Efficient 1,4-Asymmetric Induction Utilizing Electrostatic Interaction between Ligand and Substrate in the Asymmetric Hydrogenation of Didehydrodipeptides

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Electrostatic interaction between the amino group of the achiral 3-dimethylaminopropylidenebismethylenebis(diphenylphosphine) (**1**) and the carboxy group of the substrate enabled an effective 1,4-asymmetric induction in the Rh^{I}-catalysed hydrogenation of didehydrodipeptides, to give (*S,S*)- or (*R,R*)-products selectively. The selectivity reached up to 94% diastereoisomeric excess with acetyl didehydrodipeptides and 92% with benzyloxycarbonyl substrates.

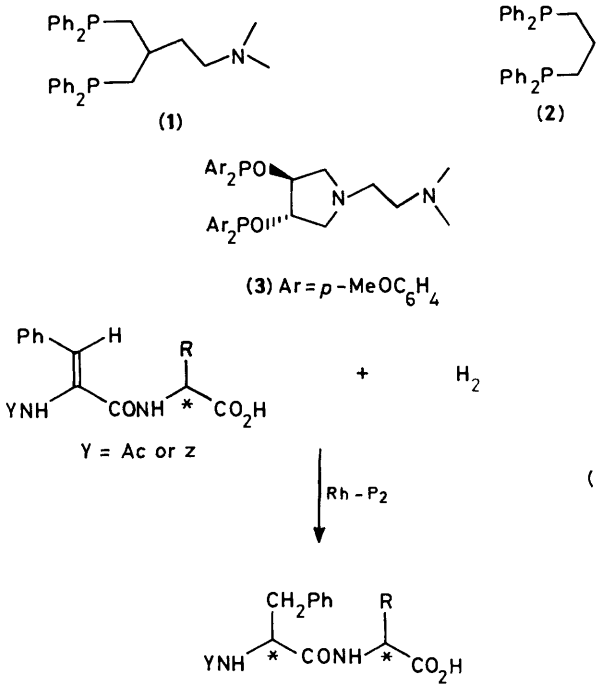
The asymmetric hydrogenation of olefinic compounds catalysed by chiral Rh^{I} complexes with various bidentate ligands has been reported; high enantioselectivity was obtained in the reactions of several didehydroamino acids.[1] The method was extended to the asymmetric hydrogenation of didehydrodipeptides, giving fragments of various biologically active oligopeptides.[2] Ligands used so far were designed to achieve asymmetric induction through only steric repulsion between substrate and ligand coordinated to the rhodium species. However, enzymes conduct highly stereoselective reactions by utilizing weak interactions, such as hydrogen bonding, electrostatic interaction, and van der Waals interaction, between enzyme and substrate as well as steric interactions.[3] Introduction of such weak interactions by means of the catalytic system would enhance stereoselectivity and widen the scope of the substrates.

We have reported the selective asymmetric hydrogenation of *N*-acetyldidehydrodipeptides with a new Rh^{I} chiral diphosphinite (**3**) catalyst system, in which the dimethylamino group of the diphosphinite was expected to interact electrostatically with the carboxy group of the substrates. The diastereoisomeric excess (d.e.) was more than 98% in the case of (**4a**).[4] In this reaction system, the stereoselectivity was mainly controlled by the chirality of the substrate rather than the chirality of the ligand.

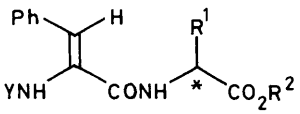
Oligopeptide syntheses by hydrogenation demand that the catalyst can be applied to substrates with various amino-protecting groups such as acetyl, benzyloxycarbonyl (Z), or t-butoxycarbonyl (Boc), *etc.* The Rh^{I}–diphosphinite (**3**) system, however, was not effective for the hydrogenation of *N*-benzyloxycarbonyldide hydrodipeptides, the % d.e. being modest and the reaction slow even at elevated temperatures (*ca.* 50 °C). The results with the diphosphinite (**3**) system suggested that the low σ-donor character of the diphosphinite was responsible for the low reactivity and selectivity for the substrate with a bulky protecting group. We have therefore designed a new achiral diphosphine ligand with a dimethylamino group, 3-dimethylaminopropylidenebismethylenebis(diphenylphosphine) (**1**), and applied it to the asymmetric hydrogenation of *N*-acetyl- and *N*-benzyloxycarbonyl-didehydrodipeptides (**4**) and (**5**).

