Tetrahedron: Asymmetry Vol. 4, No. 9, pp. 2047-2051, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

UNUSUAL AMINO ACIDS V. ASYMMETRIC HYDROGENATION OF (Z)-N-ACYLAMINO-CINNAMIC ACID DERIVATIVES BEARING DIFFERENT PROTECTIVE GROUPS

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(*Received in UK* 21 *June* 1993; *accepted* 26 *July* 1993)

Abstract The rhodium-catalyzed asymmetric hydrogenation of acylaminocinnamic acid esters, bearing different protective groups, has been investigated in the presence of PROPRAPHOS, BPPM, DIOP, and Ph-ß-GLUP as chiral ligands. The influence of the protective group on the rate and enantioselectivity of the hydrogenation is described.

Introduction N-Acetyl- and benzoylaminocinnamic acid and their esters are suitable substrates in asymmetric hydrogenations to achieve optically active phenylalanines and to check the efficiency of newly developed catalysts.

However, in general N-acetyl and benzoyl protecting groups are less suitable with regard to their deblocking properties since strong acidic conditions are necessary and in many cases partial racemization is implicated. This holds even more when considering oligo- or polypeptides, where smoothly removable protective groups are essential.In this connection the question is of interest, therefore as to how different protective groups influence the rate and enantioselectivity of the asymmetric hydrogenation. Electronic as well as steric factors may play an important role in the transition state

Here we like to report the results of such a systematic investigation. For comparison we chose the N-Ac-, N-Bz-, N-Cbz-, and N-Boc-derivatives as substrates in the rhodium-catalyzed asymmetric hydrogenation applying PROPRAPHOS, BPPM, DIOP, and Ph-ß-GLUP as chiral ligands.

Results and Discussion To prepare the substrates we used the condensation of benzaldehyde with methyl-N-acyl-2-(dimethoxyphosphinyl)-acetate described by U. Schmidt et al.[1,2]. Starting from methyl-2-benzyloxy-carbonylamino-2-(dimethoxyphosphinyl)-acetate the Cbz- and Boc-derivatives are available in good yields as the (Z)-isomers (Scheme 1). Yields and melting points are given in Table 1

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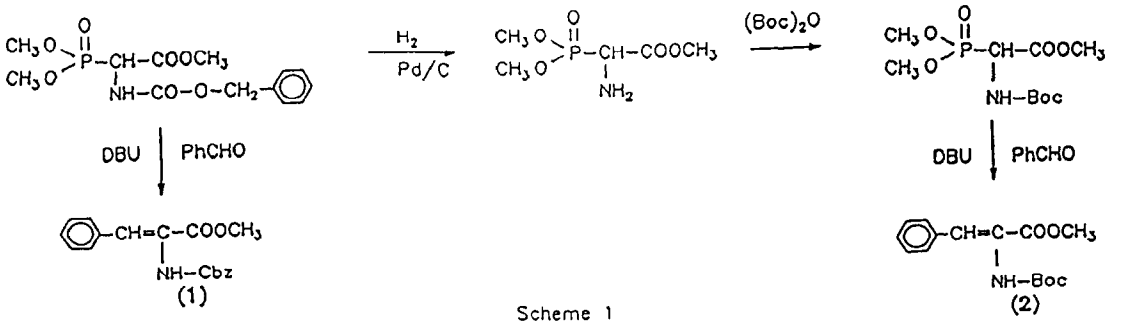
Preparation of the substrates



Scheme 1

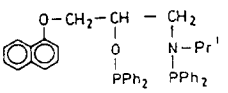
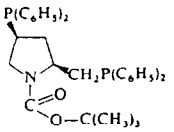
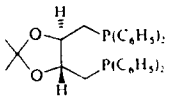
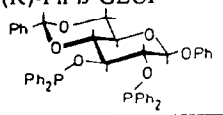
Table 1 Yields and melting points of **1** and **2**

Compound No	Protect Group	Yield /%/	m p /°C/	Lit	Ref.
1	Cbz	95	66-68	oil	(3)
2	Boc	70	82-84	77-79, 81-83	(4,5)

Asymmetric Hydrogenation: With the exception of PROPRAPHOS, which was used as the isolated cationic complex, all other catalytic systems were generated in situ by mixing the ligands with /$Rh(COD)_2/BF_4$ just before use. After the hydrogenation was complete, the optical yield was determined by GLC (Ac, Bz) or by HPLC (Cbz, Boc) The summarized results, given in Table 2, are the average obtained from three hydrogenation experiments each of them determined twice with respect to the enantiomeric excess. In addition the hydrogenation products were isolated by evaporation of the solvent in vacuo, uptake of the yellow oily residue in 2-3 ml of benzene, and adsorption of the catalyst on a small amount of Kieselgel 60 (Merck). After evaporation the samples were ready for analytical purpose

