Stereoselective Synthesis of Dipeptides by Asymmetric Reduction of Dehydropeptides Catalyzed by Chiral Rhodium Complexes[1]

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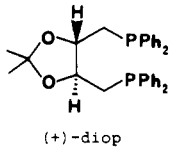
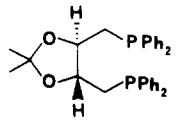
Asymmetric catalysis was used to control the creation of an asymmetric center in a chiral dehydropeptide. The reduction of Ac-ΔPhe-(*S*)-Phe-OR (R = H or Me) was studied as a model. Depending on the type of chiral rhodium catalyst used, it was possible to selectively obtain either Ac-(*S*)-Phe-(*S*)-Phe-OR or Ac-(*R*)-Phe-(*S*)-Phe-OR. Reactions were also performed on Ac-ΔPhe-(*S*)-Ala-OMe.

Asymmetric synthesis has been greatly developed during the last decade[2] and is emerging as a useful method for preparing chiral molecules. Especially spectacular has been the progress made in asymmetric catalysis where the chiral catalyst is a transition-metal complex. The most impressive results have been in the catalytic asymmetric reduction of dehydroamino acids of the type RCH=C(NHAc)CO_2H in which the catalyst was "$RhCl_2$" or $[Rh(diene)L_2]^+$ with L_2 being a chiral diphosphine. For example, with diop (1), enantiomeric excesses (ee) in the



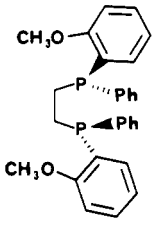
(+)-diop

1a



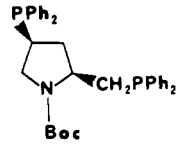
(-)-diop

1b



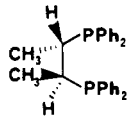
dipamp

2



bppm

3



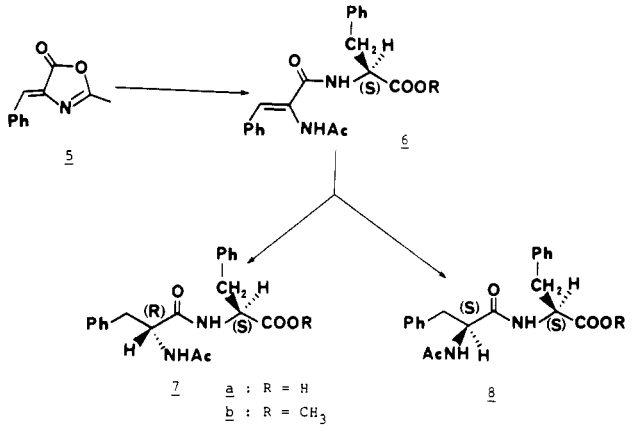
Chiraphos

4

range of 80–90% were obtained,[3] diPAMP (2) leads to 95–96% ee,[4] and bppm (3) is also highly stereoselective (91% ee).[5,6] The most efficient chiral ligand seems to be chiraphos (4) which gives almost 100% ee in some asymmetric reductions.[7]

One seldom-attacked aspect of asymmetric synthesis is the creation of an asymmetric center in a chiral molecule by using a chiral reagent. We can describe the process as the result of a double asymmetric induction, one coming from the chiral molecular framework and the other from the reagent.[8] Some reactions with double asymmetric induction are known from studies in asymmetric catalysis.[9-11] Because of the wide distribution and biological importance of the dehydropeptides,[12,13] it was interesting to investigate the potential of chiral rhodium catalysts in the preparation of peptides where one amino acid will be produced with specifically the *S* or *R* configuration. If successful, this method could be of wide interest for the specific labeling (by deuterium or tritium) of one part of a polypeptide without resorting to peptide synthesis. In addition, it would permit introduction of an "unnatural" configuration at one asymmetric center of a polypeptide.[14]

Scheme I



We chose to start this investigation by selecting Ac-ΔPhe-(*S*)-Phe-OH (**6a**) and Ac-ΔPhe-(*S*)-Phe-OMe (**6b**) as models. The chiral ligands for the rhodium catalyst were mainly (+)-diop (**1a**) and (−)-diop (**1b**), although some experiments were also performed with diPAMP (**2**) and bppm (**3**). After the completion and submission of this work a Japanese group[15] published a paper on similar experiments.