Results and Discussion

The ligand (**1**) was prepared as a viscous oil in four steps from diethyl malonate and (2-chloroethyl)dimethylamine (Scheme). The reaction with Rh^{I}–(**1**) as catalyst in ethanol proceeded smoothly at 20 °C under atmospheric hydrogen pressure irrespective of the amino-protecting group (Ac or Z). The results are compared with those by Rh^{I}–(**3**) in Tables 1 and 2. In the case of the *N*-acetyl derivatives, the diphosphine (**1**) induced high (*S,S*)- or (*R,R*)-selectivity, comparable to that of the phosphinite (**3**) system, in spite of the lack of a chiral centre (Table 1). To our knowledge, this is the first case where such a high 1,4-asymmetric induction has been achieved in homogeneous catalytic hydrogenation of linear didehydrodipeptides.[5] The ligand (**1**) was also effective for the hydrogenation of *N*-benzyloxycarbonyl derivatives; the reaction proceeded smoothly to give (*S,S*)- or (*R,R*)-products selectively (84—92% d.e.) (entries 1—4 in Table 2). This behaviour is in striking contrast to that of (**3**) (entries 5—8). On the other hand, hydrogenation by [Rh^{I}(−)-diop]† showed a much lower reactivity (entries 9 and 10). This suggests that the labile conformation of the six-membered chelate ring[6] by the achiral diphosphine (**1**) is preferable for the hydrogenation of substrates with a bulky amino-protecting group such as benzyloxycarbonyl. 1,3-Bis(diphenylphosphino)propane (**2**),



† (−)-diop = (−)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane.

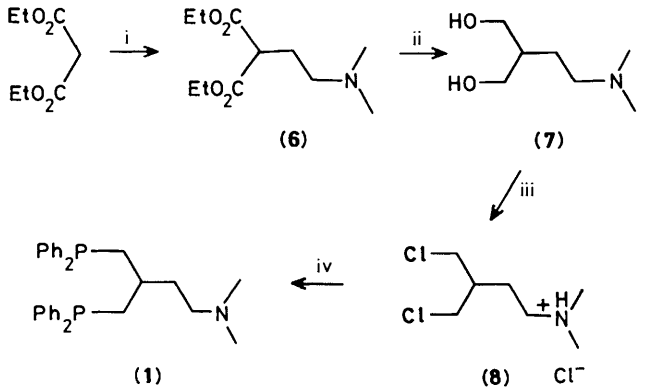


Ac-didehydrodipeptides (**4**) (Y = Ac)

(**4a**) Ac-ΔPhe-(*S*)-Phe-OH; R^1 = $PhCH_2$, R^2 = H
(**4b**) Ac-ΔPhe-(*S*)-Ala-OH; R^1 = Me, R^2 = H
(**4c**) Ac-ΔPhe-(*S*)-Val-OH; R^1 = Pr^i, R^2 = H
(**4d**) Ac-ΔPhe-(*S*)-Leu-OH; R^1 = Bu^i, R^2 = H
(**4e**) Ac-ΔPhe-(*R*)-Phe-OH; R^1 = $PhCH_2$, R^2 = H
(**4f**) Ac-ΔPhe-(*R*)-Ala-OH; R^1 = Me, R^2 = H
(**4g**) Ac-ΔPhe-(*R*)-Val-OH; R^1 = Pr^i, R^2 = H
(**4h**) Ac-ΔPhe-(*R*)-Leu-OH; R^1 = Bu^i, R^2 = H
(**4i**) Ac-ΔPhe-(*S*)-Phe-OMe; R^1 = $PhCH_2$, R^2 = Me
(**4j**) Ac-ΔPhe-(*S*)-Phe-O^-Na^+; R^1 = $PhCH_2$, R^2 = Na

