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CATALYTIC ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE β-AMINO ACIDS[1)]

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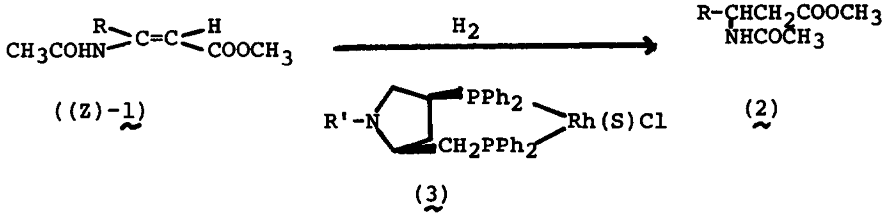
β-Amino acids[2)] are of great current interest because of their naturally occurring as the component of biologically active peptide antibiotics and also their structual relationship to the β-lactam, one of the most biologically important functional groups.

We wish to describe here the catalytic asymmetric hydrogenation of β-acetylamino acrylic acid derivatives (1) using new bisphosphines, BPPM (3c)[3)] and BZPPM (3d)[4)] as the chiral ligands, to give the optically active β-amino acids (2). BPPM-rhodium complex has been already demonstrated to be a quite effective catalyst for the synthesis of optically active α-amino acids[3)], isoquinoline alkaloid (salsolidine)[5)], α-hydroxy esters[6)]and pantolactone[7)].



1a,2a: R= CH_3-
1b,2b: R= C_6H_5-

3c: R'= $(CH_3)_3COCO$- (BPPM)
3d: R'= C_6H_5CO- (BZPPM)

In a typical experiment, the asymmetric hydrogenation of (Z)-1b (2 mmole) was run in benzene (2 ml) under an initial hydrogen pressure of 50 atm at 50°C for 45 h in the presence of the rhodium catalyst which was prepared in situ from BZPPM (2.4×10^{-2}mmole) and [Rh(1,5-hexadiene)Cl]$_2$ (1.0×10^{-2}mmole). The resulted reaction mixture was purified on preparative TLC (Silicagel, n-hexane-ether (1:2) as a developing solvent) to give 2b, mp 84-86°C, $[\alpha]_D^{20}$ +44.2°(c 2.006, methanol) in a 91.2% isolated yield. The absolute configuration and optical purity of 2b were determined by converting (+)-2b ($[\alpha]_D^{20}$ +44.2°(methanol)) into R(+)-β-N-acetylamino-β-phenylpropionic acid[8)], mp 166-168°C, $[\alpha]_D^{20}$ +54.6°(c, 0714, ethanol), on alkali hydrolysis. Similarly, 2a ($[\alpha]_D^{20}$ -14.0°(methanol)) was converted into S(+)-β-aminopropionic acid[9], mp 206-208°C, $[\alpha]_D^{20}$ +19.9°(c 2.896, H_2O), on 6N-HCl hydrolysis. Therefore, the optical rotation of pure S-2a and R-2b were calculated to be $[\alpha]_D$-26.1°(methanol) and $[\alpha]_D$+83.4°(methanol) respectively.

The results on the asymmetric hydrogenation of (Z)-1a and (Z)-1b with BPPM (3c) or (BZPPM(3d)-rhodium complex in benzene or methanol as a solvent are listed in Table I.

Table I. Asymmetric hydrogenation of methyl β-acetamidoacrylate[a,b)]

Substrate (R)	Chiral reagent (R')	Solvent	Conversion (%)	$[\alpha]_D^{20}$(MeOH) (°)	Optical y.(conf.) (%)
C_6H_5 (1b)	$(CH_3)_3COCO$ (BPPM)	Benzene	65.6[c)]	+30.6	36.7 (R)
C_6H_5 (1b)	$(CH_3)_3COCO$ (BPPM)	Methanol	88.2[c)]	- 2.2	2.6 (S)
C_6H_5 (1b)	C_6H_5CO (BZPPM)	Benzene	91.2[c)]	+44.2	53.0 (R)
C_6H_5 (1b)	C_6H_5CO (BZPPM)	Methanol	95.7[c)]	+ 6.3	7.6 (R)
CH_3 (1a)	$(CH_3)_3COCO$ (BPPM)	Benzene	75.3[d)]	- 8.7	33.3 (S)
CH_3 (1a)	$(CH_3)_3COCO$ (BPPM)	Methanol	100 [d)]	-12.3	47.1 (S)
CH_3 (1a)	C_6H_5CO (BZPPM)	Benzene	100 [d)]	-13.1	50.2 (S)
CH_3 (1a)	C_6H_5CO (BZPPM)	Methanol	100 [d)]	-14.4	55.2 (S)

a) All hydrogenations of 1b were run with 2 mmole of 1b, 0.01 mmole of $[Rh(1,5\text{-hexadiene})Cl]_2$ and 0.024 mmole of bisphosphine in 2 ml of solvent at 50°C for 45 h under an initial hydrogen pressure of 50 atm.
b) All hydrogenations of 1a were run with 4 mmole of 1a, 0.02 mmole of $[Rh(1,5\text{-hexadiene})Cl]_2$ and 0.048 mmole of bisphosphine in 4 ml of solvent under the same conditions as used with 1b.
c) Isolated yields. d) Vpc analysis. e) $[\alpha]_D$-26.1°(MeOH) and $[\alpha]_D$+83.4° (MeOH) were used for pure S-2a and R-2b respectively. See the Text.

Table I shows clearly that BZPPM-rhodium complex gave the better optical and chemical yields of the products than BPPM-rhodium complex and also the best optical yield (53.0%) of 2b was obtained when benzene was used as a solvent whereas the better result (55.2% optical yield) was attained in the methanol solution on the synthesis of 2a.

Further active investigations along this line are under way.

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