Results

[(*Z*)-*N*-Acetyldehydrophenylalaninyl]-(*S*)-phenylalanine **6a** was easily prepared according to ref 16 by treatment

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Table I. Stereochemistry of Reduction of [(*Z*)-*N*-Acetyldehydrophenylalaninyl]-(*S*)-phenylalanine 6a and Its Methyl Ester 6b in the Presence of Various Catalytic Systems

entry	catalyst[a]	substr	ratio of 8/7	% ee[b] (config)
1	Pd/C[c]	**6a**	40/60	20 (*R*)
2	Pd/C[c]	**6b**	39/61	22 (*R*)
3	$RhCl(PPh_3)_2$[d]	**6b**	50/50	0
4	$RhClPPh_2(CH_2)_3PPh_2$[d]	**6a**	60/40	20 (*S*)
5	$RhClPPh_2(CH_2)_3PPh_2$[d]	**6b**	60/40	20 (*S*)
6	$RhClPPh_2(CH_2)_4PPh_2$[d]	**6a**	69/31	38 (*S*)
7	$RhClPPh_2(CH_2)_4PPh_2$[d]	**6b**	69/31	38 (*S*)
8	RhCl-(+)-diop[d]	**6a**	95/5	90 (*S*)
9	RhCl-(+)-diop[d]	**6b**	95/5	90 (*S*)
9a	[Rh-(+)-diopCOD]$^+BF_4^-$[c]	**6b**	94/6	88 (*S*)
10	RhCl-(−)-diop[d]	**6a**	20/80	60 (*R*)
11	RhCl-(−)-diop[d]	**6b**	10/90	80 (*R*)
12	RhCl(bppm)[d]	**6b**	<5/>95	>90 (*R*)
12a	[Rh(bppm)COD$^+$]BF_4^-[c]	**6b**	<5/>95	>90 (*R*)
13	[Rh(diPAMP)NBD$^+$]BF_4^-[c]	**6b**	>95/<5	>90 (*S*)

[a] Reactions were performed at room temperature and a hydrogen pressure of ~1 atm. Yields were almost quantitative. Details on the precedure are given in the Experimental Section. [b] Calculated by the formula $(R - S)/(R + S) \times 100$ where *R* and *S* refer to the relative quantities of *R* and *S* configurations created in the reaction. This number would correspond to an enantiomeric excess after removal of the terminal (*S*)-phenylalanine. [c] Solvent was methanol. [d] Catalyst prepared in situ; solvent was methanol-benzene (2.2/1).

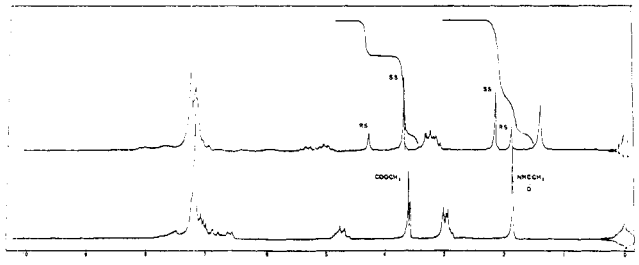

Figure 1. NMR spectra (in $CDCl_3$) of a mixture of (*R,S*)-7 and (*S,S*)-8 in presence of $Eu(fod)_3$. Relative titration of diastereomers is easy by integration in the 2-ppm and the 4-ppm areas.

of azlactone **5** with the sodium salt of (*S*)-phenylalanine (Scheme I). The methyl ester **6b** was obtained by esterification of **6a** with methanolic HCl.

Preliminary reduction experiments were performed in methanol on **6a** and **6b** with Pd/C as catalyst.[17] A mixture of the (*R,S*)-7 and (*S,S*)-8 dipeptides was obtained (7/8 ratio of 60/40). In order to analyze the steric course of the reaction, we avoided the usual procedure[18] in which the dipeptide is hydrolyzed and the optical purity of amino acids measured. We found that the dipeptides 7 and 8 are easily distinguished by ^1H NMR in the presence of a small amount of $Eu(fod)_3$. A typical spectrum is indicated in Figure 1. It permits a rapid evaluation of the relative amounts of 7 and 8 within a 5% error. Another method employed was medium-pressure liquid chromatography through silica gel with a UV detector (254 nm). This process is very accurate only when the reduction was complete, otherwise the small amounts of 6 which cannot be separated from 7 disturb the titration because of the strong absorption of 6.