Z-didehydrodipeptides (**5**) (Y = $PhCH_2OCO$)

(**5a**) Z-ΔPhe-(*S*)-Phe-OH; R^1 = $PhCH_2$, R^2 = H
(**5b**) Z-ΔPhe-(*S*)-Ala-OH; R^1 = Me, R^2 = H
(**5c**) Z-ΔPhe-(*S*)-Val-OH; R^1 = Pr^i, R^2 = H
(**5d**) Z-ΔPhe-(*R*)-Phe-OH; R^1 = $PhCH_2$, R^2 = H
(**5e**) Z-ΔPhe-(*R*)-Ala-OH; R^1 = Me, R^2 = H
(**5f**) Z-ΔPhe-(*R*)-Leu-OH; R^1 = Bu^i, R^2 = H
(**5g**) Z-ΔPhe-(*S*)-Phe-OMe; R^1 = $PhCH_2$, R^2 = Me



Scheme. Reagents: i, $ClCH_2CH_2NMe_2$·HCl, NaOEt–EtOH; ii, $LiAlH_4$–dioxane; iii, $SOCl_2$–$CHCl_3$; iv, $LiPPh_2$–$KOBu^t$–THF

forming the same chelate ring as (**1**), also showed a high reactivity in the hydrogenation of Z-protected substrates, as shown in Table 4 (entries 4 and 5). The foregoing results indicate that the diphosphine (**1**) is a good ligand for giving dipeptides with high (*S,S*)- or (*R,R*)-selectivity by 1,4-asymmetric induction, irrespective of the amino-protecting group.

The solvent seems to have a considerable influence on stereoselectivity in asymmetric hydrogenation.[7] The hydrogenation of Ac-didehydrodipeptides was performed in several alcoholic solvents (Table 3). With an increase in solvent polarity, the reactivity and stereoselectivity increased, methanol being the best solvent of those examined. A similar tendency has been reported for the asymmetric hydrogenation of styrene derivatives with a carboxy group.[8] In contrast, the reaction of Z-substrates was quite slow in methanol.

The role of the dimethylamino group in the diphosphine (**1**) was examined, for Ac-substrates in methanol and Z-substrates in ethanol (Table 4). A free carboxy group in the substrate is indispensable for high stereoselectivity in the present system; substrates with an ester group afforded low selectivities (entries 2 and 10). This observation excludes the possibility that co-ordination of the amino group of (**1**) onto the rhodium raises the stereoselectivity. Conversion of the amino group in (**1**) into an ammonium centre, or the use of the diphosphine (**2**) without an amino group, lowered the diastereoisomeric excess (entries 3—5). These results clearly indicate that both the amino group and the carboxy group are necessary for high stereoselectivity. It has been reported that addition of a tertiary amine to the reaction system raises the enantioselectivity in the asymmetric hydrogenation of didehydroamino acids[9] and itaconic acid.[10] Axial co-ordination of the carboxylate unit was assumed to explain this enhanced stereoselectivity.[10] Although the addition of a catalytic amount of triethylamine to the Rh^I–(**2**) system raised the selectivity (entry 7), the diastereoisomeric excess did not reach the level observed with Rh^I–(**1**). The addition of triethylamine to the Rh^I–(**1**) system lowered the selectivity (entry 6), in contrast with the case of Rh^I–(**2**). Therefore, axial co-ordination of the carboxylate unit formed by amine addition

Table 1. Asymmetric hydrogenation of the Ac-didehydrodipeptides (**4**) with Rh^I catalysts[a]

Ligand	Didehydrodipeptide	Temp. (°C)	Time (h)	Conv. (%)	% D.e. (Config.)
(**1**)	(**4a**)	20	0.8	100	92 (*S,S*)
(**1**)	(**4b**)	20	0.7	100	86 (*S,S*)
(**1**)	(**4c**)	20	3	100	84 (*S,S*)
(**1**)	(**4h**)	20	7	100	78 (*R,R*)
(**3**)	(**4a**)	20	0.25	100	98 (*S,S*)
(**3**)	(**4b**)	20	0.5	100	96 (*S,S*)
(**3**)	(**4c**)	20	50	100	88 (*S,S*)
(**3**)	(**4d**)	20	0.5	100	87 (*S,S*)
(**3**)	(**4e**)	20	16	90	86 (*R,R*)
(**3**)	(**4f**)	20	0.4	100	86 (*R,R*)
(**3**)	(**4g**)	25	18	100	92 (*R,R*)
(**3**)	(**4h**)	25	18	100	94 (*R,R*)

[a] The reaction was carried out in ethanol under atmospheric hydrogen pressure; (**1**):Rh 1.1:1; (**3**):Rh 1.5:1; substrate: Rh 50:1.

