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SYNTHESIS OF OPTICALLY ACTIVE N-[(N-ACETYL)-α-AMINOACYL]-β-AMINO ALCOHOLS BY HOMOGENEOUS AND HETEROGENEOUS ASYMMETRIC HYDROGENATIONS

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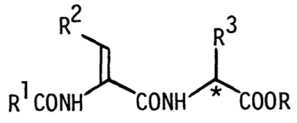
Asymmetric hydrogenations of N-(N-acetyldehydrophenylalanyl)-β-amino alcohol benzyl ethers were carried out by using either rhodium complexes with chiral and achiral phosphines or 10% palladium on carbon. The effects of the chiral center in the β-amino alcohol moiety on simple as well as double asymmetric induction are described.

Of late years, it has been disclosed that i) the asymmetric hydrogenations of dehydrodipeptides of the type 1 or 2 catalyzed by chiral rhodium complexes give the corresponding optically active dipeptides with desired configuration,[1,2] and ii) the type 1 dehydrodipeptides are very good substrates achieving quite high stereoselectivities[1] while the type 2 dehydrodipeptides realize only moderate to good stereoselectivities.[2] In the present communication, we would like to report the asymmetric hydrogenations of dehydrodipeptide analog, N-(N-acetyldehydrophenylalanyl)-β-amino alcohol benzyl ethers (3) catalyzed by rhodium complexes or 10% palladium on carbon (10% Pd-C)(eq. 1), and describe a considerably large asymmetric induction due to the chiral center in the β-amino alcohol moiety.



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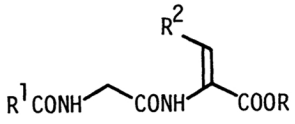

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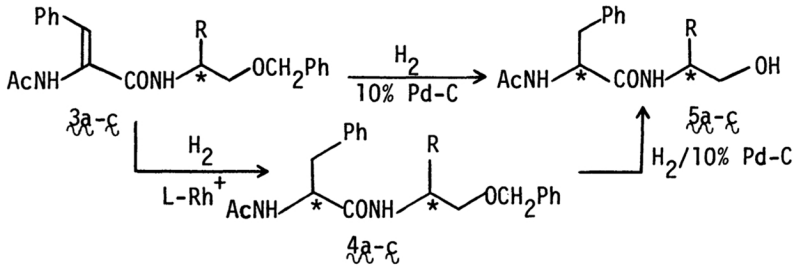
The asymmetric hydrogenation of 3 on 10% Pd-C proceeded at 25°C and 1 atm of hydrogen to give 5 directly in quantitative yield.[3,10] When the reaction was carried out at lower temperature, the HPLC analysis of the reaction mixture revealed that the reaction proceeded stepwise, i.e., 4 was the primary product, which was further converted to 5.

Table 1 summarizes the results of simple asymmetric hydrogenation of 3 catalyzed by dppb-Rh^+ [dppb = 1,4-bis(diphenylphosphino)butane] and 10% Pd-C. As a matter of course, the stereoelectronic character of substituents in chiral β-amino alcohol moiety exerts a large influence on stereoselectivity, viz., the formation of (S,S)-isomer is preferred for 3a-3c while (R,S)-isomer is predominantly formed in the case of 3d. It is clearly indicated that palladium catalyst is more sensitive to the stereoelectronic effect of the substituent than dppb-Rh^+.



a: R = CH_2Ph (S); b: R = $CH_2CH(CH_3)_2$ (S)
c: R = $CH(CH_3)_2$ (S)

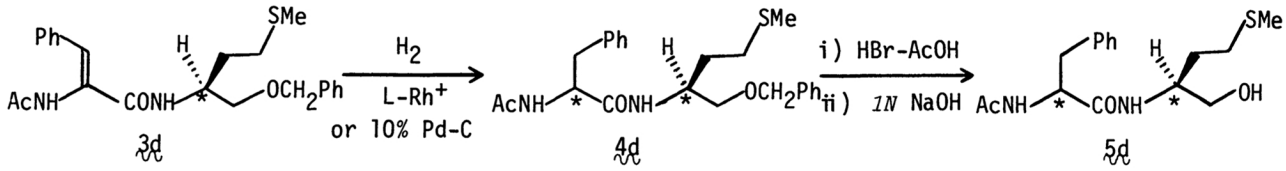


Table 1. Asymmetric Hydrogenation of N-(N-Acetyldehydrophenylalanyl)-β-amino Alcohols (3) Catalyzed by 10% Pd-C or dppb-Rh^+[a]

