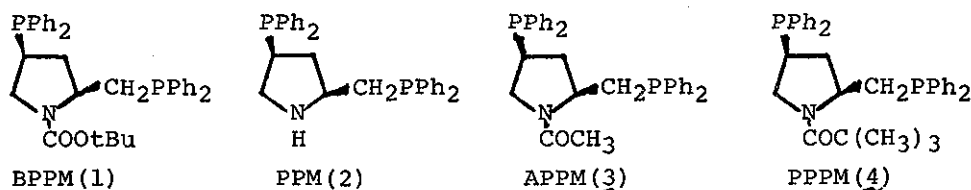


CATALYTIC ASYMMETRIC SYNTHESIS OF (S)- AND (R)-SALSOLIDINE^{1,2)}Kazuo AchiwaFaculty of Pharmaceutical Sciences, University of TokyoBunkyo-ku, Tokyo 113, Japan

Catalytic asymmetric synthesis of (S)- and (R)-salsolidine (7) with BPPM(1)-, APPM(3)- and PPPM(4)-rhodium complexes was found to proceed in 34-45% optical yields, while its optical yields and absolute configuration depended markedly on the used hydrogenation conditions.

Recently, We have reported a new type of chiral pyrrolidinephosphine ligands, BPPM(1)³⁾, PPM(2)³⁾, APPM(3)⁴⁾ and PPPM(4)⁴⁾, which were quite effective for the asymmetric synthesis of optically active phenylalanines, alanine and lactates⁵⁾, where their dramatic solvent and base effects on the optical yield of the hydrogenation products were observed.

We wish to describe here a new catalytic asymmetric synthesis of salsolidine by asymmetric hydrogenation of N-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline(5)⁶⁾, a typical cyclic enamide compound, with chiral pyrrolidinephosphine-rhodium complexes, expecting to clarify the mechanism of the solvent and triethylamine effect observed in the asymmetric hydrogenation of α -amido-acrylic acids.



Scheme I.

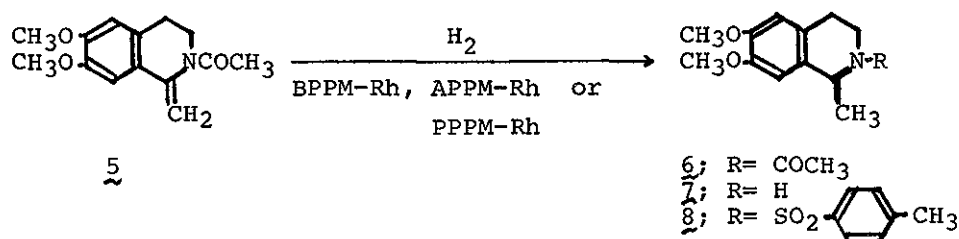


Table I. Asymmetric synthesis of N-acetylsalsolidine (6)^{a)}

Chiral reagent	Solvent	Isolated y. (%)	$[\alpha]_{\text{D}}^{20}$ (CHCl ₃) (°)	Optical y. (conf.) ^{d)} (%)
BPPM	EtOH	82	+40.8	34 (S)
BPPM	EtOH ^{b)}	94	+ 8.8	7 (S)
BPPM	Benzene	82	+13.7	11 (S)
BPPM	Benzene ^{c)}	80	+ 9.7	8 (S)
APPM	EtOH	84	-27.1	23 (R)
APPM	Benzene	78	+13.3	11 (S)
PPPM	EtOH	85	-54.1	45 (R)
PPPM	EtOH ^{c)}	92	-23.7	20 (R)
PPPM	Benzene	83	+23.4	20 (S)

a) All hydrogenations were run with 1 mmole of substrate, 0.02 mmole of [Rh(1,5-hexadiene)Cl]₂ and 0.044 mmole of bisphosphine in 10 ml of solvent at 20° under initial hydrogen pressure of 50 atm.

b) Triethylamine (1.0 mmole) was added.

c) Triethylamine (0.12 mmole) was added.

d) $[\alpha]_{\text{D}}^{+120}$ (CHCl₃) for pure (S)-6 was used. see the Text.

Although the asymmetric synthesis of salsolidine has been reported by Okawara and Kametani⁷⁾ via the sodium borohydride reduction of optically active α -alkylbenzylamine derivatives followed by hydrogenolysis (14-44% optical yields) and also by Kagan et al⁸⁾ via the asymmetric hydrosilylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (5% optical yield), the effective catalytic asymmetric synthesis has remained without success.

Hydrogenations of 5 were carried out with a catalyst formed in situ from 1, 3 or 4 and $[\text{Rh}(1,5\text{-hexadiene})\text{Cl}]_2$ as shown in Scheme I. The hydrogenation products (6) were isolated in 78-94% yields on preparative tlc purification. The absolute configuration and optical purity of 6 were determined by converting 6 ($[\alpha]_D^{20} +40.8^\circ (\text{CHCl}_3)$) into (S)-salsolidine (7) and (S)-N-tosylsalsolidine (8)⁹⁾ ($[\alpha]_D^{20} +43.0^\circ (\text{CHCl}_3)$) on diisobutylaluminium hydride reduction¹⁰⁾ and subsequent tosylation. Therefore, the optical rotation of pure (S)-6 was calculated to be $[\alpha]_D^{20} +120^\circ (\text{CHCl}_3)$. The results under the varying conditions were collected in Table I.

Table I shows clearly that BPPM-rhodium complex gave only (S)-salsolidine (7-34% optical yields) in ethanol or benzene as a solvent even in the presence of triethylamine, whereas APPM- and PPPM-rhodium complexes afforded (R)-salsolidine (23 and 45% optical yields) in ethanol and the S product (11 and 20% optical yields) in benzene. These facts may suggest that the N-substituents of PPM play an important role in affecting the optical yield of this hydrogenation.

It should be also noted that modifications of the N-substituent and bisphosphine groups of PPM may be possible for the match of substrate structure towards complete stereospecificity.

Thus, (S)- and (R)-salsolidine were obtained in 34 and 45% optical yields respectively, although the plausible explanation for solvent and triethylamine effects needs further studies¹¹⁾.

REFERENCES AND NOTES

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