Table 2. Asymmetric hydrogenation of the Z-didehydrodipeptides (**5**) with Rh^I catalysts[a]

Entry	Ligand	Didehydrodipeptide	Temp. (°C)	Time (h)	Conv. (%)	% D.e. (Config.)
1	(**1**)	(**5a**)	20	9	100	86 (*S,S*)
2	(**1**)	(**5b**)	20	6	100	86 (*S,S*)
3	(**1**)	(**5c**)	20	16	100	92 (*S,S*)
4	(**1**)	(**5f**)	20	16	100	84 (*R,R*)
5	(**3**)	(**5a**)	50	140	70	46 (*S,S*)
6	(**3**)	(**5b**)	50	164	80	42 (*S,S*)
7	(**3**)	(**5d**)	50	45	35	64 (*R,R*)
8	(**3**)	(**5e**)	50	164	100	62 (*R,R*)
9	(−)-diop	(**5d**)	20	50	100	86 (*R,R*)
10	(−)-diop	(**5e**)	20	40	40	70 (*R,R*)

[a] The reaction was carried out in ethanol under atmospheric hydrogen pressure; diphosphine:Rh 1.1:1; (**3**):Rh 1.5:1; substrate: Rh 50:1.

Table 3. Effect of solvent polarity on the hydrogenation with Rh^I–(**1**) catalyst[a]

Didehydrodipeptide	% D.e. MeOH	% D.e. EtOH	% D.e. Pr^iOH
(**4a**)	94 (0.5)[b]	92 (0.8)	56 (1.5)[c]
(**4b**)	88 (0.8)	86 (0.7)	30 (1.6)
(**4c**)	91 (1)	84 (3)	
(**4h**)	87 (1.5)	78 (7)	

[a] The reaction was carried out under atmospheric hydrogen pressure at 20 °C; didehydrodipeptide:(**1**):Rh 50:1.1:1. [b] Figures in parentheses are the times (h) required for 100% conversion unless otherwise stated. [c] Conversion 50%.

Table 4. Asymmetric hydrogenation of didehydrodipeptides (**4**) and (**5**) under various conditions[a]

Entry	Ligand	Didehydrodipeptide	Solvent	Time (h)	% D.e. (Config.)
1	(**1**)	(**4a**)	MeOH	0.5	94 (*S,S*)
2	(**1**)	(**4i**)	MeOH	5	47 (*S,S*)
3	(**1**)·HCl	(**4a**)	MeOH	5	63 (*S,S*)
4	(**2**)	(**4a**)	MeOH	0.5	34 (*S,S*)
5	(**2**)	(**4i**)	MeOH	5	38 (*S,S*)
6	(**1**) + NEt_3[b]	(**4a**)	MeOH	0.7	66 (*S,S*)
7	(**2**) + NEt_3[b]	(**4a**)	MeOH	0.3	64 (*S,S*)
8	(**2**)	(**4j**)	MeOH	12	22 (*S,S*)
9	(**1**)	(**5a**)	EtOH	9	86 (*S,S*)
10	(**1**)	(**5g**)	EtOH	0.7	48 (*S,S*)
11	(**2**)	(**5a**)	EtOH	4.5	62 (*S,S*)

[a] The reaction was carried out under atmospheric hydrogen pressure at 20 °C, didehydrodipeptide:ligand:Rh 50:1.1:1. [b] NEt_3:Rh 10:1.

cannot explain the high 1,4-asymmetric induction in our Rh[I]–(**1**) system. It is concluded that the electrostatic interaction between the amino group of (**1**) and the carboxy group of the substrate enables three-site recognition of the substrate[4] by the complex catalyst, and that the steric factor of the chiral substrate is amplified to give more efficient 1,4-asymmetric induction. The solvent effect on the stereoselectivity is not fully understood at present, but the suppression of reactivity and stereoselectivity of the Ac-substrates in less polar solvents may be ascribable to interaction between substrate molecules.