Substrate	R	Catalyst[b]	Conditions H_2 press., Temp., Time	(R,S)/(S,S) (HPLC)[d,e]	% Asymmetric Induction
3a	CH_2Ph	10% Pd-C	1 atm, 25°C, 40 h	43.0/57.0	14.0 (S)
		dppb-Rh^+	5 atm, 40°C, 40 h	39.6/60.4	20.8 (S)
3b	$CH_2CH(CH_3)_2$	10% Pd-C	1 atm, 25°C, 40 h	28.8/71.2	42.4 (S)
		10% Pd-C	1 atm, 2°C, 17 h	28.3/71.7	43.4 (S)
		10% Pd-C	1 atm, -15°C, 17 h	27.0/73.0	46.0 (S)
		dppb-Rh^+	5 atm, 40°C, 40 h	41.3/58.7	17.4 (S)
3c	$CH(CH_3)_2$	10% Pd-C	1 atm, 25°C, 40 h	29.3/70.7	41.4 (S)
		10% Pd-C[c]	1 atm, 2°C, 20 h	24.5/75.7	51.0 (S)
		10% Pd-C[c]	1 atm, -15°C, 20 h	23.8/76.2	52.4 (S)
		dppb-Rh^+	5 atm, 40°C, 40 h	27.1/72.9	45.8 (S)
3d	$CH_2CH_2SCH_3$	10% Pd-C	1 atm, 25°C, 20 h	78.2/21.8[f]	56.4 (R)
		10% Pd-C[c]	1 atm, 2°C, 48 h	80.6/19.4[f]	61.2 (R)
		dppb-Rh^+[g]	10 atm, 40°C, 46 h	50.8/49.2[f]	1.6 (R)

a All reactions were run with 0.30 mmol of substrate and 100-120 mg (0.10-0.12 mmol) of 10% Pd-C or 1.0×10^{-3} mmol of dppb-Rh^+ in ethanol unless otherwise noted. Chemical yields were almost quantitative in all cases. *b* dppb-Rh^+ was prepared in situ by mixing dppb (3.0×10^{-3} mmol) and $[Rh(NBD)_2]ClO_4$ (NBD = norbornadiene)(3.0×10^{-3} mmol) in degassed ethanol. *c* 300 mg (0.30 mmol) of 10% Pd-C was used. *d* HPLC analyses were carried out by using reversed phase column packed with TOYO SODA LS 410K (ODS SIL) and aqueous methanol as eluant. *e* The diastereomeric ratios were determined for 5 unless otherwise noted. *f* The ratio was determined for 4d. *g* 6.0×10^{-3} mmol of the catalyst was used.

Table. 2 Asymmetric Hydrogenation of N-(N-Acetyldehydrophenylalanyl)-β-amino Alcohols (3) Catalyzed by Chiral Rhodium Complexes[a]

Substrate	R	Chiral Ligand[b]	Conditions H_2 press., Temp., Time	(R,S)/(S,S) (HPLC)[c]	% Asymmetric Induction
3a	CH_2Ph	Ph-CAPP[e]	5 atm, 40°C, 40 h	97.4/2.6	94.8 (R)
		(+)BPPM	5 atm, 40°C, 40 h	0.9/99.1	98.2 (S)
		(+)DIOP	5 atm, 40°C, 68 h	11.3/88.7	77.4 (S)
		(-)DIOP	5 atm, 40°C, 68 h	87.7/12.3	75.4 (R)
3b	$CH_2CH(CH_3)_2$	Ph-CAPP[e]	5 atm, 40°C, 42 h	98.7/1.3	97.4 (R)
		(+)BPPM	5 atm, 40°C, 40 h	0.9/99.1	98.2 (S)
		(+)DIOP	5 atm, 40°C, 48 h	5.5/94.5	89.0 (S)
		(-)DIOP	5 atm, 40°C, 48 h	84.2/15.8	68.4 (R)
3c	$CH(CH_3)_2$	Ph-CAPP[e]	5 atm, 40°C, 43 h	94.4/5.6	88.8 (R)
		(+)BPPM	5 atm, 40°C, 40 h	1.4/98.6	97.2 (S)
		(+)DIOP	5 atm, 40°C, 43 h	6.7/93.3	86.6 (S)
		(-)DIOP	5 atm, 40°C, 43 h	75.1/24.9	50.2 (R)
3d	$CH_2CH_2SCH_3$	Ph-CAPP[d,e]	5 atm, 40°C, 46 h	90.7/9.3	81.4 (R)
		(+)BPPM[d]	5 atm, 40°C, 46 h	4.5/95.5	91.0 (S)
		(+)DIOP[d]	10 atm, 40°C, 48 h	10.6/89.4	78.8 (S)
		(-)DIOP[d]	10 atm, 40°C, 48 h	82.5/17.5	65.0 (R)

a All reactions were run with 0.30 mmol of substrate and 3.0×10^{-3} mmol of chiral catalyst in ethanol and chemical yields were almost quantitative. *b* Chiral catalysts were prepared in situ by reacting chiral ligands (3.0×10^{-3} mmol) with $[Rh(NBD)_2]ClO_4$ (3.0×10^{-3} mmol) in degassed ethanol unless otherwise noted. *c* See, Table 1 footnote. *d* 6.0×10^{-3} mmol of chiral catalyst was used. *e* $[(PhCAPP)Rh(COD)]ClO_4$ (COD = 1,5-cyclooctadiene) was used.

