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Amplification of Double Stereodifferentiation in the Asymmetric Hydrogenation by a Solvent Effect

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Abstract: High diastereoselectivities of more than 96 % leading to (*S*)-amino acid menthyl esters were found in the hydrogenation of *both* the newly prepared enantiomers **3** and **4** of menthyl (Z)-2-N-benzoylamidocinnamate with the rhodium(I)-chelate of (Ph-ß-glup-OH) **1** as chiral catalyst in polar solvents. The analogous chelate of (Me-α-glup) **2** forms a mismached pair with the enantiomer **4** giving the (*S*)-product in a low diastereoselectivity which can be inversed in the *apolar solvent benzene* to 86 % of the (*R*)-diastereomer. Of particular note is the possibility of obtaining high yields either of (*R*)- or (*S*)-amino acids with the *same catalyst* with a single ligand derived from D-glucose.

Bisphosphinites derived from carbohydrates are well known and readily available chiral ligands. Transition metal chelates formed by ligands of this type have been proven as potent catalysts in enantioselective syntheses[1]. While the rhodium(I) complexes have been applied in an industrial synthesis of L-DOPA by asymmetric hydrogenation[2], the corresponding nickel chelates have been shown to be promising catalysts in the asymmetric hydrocyanation of prochiral olefins[3]. However, a major disadvantage of carbohydrates is that usually only one enantiomer is available from the chiral pool. On the other hand, some 3,4-O-bis(diphenylphosphino-D-glucopyranosides have been synthesized recently which as rhodium(I) chelates are able to induce enantioselectivities from 90 to 96 % ee for the (R)-amino acid[4,5].

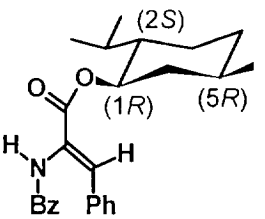
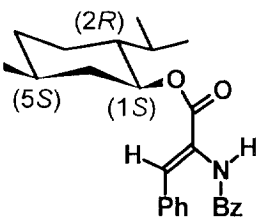
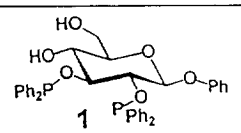
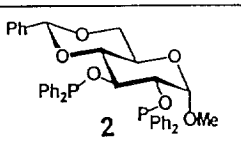
Application of cationic rhodium chelates derived from phenyl 2,3-bis(O-diphenylphosphino)-β-D-glucopyranoside **1** in asymmetric hydrogenations of (Z)-N-acyldehydroamino acids and their esters give exclusively the corresponding (*S*)-amino acid derivatives. However, for rhodium(I) chelates derived from methyl 4,6-O-benzylidene-2,3-bis(O-diphenylphosphino)-α-D-glucopyranoside **2** a relatively strong influence of the solvent on the stereoselectivity has been observed which culminates in benzene as solvent to form the (***R***)-N-acetyl-phenylalanine methyl esters in low enantioselectivities of less than 10 % ee[6].

To improve further the selectivity towards (*R*)-amino acids, we wanted to enhance this effect by double stereodifferentiation[7,8]. For this reason the enantiomeric esters (1*R*,2*S*,5*R*)-(-)-menthyl- and (1*S*,2*R*,5*S*)-(+)-menthyl-2'-N-benzoylamidocinnamate **3** and **4** were prepared by an optimised procedure for the nucleophilic ring opening of the azlactone 4-[(Z)-benzylidene]-2-phenyl-4H-oxazol-5-one[9]. Upon hydrogenation of either **3** or **4** with the catalyst [Rh (**1**) (COD)]BF_4 the products with the (*S*)-amino acid were formed in a very high diastereoselectivity for all the solvents employed (see Table 1). This result was expected since the catalyst derived from **1** has shown a very high (*S*)-directing potency for a large number of substrates under varying conditions[10].