Didehydrodipeptides with a benzyloxycarbonyl substituent as amino-protecting group are easily prepared,[11] and this group is removed from dipeptides easily under mild conditions (hydrogenolysis with palladium–charcoal under atmospheric hydrogen pressure).[12] Thus the present catalyst system, with achiral (**1**), would be useful for the preparation of oligopeptide fragments. The introduction of tritium into oligopeptides is a possibility, to give substrates of specific activity. Application of the Rh[I]–(**1**) catalyst to other substrates (didehydrotripeptides, and carbonyl compounds with a carboxy group) is under investigation.

Experimental

^1H N.m.r. spectra were recorded with a Hitachi R-24 instrument, with tetramethylsilane as internal standard. ^{31}P N.m.r. spectra were recorded with a JEOL FX-90A spectrometer for solutions in $CDCl_3$, with 85% H_3PO_4 as external standard. Mass spectra were recorded with a JEOL DX-300 instrument, in electron impact (e.i.) and fast atom bombardment (f.a.b.) ionization modes. In the latter mode a *m*-nitrobenzyl alcohol matrix was used.

Diethyl 2-(2-Dimethylaminoethyl)malonate (**6**).—To a solution of sodium ethoxide (0.25 mol) in ethanol (50 ml) was added a solution of diethyl malonate (40 g, 0.25 mol) in ethanol (50 ml). 2-Chloroethyl(dimethyl)amine hydrochloride (17.5 g, 0.12 mol) was added to the malonate solution in one portion, and the mixture was stirred for 24 h at 50 °C. The solvent was evaporated off and water was added to the residue. The separated malonate was taken up in ethyl acetate (30 ml) and the water layer was further extracted with ethyl acetate (30 ml × 2). The combined extract was dried and evaporated. Distillation under reduced pressure gave the diester (**6**) (19.5 g, 70%), b.p. 116—118 °C (16 mmHg); $\delta_H(CDCl_3)$ 1.25 (6 H, t, *J* 7.1 Hz, OCH_2CH_3), 2.20 [6 H, s, $N(CH_3)_2$], 1.80—2.20 (4 H, m, $CHCH_2CH_2N$), 3.45 [1 H, t, *J* 7.0 Hz, $(-OC)_2CHCH_2$], and 4.22 (4 H, q, *J* 7.1 Hz, OCH_2CH_3).

2-(2-*Dimethylaminoethyl*)*propane*-1,3-*diol* (**7**).—To a suspension of $LiAlH_4$ (0.8 g, 21 mmol) in dioxane (70 ml) was added the diester (**6**) (4.5 g, 19 mmol) dissolved in dioxane (10 ml). The mixture was stirred under reflux for 30 min, and treated with ethyl acetate, then with aqueous sodium hydroxide. Inorganic salts were filtered off and washed with tetrahydrofuran (THF) (40 ml × 2). The combined organic solution was evaporated and the residue was taken up in ethyl acetate. The ethyl acetate solution was dried and evaporated. Distillation of the oily residue under reduced pressure gave the diol (**7**) (1.24 g, 44%) as a viscous oil, b.p. 133—134 °C (4 mmHg); $\delta_H(CDCl_3)$ 1.37—1.87 (3 H, m, $CHCH_2CH_2N$), 2.23 [6 H, s, $N(CH_3)_2$], 2.35 (2 H, t, *J* 5.6 Hz, CH_2CH_2N), 3.50 (4 H, d, *J* 7.0 Hz, $HOCH_2CH$), and 5.47 (2 H, br, $HOCH_2$); *m/z* (f.a.b.) 132 (MH^+). In this reduction step, 4-dimethylamino-2-methylenebutan-1-ol was formed as a by-product [*ca.* 10% *vs.* the diester (**6**)]; $\delta_H(CDCl_3)$ 2.20 [6 H, s, $N(CH_3)_2$], 2.09—2.49 (4 H, m, CCH_2CH_2N), 3.99 (2 H, s, $HOCH_2C$), 4.90 (1 H, br, C=CH), 5.06 (1 H, br, C=CH), and 5.99 (1 H, s, $HOCH_2$). The proportion of this by-product increased on prolonged reaction.

