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Chiral sulfonated phosphines

VIII *. Hydrogenation of dehydropeptides in a two-phase system

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Abstract

Dehydropeptides have been reduced in a two-phase system using [{Rh(COD)Cl}$_2$] associated with chiral water-soluble ligands derived from cyclobutanediop and BDPP. Diastereoselectivities of up to 87% were obtained with tetrasulfonated BDPP.

Introduction

Homogeneous asymmetric hydrogenation of amino acid precursors using chiral rhodium or ruthenium complexes has developed greatly during the last few years and optical yields higher than 95% have been obtained [2–8]. Hydrogenation of dehydropeptides has also been carried out by homogeneous catalysis, and it was generally found that the chiral centre in the dehydropeptide has little influence on the stereoselectivity of hydrogenation [9–13].

We, and others, have recently described the asymmetric two-phase hydrogenation of amino acid precursors using chiral phosphines containing sulfonate groups [14] or methyl quarternized amines [15]. It was found that these ligands, particularly the 1,4-diphosphines, gave lower enantioselectivity in water than in an organic phase. This led us to examine the hydrogenation of dehydropeptides in a two-phase

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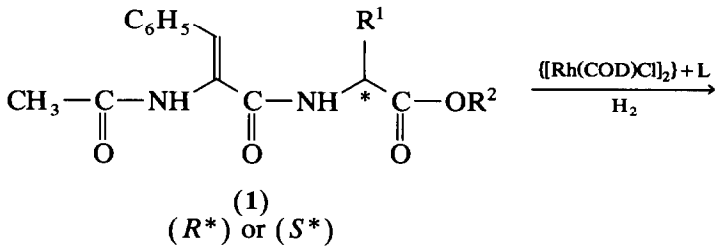
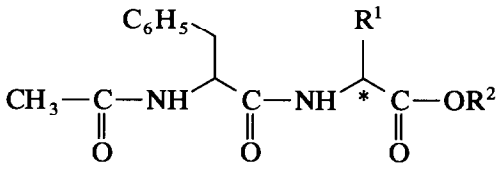
* For Part VII see ref. 1.



(1)
(*R**) or (*S**)



(2)
(*R*,*R** + *S*,*R**) or (*R*,*S** + *S*,*S**)

a: $R^1 = H$, $R^2 = CH_3$; **b**: $R^1 = CH_3$, $R^2 = CH_3$; **c**: $R^1 = C_6H_5$, $R^2 = H$;
d: $R^1 = C_6H_5$, $R^2 = CH_3$.

Scheme 1.

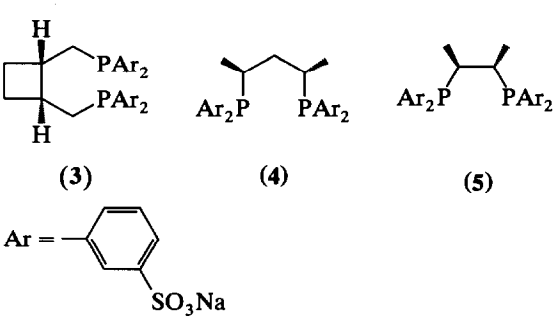
system, to determine the influence of a chiral centre in the substrate on the diastereoselectivity.

Results and discussion

Due to the problem of solubility, most of the hydrogenations were performed on the methyl esters of the dehydro(amino acids) in a two-phase system of water–dichloromethane. Some preliminary experiments, with the acids in a two-phase system (water-ethyl acetate) clearly showed that the hydrogenation is sluggish.

The systems used are shown in Schemes 1 and 2.

Hydrogenation of Ac-Δ-Phe-Gly-OCH_3 (**1a**) in the presence of $[\{Rh(COD)Cl\}_2]$ plus tetrasulfonated (*S*,*S*)-cyclobutanediop (**3**) or tetrasulfonated (*S*,*S*)-BDPP (**4**) gives e.e. up to 7% (entry 1) and 19% (entry 2) (Table 1) respectively. These low enantioselectivities are quite similar to those obtained previously in the hydrogena-



(3) (4) (5)

Scheme 2.

