

EFFECTIVE CATALYTIC ASYMMETRIC SYNTHESIS OF S-(-)-3-METHOXY-CARBONYL-4-(3,4-METHYLENEDIOXYPHENYL)BUTANOIC ACID. A SIMPLE AND EFFECTIVE ROUTE TO CHIRAL LIGNANS¹⁾

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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 studies¹⁴⁾ 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)-1¹⁵⁾, a β,γ -unsaturated acid derivative, to give S-2, a key intermediate for the synthesis of chiral lignans, steganacin, steganagin and podophyllotoxin, antileukemic agents¹⁶⁾. 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]⁺ClO₄⁻ (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, [α]_D²⁰ -27.3° (c 2.53, methanol) in a 91% isolated yield. The absolute configuration and optical purity of 2 were determined by converting (-)-2 ([α]_D²⁰ -26.3° (methanol)) into S-3¹⁷⁾, [α]_D²⁰ -2.6° (c 1.058, chloroform), on LiAlH₄ reduction. Therefore, the specific rotation of pure S-2 was calculated to

be $[\alpha]_D -35^\circ$ (methanol).

Scheme I.

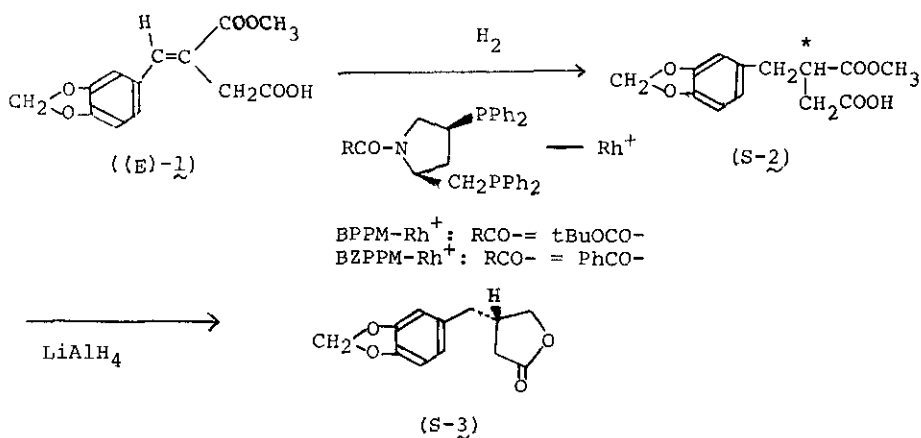


Table I. Catalytic asymmetric hydrogenation of the β,γ -unsaturated acid^{a)}

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]⁺ClO₄⁻ 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) $[\alpha]_D -35^\circ$ (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 lignans¹⁶⁻¹⁹).

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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