1,3-*Dichloro*-2-(2-*dimethylaminoethyl*)*propane Hydrochloride* (**8**).—To a solution of $SOCl_2$ (2.56 g, 21.5 mmol) in $CHCl_3$ (2 ml) was added a solution of the diol (**7**) (0.90 g, 6.16 mmol) in $CHCl_3$ (2 ml) over 20 min at 0 °C. Then the mixture was refluxed for 3 h and evaporated. The residue was dissolved in ethanol and the solution was refluxed for 15 min. After evaporation, the residual mass was recrystallized from EtOH–Et_2O to give the dichloride (**8**) (1.07 g, 78%) as white crystals, $\delta_H(CDCl_3)$ 1.90—2.45 (3 H, m, $CHCH_2CH_2N$), 2.83 [6 H, d, *J* 4.8 Hz, $HN^+(CH_3)_2$], 3.02—3.44 (3 H, m, $CH_2CH_2{}^+NHCH_3$), and 3.65 (4 H, d, *J* 4.6 Hz, $ClCH_2$); *m/z* (f.a.b.) 184, 186, and 188 (M^+).

3-*Dimethylaminopropylidenebismethylenebis*(*diphenylphosphine*) (**1**).—To a solution of lithium diphenylphosphide (12 mmol) prepared from chlorodiphenylphosphine and lithium metal in THF (10 ml) was added potassium t-butoxide (1.35 g, 12 mmol), and the solution was cooled to 0 °C. The dichloride (**8**) (1.07 g, 4.8 mmol) was added in portions to the phosphide solution and the mixture was stirred for 24 h at room temperature, then evaporated. Water (5 ml) was added and the mixture was extracted with Et_2O (5 ml × 3). Addition of concentrated HCl (1 ml) to the ethereal extract at 0 °C resulted in precipitation of the diphosphine hydrochloride salt. Recrystallization from ethanol at −50 °C gave the *hydrochloride salt* of (**1**) (1.2 g, 47%) as white crystals (Found: C, 71.5; H, 6.7; N, 2.4. $C_{31}H_{36}ClNP_2$ requires C, 71.6; H, 7.0; N, 2.7%); $\delta_H(CDCl_3)$ 1.28—2.48 [7 H, m, $(PCH_2)_2CHCH_2CH_2$], 2.48—3.20 [3 H, m, $CH_2N^+H(CH_3)_2$], 2.60 [6 H, d, *J* 4.8 Hz, $N(CH_3)_2$], and 7.28 (20 H, s, Ph_2P); *m/z* (f.a.b.) 484 (M^+). To a Schlenk tube containing the hydrochloride of (**1**) (256 mg, 0.492 mmol) and NaOH (22 mg, 0.55 mmol), ether (10 ml) and water (5 ml) were added at 0 °C with stirring. After 15 min, the ether layer was separated and the water layer was extracted with ether (10 ml × 2). The combined ether extract was dried and evaporated to give the diphosphine (**1**) (230 mg, 97%) as a very viscous oil, $\delta_H(CDCl_3)$ 1.40—1.95 [3 H, m, $(PCH_2)_2CHCH_2CH_2N$], 2.11 [6 H, s, $N(CH_3)_2$], 1.95—2.5 [6 H, m, $(PCH_2)_2CH$ and CH_2CH_2N], and 7.27 (20 H, s, Ph_2P); $\delta_P(CDCl_3)$ −22.5; *m/z* 483 (M^+) (e.i.) and 484 (MH^+) (f.a.b.). All procedures were performed under nitrogen.