Table 1

Hydrogenation of dehydropeptides **1** in the presence of $[\{Rh(COD)Cl\}_2]+L$ [a]

Entry	Substrate	Ligand	pH_2 (atm)	Conversion [b] (%)	e.e (%) or d.e. (%) (conf.) [c]
1	**1a**	**3**	5	100	7 (S)
2	**1a**	**4**	10	100	19 (R)
3	**1b** (*R*)	**3**	5	100	14 (S)
4	**1b** (*S*)	**3**	5	100	3 (R)
5	**1c** (*R*) [d]	**3**	1	100	40 (S)
6	**1c** (*S*) [d]	**3**	1	100	20 (S)
7	**1d** (*R*)	**3**	5	69	13 (S)
8	**1d** (*S*)	**3**	5	93	2 (S)
9	**1b** (*R*)	**4**	5	80	6 (R)
10	**1b** (*R*)	**4**	20	100	10 (R)
11	**1b** (*R*)	**4** [e]	10	100	18 (S)
12	**1b** (*S*)	**4**	10	100	66 (R)
13	**1b** (*S*)	**4**	20	100	72 (R)
14	**1b** (*S*)	**4** [e]	10	100	87 (R)
15	**1d** (*R*)	**4**	30	55	6 (R)
16	**1d** (*S*)	**4**	30	80	87 (R)

[a] [Substrate] = 5×10^{-2} M; [substrate]:[Rh]:[L] = 25:1:1.1; solvent H_2O: CH_2Cl_2 (5 ml:10 ml), 25°C; 24 h. [b] Determined by ^1H NMR. [c] Determined by gas chromatography on a Chirasil–Val column. [e] Mixture of monosulfonated (25%), disulfonated (70%), and trisulfonated (5%) diphosphine. [d] A water–ethyl acetate two-phase system was used (5 ml:10 ml).

tion of amino acids precursors using the same complexing agents in a two-phase system [14a].

Reduction of Ac-Δ-Phe-Ala-OCH_3 (*R*) or (*S*) (**1b**), of Ac-Δ-Phe-Ph-OH (*R*) or (*S*) (**1c**) or its methyl ester **1d** in the presence of the catalyst obtained from $[\{Rh(COD)Cl\}_2]$ and tetrasulfonated (*S,S*)-cyclobutanediop (**3**) also gives very modest diastereoselectivities: 14% (*R,S*), 40% (*R,S*) and 13% (*R,S*) in the hydrogenation of **1** (*R*), and 3% (*R,S*), 20% (*S,S*) and 2% (*S,S*) in the hydrogenation of **1** (*S*). However it seems that the presence of an (*R*) amino acid in the dehydropeptide induces a higher stereoselectivity (for examples entries 3–6 in Table 1).

Hydrogenation using tetrasulfonated (*S,S*)-BDPP (**4**) as the chiral ligand gives higher diastereoselectivities. If Ac-Δ-Ph-(*R*)-Ala-OCH_3 (**1b**) is reduced with only 10% diastereoselectivity, Ac-Δ-Ph-(*S*)-Ala-OCH_3 (**1b**) gives the dipeptide **2b** (*S,R*) with a diastereoselectivity up to 72%. The same behaviour is found for the dehydropeptide **1d** (*R*) and **1d** (*S*): a diastereoselectivity up to 87% was found for the latter compound (entry 16, Table 1). In this case, intrinsic asymmetric induction in the substrate **1d** (*S*) and the catalyst Rh/tetrasulfonated (*S,S*)-BDPP are probably in the same direction (matched pair); on the other hand, asymmetric induction in the substrate **1d** (*R*) and the catalyst are the mismatched pair. We noticed also that the use of a mixture of sulfonated BDPP gives also quite different results; when the matched pair gives higher diastereoselectivity (87%, entry 14), the mismatched pair gives now the (*R,S*) dipeptide **2b** with 18% diastereoselectivity.

Some experiments were also done using tetrasulfonated (*S,S*)-chiraphos (**5**) diastereoisomeric excesses of only 10–20% were obtained. However, the hydro-

genation was very sluggish and the formation of colloidal rhodium cannot be excluded.

