EFFECTIVE CATALYTIC ASYMMETRIC SYNTHESIS OF S-(-)-3-METHOXY-CARBONYL-4-(3,4-METHYLENEDIOXYPHENYL)BUTANOIC ACID. A SIMPLE AND EFFECTIVE ROUTE TO CHIRAL LIGNANS[1)]

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Abstract - Effective catalytic asymmetric synthesis of S-2, a key intermediate for the synthesis of chiral lignans, was described. Thus, BPPM-Rh^+ in the presence of triethylamine gave S-2 in 78% optical yield.

Chiral pyrrolidinephosphine-rhodium catalysts have been proven to be practically useful for the preparation of chiral α-amino acids (83-91% optical yields)[2,3)], salsolidine (45%)[4)], α-hydroxy esters (78.5%)[5,6)], R-(-)-pantolactone (80.5-86.7%)[7,8)], β-amino acids (53-55%)[9)], α-methylsuccinic acid (94.2%)[10-12)] and β-methylaspartic acid (58.2%)[13)], and also the mechanistic studies[14)] on these asymmetric hydrogenations suggested that the β,γ-unsaturated acid is one of the most suitable substrates for the asymmetric hydrogenations catalyzed by chiral pyrrolidinephosphine-rhodium complexes to obtain the high optical yields.

I wish to describe here an effective asymmetric hydrogenation of (E)-1[15)], a β,γ-unsaturated acid derivative, to give S-2, a key intermediate for the synthesis of chiral lignans, steganacin, steganagin and podophyllotoxin, antileukemic agents[16)]. The reaction sequences are shown in Scheme I.

In a typical experiment, the asymmetric hydrogenation of (E)-1 (1 mmole) was run in methanol (3 ml) under an initial hydrogen pressure of 50 atm at 50°C for 20 h in the presence of $[Rh(COD)BPPM]^+ClO_4^-$ (BPPM-Rh^+) (0.01 mmole). After removal of the solvent, the residue was treated with 3 ml of 0.5N-NaOH and the mixture was filtered to remove the catalysts. Then, the filtrate was acidified with HCl and ethereal extract gave 2, $[\alpha]_D^{20}$ -27.3° (c 2.53, methanol) in a 91% isolated yield. The absolute configuration and optical purity of 2 were determined by converting (-)-2 ($[\alpha]_D^{20}$ -26.3° (methanol)) into S-3[17)], $[\alpha]_D^{20}$ -2.6° (c 1.058, chloroform), on $LiAlH_4$ reduction. Therefore, the specific rotation of pure S-2 was calculated to

be $[\alpha]_D$ -35° (methanol).

Scheme I.

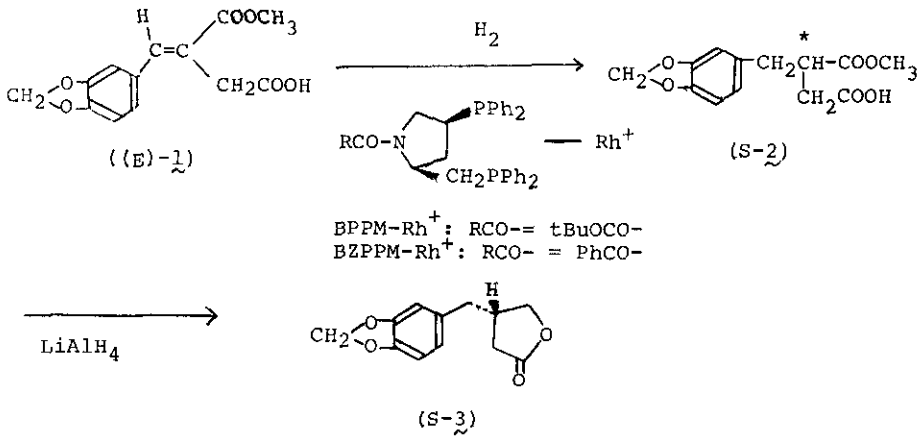

Table I. Catalytic asymmetric hydrogenation of the β,γ-unsaturated acid[a)]

Chiral reagent(RCO-)	Solvent	$[\alpha]_D^{20}$(methanol)	Optical y.	(conf)[d)]
BPPM-Rh$^+$ (t-BuOCO-)	methanol	-20.1°	57%	(S)
BPPM-Rh$^+$ (t-BuOCO-)	methanol[b)]	-27.3	78	(S)
BPPM-Rh$^+$ (t-BuOCO-)	methanol[b,c)]	-27.4	78	(S)
BPPM-Rh$^+$ (t-BuOCO-)	tetrahydrofuran[b)]	- 8.1	23	(S)
BZPPM-Rh$^+$ (PhCO-)	methanol	-23.5	67	(S)
BZPPM-Rh$^+$ (PhCO-)	methanol[b)]	-26.3	75	(S)
BZPPM-Rh$^+$ (PhCO-)	tetrahydrofuran[b)]	-10.0	29	(S)

a) All hydrogenations were run with 1 mmole of substrate, 0.01 mmole of [Rh(COD)bisphosphine]$^+ClO_4^-$ in 3 ml of solvent at 50°C for 20 h under an initial hydrogen pressure of 50 atm unless otherwise cited.

b) Triethylamine (0.5 mmole) was added.

c) At 20°C for 30 h.

d) $[\alpha]_D$ -35° (MeOH) was used for pure S-2. See the Text.

Table I indicated clearly that BPPM-Rh^+ gave the better optical yields than BZPPM-Rh^+. This fact suggests that the suitable modifications of the N-substituent of the chiral ligands may improve the optical yields of the product. It should be also noted that this hydrogenation offered the practically useful route to chiral lignans[16-19].

Further modifications of chiral catalysts and applications of the catalytic asymmetric hydrogenations catalyzed by pyrrolidinephosphine-rhodium complexes to the synthesis of chiral and biologically active compounds are actively under way.

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17. The maximum rotation of R-3 is $[\alpha]_D^{20}$ + 4.8° (c 1.142, $CHCl_3$); M.Kuhn and A von Wartburg, Helv.Chim.Acta, 1967, 50, 1546. This compound (S-3) thus obtained was also converted to (2R,3S,6R)-podorhizol and (2R,3S,6S)-epi-podorhizol according to the reported conditions[18].
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