Hydrogenation of the substrate **4** with the catalyst [Rh (**2**) (COD)]BF_4 in acetone leads under formation of the mismatched pair to a low diastereoselectivity of the (*S*)-amino acid ester as compared to the matched pair which is formed with **3** (see table 1). However, in benzene as solvent this behaviour is changed and now upon hydrogenation of **4** the matched pair is formed leading to the (*R*)-amino acid ester in a considerable diastereoselectivity of 86%.

Our observations demonstrate that it is possible to cover the range from 86% ds (2'***S***)-N-benzoyl-phenylalanine-(1*R*,2*S*,5*R*)-menthylester to 86% ds (2'***R***)-N-benzoyl-phenylalanine-(1*S*,2*R*,5*S*)-menthylester by the same catalyst just by amplification of the double stereodifferentiation effect under the directing influence of different solvents.

Table 1
Hydrogenation of 1 mmol (Z)-PhCH=C(COOMenth*)NHCOPh **3** or **4**;
percentage of the formed diastereomer menthyl N-benzoyl phenylalaninates

Conditions: 1 mmol substrate 0.01 mmol Catalyst or 50 mg Pd 15 ml solvent 25 °C, 0.1 MPa H_2		Substrate **3**  (1*R*,2*S*,5*R*)-(-)-menthyl ester		Substrate **4**  (1*S*,2*R*,5*S*)-(+)-menthyl ester	
Configuration of the newly formed stereogenic centre in the product →		(*S*)	(*R*)	(*S*)	(*R*)
Relative configuration of the hydrogenation product →		(uuu)	(luu)	(luu)	(uuu)
Pd black	acetone	61	39	39	61
Pd black	MeOH	59	41	41	59
Pd black	benzene	57	43	43	57
 **1**	acetone	**96.5**	3.5	**96.0**	4.0
	MeOH	**96.3**	3.7	**97.4**	2.6
	benzene	91	9	79	21
 **2**	acetone	**86**	14	57	43
	MeOH	81	19	66	34
	benzene	75	25	14	**86**

Experimental

The diastereomeric excess of the hydrogenation products was determined by HPLC on a Hewlett-Packard Liquid Chromatograph 1090 Series II equipped with a diode array detector and a Chiralyser from IBZ Meßtechnik Hannover, Germany. Separations were carried out on a CHIRALCEL OD-H analytical column 4.6*250 mm I.D (Baker) with the eluent hexane:isopropanol 99:1 (v:v). Hydrogenations of the substrates **3** and **4** were carried out as usual[11]. The chelates [Rh (**1**) (COD)]BF_4 and [Rh (**2**) (COD)]BF_4 were prepared according to the literature[11,12].