Experimental

^{1}H NMR spectra were recorded on a Bruker WP 80 CW (90 MHz) spectrometer. The optically pure amino acids ((*R*)- and (*S*)-alanine, (*R*)- and (*S*)-phenylalanine) were commercial samples. Tetrasulfonated (*S,S*)-cyclobutanediop (or (*S,S*)-1,2-bis(diphenylphosphino)methylcyclobutane), tetrasulfonated (*S,S*)-BDPP (or (*S,S*)-2,4-bis(diphenylphosphino)pentane) and tetrasulfonated (*S,S*)-chiraphos are prepared as previously described [14a]. The dehydropeptides were prepared according to Bergmann [16] and Kagan [9].

Hydrogenation

Hydrogenations were performed at room temperature under atmospheric pressure in a glass hydrogenation flask or under pressure in a stainless glass autoclave using the procedure described previously [14a]. After 24 h, the organic layer was separated and the solvent evaporated. Analysis of this mixture was done by ^{1}H NMR spectroscopy. The optical purity of the dipeptide was obtained by gas chromatography on a chiral phase Chirasil–Val of each sample, derivatized according to well known procedures [17,18].

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References

1 D. Sinou, M. Safi, C. Claver and A. Masdeu, J. Mol. Catal., 68 (1991) L9.
2 J.D. Morrison (Ed.), Asymmetric Synthesis, Academic Press, New York, 1985, Vol. 5.
3 I. Ojima, N. Clos and C. Bastos, Tetrahedron, 45 (1989) 6901.
4 H. Brunner, Top. Stereochem., 18 (1988) 129.
5 H.B. Kagan, Bull. Soc. Chim. Fr., (1988) 846.
6 R. Noyori and M. Kitamura, in R. Scheffold (Ed.), Modern Synthetic Methods 1989, Springer, Berlin, 1989, p. 115.
7 S.L. Blystone, Chem. Rev., 89 (1989) 1663.
8 R. Noyori and H. Takaya, Acc. Chem. Res., 23 (1990) 345.
9 D. Meyer, J.C. Poulin, H.B. Kagan, H. Levine-Pinto, J.L. Morgat and P. Fromageot. J. Org. Chem., 45 (1980) 4680.
10 S. El-Baba, J.M. Nuzillard, J.-C. Poulin and H.B. Kagan, Tetrahedron, 42 (1986) 3851.
11 I. Ojima, N. Yoda, M. Yatabe, T. Tanaka and T. Kogure, Tetrahedron, 40 (1984) 1255.
12 M. Yatagai, T. Yamagishi and M. Ida, Bull. Chem. Soc. Jpn., 57 (1984) 823.
13 D. Sinou, D. Lafont, G. Descotes and A.G. Kent, J. Organomet. Chem., 217 (1981) 119.
14 (a) Y. Amrani, L. Lecomte, D. Sinou, J. Bakos, I. Toth and B. Heil, Organometallics, 8 (1989) 542; (b) L. Lecomte and D. Sinou, J. Mol. Catal., 52 (1989) L 21; (c) L. Lecomte, D. Sinou, J. Bakos, I. Toth and B. Heil, J. Organomet. Chem., 370 (1989) 277; (d) M. Laghmari and D. Sinou, J. Mol. Catal., 66 (1991) L 15.
15 (a) I. Toth, B.E. Hanson and M.E. Davis, Organometallics, 9 (1990) 675; (b) ibid., Catal. Lett., 5 (1990) 183; (c) ibid., J. Organomet. Chem., 396 (1990) 363; (d) ibid., J. Organomet. Chem., 397 (1990) 109; (e) I. Toth and B.E. Hanson, Tetrahedron Asymmetry, 1 (1990) 895; (f) I. Toth, B.E. Hanson and M.E. Davis, Tetrahedron Asymmetry, 1 (1990) 913.
16 D.G. Doherty, J.E. Tietzman and M. Bergmann, J. Biol. Chem., 147 (1943) 617.
17 H. Frank, C.J. Nicholson and E. Boyer, J. Chromatogr. Sci., 15 (1977) 174.
18 S. El-Baba, J.-C. Poulin and H.B. Kagan, Tetrahedron, 40 (1984) 4275.