The investigated catalysts represent three types Aminophosphine phosphinite (PROPRAPHOS), bisphosphinite (Ph-ß-GLUP), and bisphosphine (BPPM, DIOP). All ligands form seven-membered chelates with rhodium. The substrate specificity of the catalysts is quite different in some examples concerning the hydrogenation rate as well as the enantioselectivity From Table 2 it follows that a decrease in rate is seen with increasing bulkiness of the protecting group, at which the Cbz has an exceptional position in case of the aminophosphine phosphinite and the bisphosphinite ligand. The general usefulness of N-Cbz residues in the asymmetric hydrogenation has already been demonstrated by Achiwa when he used N-Cbz-acrylic acid in the presence of BPPM-Rh, however the enantiomeric excess was moderate[3] With this respect and concerning the hydrogenation rate the Boc group seems to be more advantageously as outlined in other cases[4].

Table 2 Results of asymmetric hydrogenation

Catalyst (ligand)	Protective group	t/2 (min.)	Optical yield (% ee)	Abs. config. (R/S)
(S)-PROPRAPHOS 	Ac	1 6	86	R
	Bz	1 0	90	R
	Cbz	12 0	88	R
	Boc	5 0	93	R
(2S,4S-BPPM 	Ac	1 6	93	R
	Bz	1 5	80	R
	Cbz	6 0	87	R
	Boc	8 0	82	R
(4R,5R)-DIOP 	Ac	1 5	68	R
	Bz	1 6	26	R
	Cbz	5 0	33	R
	Boc	6 0	9	R
(R)-Ph-ß-GLUP 	Ac	6 0	90	S
	Bz	7 0	85	S
	Cbz	incomplete hydr	57	S
	Boc	" 128 0	87	S

rates < 5 min are diffusion controlled rather than true reaction rates.

In our comparative investigation we found that the use of Boc-protected substrate leads to a prolonged hydrogenation time by the factor 3-5 in comparison with the acetyl or benzoyl derivative The only exception is Ph-ß-GLUP, where the factor is about 20 Methyl- N-Cbz-aminocinnamate gives nearly the same results with the exceptions, that PROPRAPHOS needs the twofold time and the Ph-ß-GLUP system is unable to catalyze the hydrogenation of this substrate in a reasonable time. This fact is somewhat surprising and shows the strong influence of the acyl group on this type of catalyst

The influence of the protective group on the enantioselectivity is different in the investigated systems and can lead to increasing as well as decreasing optical yields. Both cases are demonstrated in Table 2 for PROPRAPHOS and BPPM The loss of enantioselectivity using DIOP in going from acetyl to benzoyl protected substrate has been reported by H Brunner et al in the range of 55 % ee[5]. This effect is increased, if the Boc-derivative is used. Only 9 % ee could be realized. That means a loss of 59 % ee (see Table 2). But one has to consider that this findings were obtained under normal conditions. Differing relations may lead to other results, because the enantiodiscrimination depends on hydrogen pressure and temperature.

Experimental: ^1H NMR and ^{13}C NMR spectra were recorded on a 250 MHz spectrometer (Bruker, AC 250). Infrared spectra were recorded on a Nicolet Magna 550 spectrometer.

Optical rotation was measured on a GYROMAT-HP polarimeter (Fa. Dr. Kernchen, Seelze). The enantiomeric excesses (% ee) were determined by GLC on a Hewlett-Packard chromatograph HP 5880 A fitted with a 4.3 m capillary column XE-60 (N-L-valin-tert.butylamide) FID, split 1:60, 175 °C) for the acetyl- and benzoyl-derivative, 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 Cbz- and Boc-derivatives. Melting points were determined on a Boetius microscope.

Hydrogenation, general procedure: The hydrogenation experiments were performed in a standard apparatus, 1 mmol of substrate, 15 ml of methanol at 25 °C and 0.1 MPa H_2, substrate:catalyst = 100:1.

Deacyclation: The Cbz protective group was removed by usual hydrogenation in the presence of Pd/C and hydrochloric acid in methanol. In case of the Boc-derivative the deprotection was carried out using 4N HCl in methanol.

Methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphinyl)-acetate and methyl 2-(tert.-butoxy-cabonyl-amino)-2-(dimethylphosphinyl)-acetate were prepared following Schmidt's procedure[1]. The yields could be confirmed, the melting point of the Boc-derivative was found to be 59-62 °C (Lit.: 47-48 °C).

N-Cbz-(Z)-aminocinnamic acid methyl ester (1) was prepared according to the general procedure described by U. Schmidt et al (2). Starting from 11 mmol 3.2 g (95 %) were isolated. M.p. 66-68 °C (Et_2O/hexane). Ref. 6: The compound is described as an oil.