Trimethylenebis(*diphenylphosphine*) (**2**).—Compound (**2**) was prepared from 1,3-dichloropropane and lithium diphenylphosphide by the usual method, and was obtained as colourless needles (65%), $\delta_H(CDCl_3)$ 1.20—1.95 (2 H, m, $CH_2CH_2CH_2$),

1.95—2.43 (4 H, m, PCH_2CH_2), and 7.24 (20 H, s, Ph_2P); $\delta_P(CDCl_3)$ −17.7.

The diphosphinite (**3**) was prepared by the method previously reported.[4]

Substrates.—The *N*-acetyldidehydrophenylalanyl-amino acids (**4a**—**h**) were prepared from didehydrophenylalanine azlactone and the appropriate amino acids according to the procedure reported by Bergmann *et al.*[13] *N*-Benzyloxycarbonyl-didehydrophenylalanine was prepared from *N*-benzylcarbamate and phenylpyruvic acid according to the method of Shin.[11] *N*-Benzyloxycarbonyldidehydrophenylalanyl-amino acids (**5a**—**f**) were prepared by the coupling of Z-didehydrophenylalanine with amino acids, by use of *N*,*N*′-dicyclohexylcarbodi-imide and *N*-hydroxysuccinimide.[14] A typical procedure is as follows: to a solution of Z-ΔPhe-OH (1.50 g, 5.04 mmol) and *N*-hydroxysuccinimide (0.58 g, 5.14 mmol) in dioxane (10 ml) was added *N*,*N*′-dicyclohexylcarbodi-imide (1.04 g, 5.04 mmol) at 15 °C. The mixture was stirred for 3 h, then the precipitated dicyclohexylurea was filtered off and washed with dioxane. The dioxane solutions were combined and added to an aqueous solution (10 ml) of sodium hydrogen carbonate (0.43 g, 5.11 mmol) and (*S*)-alanine (0.45 g, 5.04 mmol). The mixture was stirred overnight at ambient temperature, then concentrated and acidified with 6M HCl to pH 2 at 0 °C. The precipitates were taken up in ethyl acetate (200 ml × 3). The organic extract was washed with water, dried, and concentrated. By addition of hexane to the concentrate, the dipeptide (**5b**) was obtained as white crystals (1.47 g, 80%), $\delta_H[(CD_3)_2SO]$ 1.36 (3 H, d, *J* 7.4 Hz, CH_3CH), 4.44 (1 H, quint, *J* 7.4 Hz, CH_3CHNH), 5.12 (2 H, s, $PhCH_2O$), 7.23 (1 H, s, C=C*H*Ph), 7.43 (5 H, s, *Ph*CH_2O), 7.0—7.48 (5 H, m, C=CH*Ph*), 9.04 (1 H, s, N*H*C=C), and 9.29 (1 H, d, *J* 7.0 Hz, N*H*CH); $[\alpha]_D^{25}$ +34.0° (*c* 1.03 in 95% EtOH).

Other Z-protected didehydrodipeptides (**5a**) and (**5c**—**f**) were prepared similarly and analysed. All Ac- and Z-substrates had the *Z*-configuration of the C=C bond.[11b,15]

Asymmetric Hydrogenation.—The catalyst solution of Rh^I–diphosphine or –diphosphinite, prepared from $[Rh(cod)_2]BF_4$* and the ligand, was transferred to the hydrogenation vessel containing didehydrodipeptide with a fine stainless tube, to avoid contamination by oxygen. The substrate–catalyst solution was stirred under N_2 for 1 h and then hydrogen was introduced. The reaction was followed by monitoring the amount of H_2 consumed at regulated temperature. The mixture was evaporated after removal of Rh catalyst with Dowex 50 cation-exchange resin and dipeptides were converted into methyl esters in methanol–HCl. The diastereomeric excess was determined by an n.m.r. method, using $Eu(fod)_3$, and the signals of the diastereotopic methyl protons of the ester unit of the *N*-protected dipeptides.[2a]

* Cod = cyclo-octa-1,5-diene.

Acknowledgements

A part of this work was financially supported by a Grant-in-Aid for Scientific Research (No. 61470089) from the Ministry of Education, Science, and Culture, Japan.

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Received 4*th August* 1987; *Paper* 7/1444