4 (C-1); 155.0 (NHCO); 149.8

(C-4'); 132.9 (C-1'); 128.9 (C-2'); 125.4 (C-3'); 79.8 ($CH_3O$); 54.4 (C-2); 52.1 (($CH_3)_3\underline{C}O$); 37.8 (C-3); 34.4 (($CH_3)_3\underline{C}$(ph)); 31.3 (($\underline{C}H_3)_3$C(ph); 28.3 (($\underline{C}H_3)_3$CO).

**Acknowledgement**

The authors are grateful to Dr. Schareina for the CD spectra, Dr. Michalik for the NMR spectra and Mrss. S. Buchholz, I. Stahr, A. Modler, and B. Harzfeld for technical assistance. We thank the Welding GmbH & Co., Hamburg for the generous gift of Pindolol, and the Fonds der Chemischen Industrie for financial support.

**References**

1. Pracejus, G., Pracejus, H.; *J. Mol. Catal.* **1984**, 24, 227-230
2. Karim A., Mortreux, A., Petit, F., Bruno, G., Pfeiffer, G., Siv, C.; *J. Organomet. Chem.* **1986**, 317, 93-104
3. Pracejus, H., Pracejus, G., Costisella, B.; *J. prakt. Chem.* **1987**, 329, 235-245
4. Döbler, Chr., Kreuzfeld, H.-J.; Pracejus, H.; *J. Organomet. Chem.* **1988**, 344, 89-92
5. Mortreux, A., Petit, F., Buono, G., Pfeiffer, G.; *Bull. Soc. Chim. Fr.* **1987**, 631
6. Agbossou, F., Carpentier, J. F., Hatat, C., Kokel, N., Mortreux, A., Betz, P., Goddard, R., Krüger, C.; *Organometallics* **1995**, 14, 2480-2489
7. Cesarotti, E., Grassi, M., Prati, L., Demartin, F.; *J. Chem. Soc. Dalton Trans.* **1991**, 2073
8. Suisse, J., Briecout, H., Mortreux, A.; *Tetrahedron Lett.* **1994**, 35, 413
9. Portier, Y., Mortreux, A., Petit, F.; *J. Organomet. Chem.* **1989**, 370, 333
10. Krause, H. W., Foken, H., Pracejus, H.; *New J. Chem.* **1989**, 13, 615-620
11. (a) Krause, H. W., Wilcke, F.-W., Kreuzfeld, H.-J., Döbler, Chr.; Chirality **1992**, 4, 110-115
    (b) Krause, H. W., Kreuzfeld, H.-J., Döbler, Chr., Taudien, S.; *Tetrahedron: Asymmetry* **1992**, 3, 555-566
    (c) Taudien, S., Schinkowski, K., Krause, H. W.; *Tetrahedron: Asymmetry* **1993**, 4, 73-84
    (d) Döbler, Chr., Kreuzfeld, H.-J., Krause, H. W., Michalik, M.; *Tetrahedron: Asymmetry* **1993**, 4, 1833-1842
    (e) Kreuzfeld, H.-J., Döbler, Chr., Krause, H. W., Facklam, Chr.; *Tetrahedron: Asymmetry* **1993**, 4, 2047-2051
12. Achiwa, K., Chaloner, P. A., Parker, D.; *J. Organomet. Chem.* **1981**, 218, 249-260
13. Schmidt, U., Griesser, H., Leitenberger, V., Liebermann, A., Mangold, R., Riedl., B.; *Synthesis* **1992**, 487-490
14. Nestor, Jr., J. J., Ho, T. L., Simpson, R. A., Horner, B. L., Jones, G. H., McRae, G. I., Vickery, B. H.; *J. Med. Chem.* **1982**, 25, 795-801
15. Porter, J., Dykert, J., Rivier, J., Int. *J. Peptide Protein Res.* **1987**, 30, 13-21
16. Krause, H. W., Kreuzfeld, H.-J., Schmidt, U., Döbler, Chr., Michalik, M., Taudien, S., Fischer, Chr.; Unusual Amino Acids, part VI, *Chirality* in press

(*Received in UK* 18 *December* 1995; *accepted* 28 *February* 1996)