The stereochemistries of 7 and 8 were established on the following grounds. The two pure dipeptides **7b** and **8b** were prepared from various reductions of **6b** and subsequent recrystallization. (*S,S*)-**8b** was identified by CD because of its important negative signal (two dichroic bands at 262 and 268 nm) due to the additive contributions of the two residues of *S* configuration.[20] In the case of (*R,S*)-**7b** the contributions appeared to be of opposite sign, and the resultant was a weak positive signal. Complete annulation was not obtained on account of the two phenyl rings not having the same environment. The diastereomer **8b** was eluted more rapidly; the same elution order has been seen before.[21] The reduction by homogeneous catalysis was conducted in methanol under 1 bar of hydrogen. The catalyst was either "$RhClL_2$" formed in situ or a preformed cationic catalyst, $[Rh(COD)L_2]^+$. These catalysts, where L_2 is a chiral diphosphine,[3,22] were prepared by well-known procedures. For comparison, achiral diphosphines were also used in reduction of **6**. Results are indicated in Table I.

Discussion

The asymmetric center with *S* configuration in either **6a** or **6b** induces an *S* configuration in the reduction (entries 4–7) with the homogeneous achiral rhodium catalyst in which $PPh_2(CH_2)_nPPh_2$ ($n = 3$ or 4) is the ligand. With PPh_3 as the ligand there is no stereoselectivity. This could reflect a difference of catalyst structure and reaction mechanism when a monophosphine is exchanged for a diphosphine in a Wilkinson catalyst.[23] By use of a heterogeneous catalyst (Pd/C), a slight excess of diastereomer (*R,S*)-7 is obtained (7/8 ratio of 60/40).

It is known[3] that (+)-diop (**1a**) gives a rhodium catalyst which is able to induce asymmetric reduction of (*Z*)-*N*-acetyl-Δ-phenylalanine with a strong *S* stereoselectivity (82% ee). The same trend could be expected for the double bond of **6**. Indeed, **6a** and **6b** give more than 95% of the *S,S* diastereomer 8 which means more than 90% ee at the level of the new asymmetric center. Of course, (−)-diop has an *R* stereoselectivity for α-amino acid synthesis.[3] When this ligand was used in an asymmetric rhodium catalyst for reduction of **6**, an excess of *R,S* diastereomer 7 was produced. However, the stereoselectivity was less pronounced than that with (+)-diop (entries 10 and 11). It is qualitatively explained by the combination of two asymmetric inductions.[8] When the intrinsic asym-

(17) Reduction of several dehydropeptides catalyzed by Pd/C is known. Usually the stereoselectivity is weak[18] for linear peptides but can be very high with some cyclic peptides.[19]

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metric induction in the substrate and the catalyst are in the same direction, an overall high stereoselectivity can be expected through a cooperative effect. This was observed with the combination of (*S*)-**6** and (+)-diop. Asymmetric induction was higher than 90%, leading to almost exclusive formation of **8**. If (−)-diop was reacted with (*S*)-**6**, the asymmetric induction from the chiral catalyst controls the steric course of the reaction. (*R*,*S*)-**7a** was obtained with 60% asymmetric induction and (*R*,*S*)-**7b** with 80% asymmetric induction. The highly interesting conclusion is that in a dehydropeptide such as **6** the absolute configuration of a chiral catalyst controls to a great extent the steric course of the reduction. Moreover, we can predict in which case the stereoselectivity will be the highest by simple consideration of some separate asymmetric inductions. This conclusion is supported by additional experiments with homogeneous catalysts which incorporate very efficient chiral ligands. For example, bppm (**2**) and diPAMP (**3**) are known to catalyze asymmetric synthesis of *N*-acetylphenylalanine with 91% ee *R*[6] and 96% ee *S*,[4] respectively. In our case (entries 12 and 13) these catalysts give rise to almost exclusive formation of **8** or **7**, respectively. At the present time a detailed discussion of these asymmetric reductions is not possible, especially because our evaluation of relative amounts of **7** and **8** is not accurate for high stereoselectivities. It would be interesting, for example, to compare more precisely data with (+)-diop, bppm, and diPAMP (which are ligands of increasing efficiency in asymmetric reduction of α-amino acid precursors). It would be interesting to know the results of asymmetric reduction of Ac-ΔPhe-(*R*)-Phe-OR with diPAMP (**2**) or bppm (**3**), for comparison with entries 12 and 13.

It is possible to make some comparisons with the paper by Ojima and Susuki[15] in which the authors investigated the reduction of **6b** in presence of some chiral rhodium catalysts involving (−)-diop, diPAMP, and bppm as ligands. The analysis of the relative amounts of **8b** and **7b** was performed by high-pressure LC, with an accuracy higher than that obtained by ^{1}H NMR. For example, in entry 13 (Table I) the ratio **8b**/**7b** was estimated to >95/<5; the high-pressure LC method[15] gave a ratio of 98/2. There is good general agreement between both works.