As for the asymmetric hydrogenation of cyclic dehydrodipeptides on Pd-C, Izumiya et al. reported extremely high asymmetric inductions.[4] However, only low stereoselectivities (0-20% asymmetric induction) have been realized in the open-chain dehydrodipeptides as far as the reported data and our experiments are concerned.[5] Accordingly, the asymmetric inductions of 46.0%, 52.4%, and 61.2 achieved in the reactions of 3b, 3c, and 3d, respectively, are remarkably good values for the simple open chain systems.

On the other hand, the asymmetric hydrogenation of 3 catalyzed by chiral rhodium complexes proceeded smoothly at 40°C and 5-10 atm of hydrogen to give the corresponding dipeptide analog (4) in quantitative yield,[6] which was further transformed to N-[(N-acetyl)phenylalanyl]-β-amino alcohol (5) by the hydrogenolysis of benzyl protecting group on 10% Pd-C.[10]

Table 2 summarizes the results on using Ph-CAPP,[7] (+)BPPM,[8] (+)DIOP,[9] and (-)-DIOP[9] as chiral ligands.

As Table 2 shows, a large double asymmetric induction was observed in the case of 3b, 3c, and 3d, the (S,S)-isomer being preferred, while the effect of chiral

center in 3a turned out to be virtually negligible. The (R,S)-isomer with high optical purities were produced by the entry of Ph-CAPP. At any rate, it is demonstrated that chiral dipeptide analogs, 4 and 5, with high optical purities can be obtained with the proper choice of chiral ligands.

Further investigation on the asymmetric synthesis of oligopeptides bearing chiral β-amino alcohol residue at the C-terminus by using the present method is now actively underway.

References

1. (a) I. Ojima and T. Suzuki, Tetrahedron Lett., 21, 1239 (1980). (b) I. Ojima, T. Kogure, N. Yoda, T. Suzuki, M. Yatabe, and T. Tanaka, J. Org. Chem., 47, 1329 (1982). (c) D. Meyer, J.-P. Poulin, H. B. Kagan, H. Levine-Pinto, J.-L. Morgat, and P. Fromageot, J. Org. Chem., 45, 4680 (1980). (d) H. Levine-Pinto, J. L. Morgat, P. Fromageot, D. Meyer, J. C. Poulin, and H. B. Kagan, Tetrahedron, 38, 119 (1982). (e) K. Onuma, T. Ito, and A. Nakamura, Chem. Lett., 1980, 481.
2. A. Kleemann, J. Martens, M. Samson, and W. Bergstein, Synthesis, 740 (1981).
3. The structures of the products (5) were identified by NMR and IR spectra. In the case of 3d, the reaction afforded 4d instead of 5d at 25°C.
4. (a) N. Izumiya, S. Lee, T. Kanmera, and H. Aoyagi, J. Am. Chem. Soc., 99, 8346 (1977). (b) S. Lee, T. Kanmera, H. Aoyagi, N. Izumiya, Int. J. Peptide Protein Res., 13, 207 (1979).
5. For example, Ac-ΔPhe-(S)-Phe-OMe: 10% Pd-C, 1 atm of H_2, 25°C, (R,S)/(S,S) = 60.2/39.8 [See also ref. 1 (c)]; Ac-ΔPhe-(S)-Phe-OH: 10% Pd-C, 1 atm of H_2, 25°C, (R,S)/(S,S) = 60/40 [See ref. 1 (c)]; Ac-ΔPhe-(S)-Val-OMe: 10% Pd-C, 1 atm of H_2, 25°C, (R,S)/(S,S) = 44.1/55.9, -15°C, (R,S)/(S,S) = 47.8/52.2; Ac-ΔPhe-(S)-Val-OH: 10% Pd-C, 1 atm of H_2, 25°C, (R,S)/(S,S) = 47.6/52.4; ^{t}BOC-(S)-Leu-ΔAla-OMe : Pd black, 1 atm of H_2, 25°C, (R,S)/(S,S) = 50/50 [See ref. 4 (b)].
6. The structures of the products (4) were identified by NMR and IR spectra.
7. Ph-CAPP stands for (2S,4S)-N-(N-phenylcarbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine: I. Ojima and N. Yoda, Tetrahedron Lett., 21, 1051 (1980).
8. (+)BPPM stands for (2R,4R)-N-(t-butoxycarbonyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine: G. L. Baker, S. J. Fritschel, J. R. Stille, and J. K. Stille, J. Org. Chem., 46, 2954 (1981); See also ref. 1 (b).
9. DIOP stands for 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane: H. B. Kagan and T.-P. Dang, J. Am. Chem. Soc., 94, 6429 (1972).
10. As for 4d, the benzyl group could not be removed by hydrogenolysis on 10% Pd-C. Thus, hydrogen bromide-acetic acid was empolyed for deblocking follwed by the treatment with 1*N* sodium hydroxide in methanol to give 5d in high yield.

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