(Z)-2'-N-Benzoylamidocinnamic acid menthyl esters 3 and 4: A 500 ml flask is charged with NaH (1.19 g, 49.4 mmol), purged with argon (three times), and then dry THF (50 cm^3) is added. After addition of menthol (7.03 g, 45 mmol) the mixture is kept under reflux until all NaH has been dissolved. To the obtained pale yellow solution of sodium mentholate a solution of the azlactone 4–[(Z)-benzylidene]-2-phenyl-4H-oxazol-5-one (9.35 g, 37.5 mmol) in THF (90 ml) is added in one portion. Immediately after the addition a slightly exothermic reaction occurs which is completed by heating to reflux until all of the azlactone has been consumed (ca. 5 hours as monitored by TLC control: quench a small sample of the reaction mixture by addition of water and extract with ether; CH_2Cl_2, vanillin reagent). The THF is then removed on a rotavapor and the residue redissolved in ether (ca. 170 ml). The obtained solution is poured into diluted phosphoric acid (2 g 85% H_3PO_4 in 100 ml water). After separating the organic layer and extraction of the inorganic layer three times with ether (150 ml portions each) the combined organic layers are dried ($MgSO_4$). Removal of the solvent affords 13.4 g (88%) of the crude product. Recrystallisation from toluene (65 cm^3) yields 7.5 g (49.3%) of the product as colorless crystals. A further crop of 2.15 g (14%) as pale yellow crystals may be obtained by concentrating the mother liquor. (Z)-(+)-2'-N-benzoylamidocinnamic acid (1*S*,2*R*,5*S*)-menthyl ester **3**: mp. = 154-155 °C; $[\alpha]_D^{25}$ +30.2 (c = 2, EtOH). (Z)-(-)-2'-N-benzoylamidocinnamic acid (1*R*,2*S*,5*R*)-menthyl ester **4**: mp. = 153.5 - 154 °C; $[\alpha]_D^{25}$ = -30.4 (c = 2, EtOH); Analysis: C calcd. 35.97, found 36.37; H calcd. 4.15, found 4.27; N calcd. 29.94, found 29.64. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.80 (d, 3, ^3J = 6.9 Hz, menth H-8); 0.90 (d, 3, ^3J = 7.0 Hz, menth H-9); 0.90 (menth H-4_{ax}); 0.92 (d, 3, ^3J = 6.3 Hz, menth H-10); 1,00-1,25 (m, 2, menth H-6_{ax}, H-3_{ax}); 1.50 (br "tr", 2, menth H-2_{ax}, H–5_{ax}); 1.71 (br "d", 2, menth H-3_{eq}, H-4_{eq}); 1.96 (d/sept, 1, ^3J H–2_{ax},H-7_{ax} = 2.5 Hz, menth H-7); 2.11 (br d, 1 , menth H-6_{eq}); 4.85 (d/tr, 1, ^3J H-1_{ax},H-6_{eq} = 4.3 Hz; ^3J H-1_{ax},H-2_{ax} ≈ ^3J H-1_{ax},H-6_{ax} ≈ 10.8 Hz, menth H-1); 7.27-7.39 ppm (m, 3, Ph m-H, PhC**H**=CH); 7.42-7.58 ppm (m, 6, NBz p-H, NBz mH, Ph o-H, Ph p-H); 7.80-7.90 ppm (m, 3, NBz o-H, NH). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ 16.43, 20.72, 21.96, 23.55, 26.37, 31.44, 34.21, 40.75, 47.19, 76.21 (menth C-8, C-9, C-10, C-3, C-7, C-5, C-4, C-6, C-2, C-1); 124.38 (C=**C**(NBz)COO); 127.42 (NBz o-C); 128.47 (Ph m-C); 128.71 (NBz m-C); 129.24 (Ph**C**=C); 129.62 (Ph o-C); 130.58 (NBz p-C); 132.03 (Ph p-C); 133.96, 134.25 (NBz ipso-C, Ph ipso-C); 164.99 (**C**OOmenth); 165.43 ppm (NH**C**OPh).

(2'*S*)-(+)-N-Benzoyl-phenylalanine (1*R*,2*S*,5*R*)-menthyl ester: Prepared by hydrogenation of 1 mmol **3** with 0.01 mmol [Rh (**1**) (COD)]BF_4 in 15 ml acetone; fine needles (toluene), mp. 155 °C; $[\alpha]_D^{25}$ = +10.0 (c = 2, $CHCl_3$) ; diastereomeric purity by HPLC 99.9 %; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.72 (d, 3, ^3J = 6.9), 0.83 (d, 3, ^3J = 7.0, menth H-8, H-9); 0.86 (d, 3, ^3J = 6.7, menth H-10); 0.9 - 1.1 (m, 3), 1.3 - 1.5 (m, 2), 1.55 - 1.70 (m, 2), 1.75 (d/sept, 1, ^3J = 2.0 Hz, ^3J = 7 Hz, menth H-7); 1.95 - 2.05 (m, 2); 3.23, 3.31 (ABX, 2, $|^2J|$ = 13.8, ^3J = 5.0, ^3J = 6.0, PhC$\mathbf{H}_2$); 4.69 (d/tr, 1, ^3J = 4.4, ^3J ≈ 10.9, menth H-1); 5.04 (ABX, 1, NC**H**CH_2PH);