$C_{18}H_{17}NO_4$ (311.3) calcd C 69.44 H 5.50 N 4.50 MS: M^+ 311, found C 69.26 H 5.44 N 4.62 IR(KBr): 1644 (C=C); 3326 (NH); 1731 (COOMe; 1700 (COOBzl). ^1H NMR (CDCl3): 3.80 (s, 3H, OCH3); 5 10 (s, 2H, CH2), 6.43 (s, 1H, NH); 7.30 (m, 1H, CH); 7.25-7.55 (m, aromat.).

N-Boc-(Z)-aminocinnamic acid methyl ester (2) was prepared in the same manner.

Yield: 2.3 g (76 %), m p. 83-84 °C (Et_2O/hexane) Lit.: m.p. 77-79 °C (Ref. 8), m.p. 81-83 °C (Ref. 7)

$C_{15}H_{19}NO_4$ (277.3) calcd. C 64.96 H 6.91 N 5.05 MS: M^+ 277, found C 64.65 H 6.85 N 5.10 IR(KBr): 1644.1 (C=C), 3327 (NH); 1724 (COOMe); 1701 (COOt.Bu). ^1H NMR ($CDCl_3$): 1.39 (s, 9H, $C(CH_3)_3$); 3.85 (s, 3H, OCH_3), 6 23 (s, 1H, NH); 7.22 (m, 1H, NH); 7.25-7,55 (m, aromat.).

N-Cbz-(D)-phenylalanine methyl ester (3):

$C_{18}H_{19}NO_4$ (313.3) calcd. C 68.99 H 6.11 N 4.47 MS: M^+ 313, $/\alpha/_D^{25}$ +12.2 (c 1, MeOH)
found C 69.02 H 6.33 N 4.48 HPLC: 88 % ee, oil.

IR (KBr): 3342 (NH) 1724 (br CO acyl and ester). ^1H NMR ($CDCl_3$) 3 11 (dq, 2H, CH_2), 3.71 (s, 3H, $COOCH_3$), 4 68 (m, 1H, CH), 5.12 (m, 3H, OCH_3), 5.26 (d, 1H, NH), 7.08-7.53 (m, aromat.). ^{13}C NMR ($CDCl_3$): 38.2 (CH_2), 52.2 (OCH_3), 54.8 (CH), 66.9 (OCH_2), 127.1 (4'), 127.9, 128.1 (2", 4"), 128.4 (2'), 128.5 (3"), 129 2 (3'), 135.7 (1'), 136.2 (1"), 155.6 (NHCO), 171.9 ($COOCH_3$).

N-Boc-(D)-phenylalanine methyl ester (4):

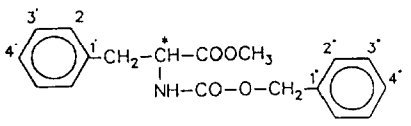
$C_{15}H_{21}NO_4$ (279.3) calcd. C 64.50 H 7.58 N 5.01 MS: M^+ 279, $/\alpha/_D^{25}$ +4.8 (c 1, MeOH)
found C 64.71 H 7.35 N 5.04 HPLC. 93 % ee, m. p. 48-53 °C

IR (KBr): 3354 (NH), 1709 (CO, acyl), 1737 (CO, ester). ^1H NMR ($CDCl_3$): 1.40 (s, 9H, $C(CH_3)_3$), 3.07 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 4.56 (m, 1H, CH), 4.97 (d, 1H, NH), 7.10-7.34 (m, aromat.), ^{13}C NMR 79.9 ($C(CH_3)_3$), 127.0 (4'), 128.5 (2'), 129.3 (3'), 136.1 (1'), 155.1 (NHCO), 172.3 ($COOCH_3$).

(D)-Phenylalanine methyl ester hydrochloride:

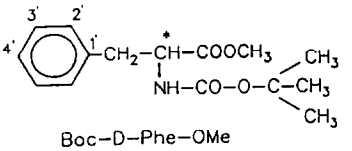
From N-Boc-(D)-phenylalanine methyl ester after deprotection

m. p. 160 °C, $/\alpha/_D^{25}$ -35 5 (c 1, EtOH), after one crystallization from methanol/ether. Optical purity 93 % ee, based on 38 ± 1



Cbz–D–Phe–OMe

(3)



Boc–D–Phe–OMe

(4)

Acknowledgement This work was generously supported by the Berlin-Chemie AG. We are grateful for Dr. M. Michalik for NMR-spectra and Mrs. K. Kortus for GLC analysis, to Mrs. Chr. Fuhrmann and Mrs. I. Stahr for technical assistance

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