Preliminary experiments have shown that Ac-ΔPhe-(*S*)-Ala-OMe behaves similarly to **6** in asymmetric reductions. For example, the catalyst RhCl-(+)-diop formed in situ gives a 8/7 ratio of 90/10 while RhCl-(−)-diop leads to a 8/7 ratio of 10/90. More experiments are needed to know how general the control of asymmetric reduction of dehydropeptides[26] by chiral homogeneous catalysts can be. Our first results have established the usefulness of the method for the synthesis of some dipeptides. In addition, these dehydropeptides can be tritiated with a high stereoselectivity (8/7 ratio of 90/10) and with a theoretical specific radioactivity (58 Ci/mmol) as checked by ^{3}H NMR.[24]

Experimental Section

Instrumentation. Proton NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Circular dichroism measurements were performed on a Dichrograph III (CNRS-Roussel-Jouan).

Chemicals and Solvents. (*S*)-Phenylalanine and (*S*)-alanine were purchased from Fluka and used as received. $Ph_2P(CH_2)_3PPh_2$ was purchased from Eastman Kodak, and $Ph_2P(CH_2)_4PPh_2$ was prepared as described.[25] Benzene was purified by distillation over calcium hydride and stored under nitrogen. Methanol was distilled over magnesium powder and stored under nitrogen.

Ac-ΔPhe-(*S*)-Phe-OH (6a) and Ac-ΔPhe-(*S*)-Ala-OH. These were prepared according to Bergmann[16] by reaction of the sodium salt of (*S*)-phenylalanine or (*S*)-alanine, respectively, with the unsaturated azlactone of *N*-acetylphenylalanine (**5**).

Ac-ΔPhe-(*S*)-Phe-OMe (6b) and Ac-ΔPhe-(*S*)-Ala-OMe. A solution of 5 g of Ac-ΔPhe-(*S*)-Phe-OH (or Ac-ΔPhe-(*S*)-Ala-OH) in 100 mL of methanol and 2 mL of concentrated HCl was kept at 0 °C for 16 h. The resultant crystals were recrystallized from hot methanol solution; yield ~70%. For Ac-ΔPhe-(*S*)-Phe-OMe: $[\alpha]^{20}_D$ −9.6° (*c* 2, pyridine); mp 188–189 °C. For Ac-ΔPhe-(*S*)-Ala-OMe: $[\alpha]_D$ +43.8° (*c* 2.02, pyridine); mp 163–164 °C.

Catalyst Prepared in Situ. As described in ref 3, to a solution of 0.03 mmol (11.6 mg) of $[Rh(C_2H_4)_2Cl]_2$ in 6.6 mL of C_6H_6 under N_2 was added 0.063 mmol of diphosphine. After 15 min the solution was introduced into the hydrogenation flask.

Cationic Catalysts. These were prepared according to the general procedure used by Glaser.[22] $[Rh(diPAMP)NBD]^+BF_4^-$ was a gift from Dr. Koenig (Monsanto Co.).

Hydrogenations were performed under atmospheric pressure and at room temperature as follows. To a solution of 3 mmol of dehydropeptide in 15 mL of methanol under hydrogen was introduced the solution of the catalyst prepared in situ. For cationic catalysts 0.06 mmol of the catalyst and 3 mmol of the dehydropeptide were dissolved under hydrogen in 20 mL of methanol. After the hydrogenation the solvent was distilled off under vacuum to dryness, the Ac-Phe-Phe-OH obtained was esterified with CH_2N_2 in diethyl ether, and all the N-acetylated dipeptide methyl esters were observed by ^{1}H NMR spectroscopy for titration in $CDCl_3$ solution with small amounts of Eu(fod)$_3$ (approximately 5 mg/50 mg of substrate) or by medium-pressure chromatography through silica gel with CH_2Cl_2 with 1% CH_3OH as eluent.

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Registry No. 6a, 42291-22-5; **6b**, 57986-20-6; **7a**, 24809-18-5; **7b**, 32435-70-4; **8a**, 10030-31-6; **8b**, 2562-48-3; Ac-ΔPhe-(*S*)-Ala-OH, 42291-21-4; Ac-ΔPhe-(*S*)-Ala-OMe, 74986-31-5; Ac-(*R*)-Phe-(*S*)-Ala-OMe, 27842-13-3; Ac-(*S*)-Phe-(*S*)-Ala-OMe, 28945-11-1.

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