6.89 (br d, 1, ^3J = 7.9, NH); 7.13 - 7.45 (m, 9, Ar-H); 7.63-7.70 (m, 2, NBz o-H). ^{13}C-NMR ($CDCl_3$): δ 16.32, 20.71, 22.02, 23.40, 26.18, 31.42, 34.11 (menth C-8, C-9, C-10, C-3, C-7, C-5. C-4); 37.79 (Ph**C**H_2); 40.80, 46.98 (menth C-6, C-2); 53.46 (**C**H(NBz)COO); 76.07 (menth C-1); 127.09 (Ph p-C); 127.00, 128.45, 128.63, 129.66 (Ph o-C, m-C, NBz o-C, m-C); 131.71 (NBz p-C); 134.15 (NBz ipso-C); 135.96 (Ph ipso-C); 166.76 (N**C**OPh); 171.18 (**C**OOmenth).

(2'*S*)-(+)-N-Benzoyl-phenylalanine (1*S*,2*R*,5*S*)-menthyl ester: Prepared by hydrogenation of 1 mmol **4** using 0.01 mmol catalyst [Rh (**1**) (COD)]BF_4 in 15 ml acetone; prisms (ether), mp. 86 °C; $[\alpha]_D^{25}$ = +79,0 (c = 2, $CHCl_3$); $[\alpha]_D^{25}$ = + 6.7 (c = 2, EtOH); diastereomeric purity by HPLC 99.4 %. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.72 (d, 3, ^3J = 6.9), 0.83 (d, 3, ^3J = 7.0, menth H-8, H-9); 0.87 (d, 3, ^3J = 6.7, menth H-10); 0.90 - 1.07 (m, 1), 1.28 - 1.50 (m, 2), 1.57 - 1.70 (m, 2), 1.75 (d/sept, 1, ^3J = 2.0 Hz, ^3J = 7 Hz, menth H-7); 1.98 - 2.06 (m, 2); 3.22, 3.30 (ABX, 2, $|^2J|$ = 13.9, ^3J = 5.3, ^3J = 6.1, PhC**H**$_2$); 4.74 (d/tr, 1, ^3J = 4.4, $^3J \approx$ 10.9, menth H-1); 5.06 (ABX, 1, NC**H**CH_2PH); 6.72 (br d, 1, ^3J = 7.3, NH); 7.13 - 7.51 (m, 9, Ar-H); 7.70-7.76 (m, 2, NBz o-H). ^{13}C-NMR ($CDCl_3$): δ = 15.89, 20.87, 21.93, 22.97, 25.79, 31.37, 34.09 (menth C-8, C-9, C-10, C-3, C-7, C-5, C-4); 37.92 (Ph**C**H_2); 40.61, 46.79 (menth C-6, C-2); 53.85 (**C**H(NBz)COO); 76.02 (menth C-1); 127.01, 128.46, 128.49, 129.35 (signal at 127.01 integrates to 3 C; Ph p-C, Ph o-C, m-C, NBz o-C, m-C); 131.55 (NBz p-C); 134.05 (NBz ipso-C); 136.02 (Ph ipso-C); 166.88 (N**C**OPh); 171.48 (**C**OOmenth).

(2'*R*)-(-)-N-Benzoyl-phenylalanine (1*S*,2*R*,5*S*)-menthyl ester: Prepared by hydrogenation of 1.21 g (3 mmol) **4** using 0.03 mmol [Rh (**2**) (COD)]BF_4 in 45 ml benzene; after two recrystallisations from ethanol 0.745 g (61%) fine needles , mp. 153 °C; $[\alpha]_D^{25}$ = -9,5 (c = 2, $CHCl_3$); diastereomeric purity by HPLC 99.9 %.

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