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HOMOGENEOUS CATALYTIC ASYMMETRIC HYDROGENATION OF (Z)-2-ACETAMIDO-3-METHYL-FUMARIC ACID ESTER, A TETRASUBSTITUTED OLEFIN[1)]

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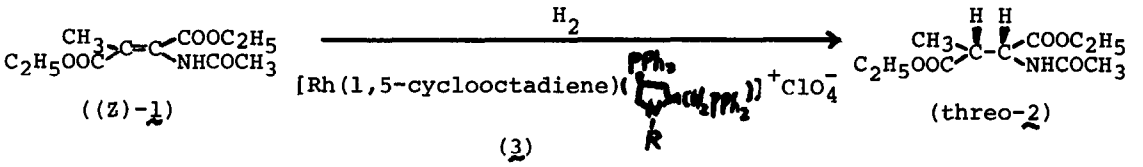
Catalytic asymmetric syntheses[2)] have recently been proven to be practically useful for the preparation of the chiral steroid hormones[3)], α-amino acids[4)], pantolactone[5)] and α-methylsuccinic acid[6)]. However, these syntheses are limited only to the new creation of one asymmetric carbon atom and the stereospecific chiral induction of adjacent two asymmetric carbon atoms remains without success.

We wish to describe here a simple and novel method for the synthesis of chiral threo-β-methylaspartic acid, a component of some peptide antibiotics[7)], by homogeneous catalytic asymmetric hydrogenation of (Z)-2-acetamido-3-methylfumaric acid ester (1), a tetrasubstituted olefin, using cationic pyrrolidinephosphine-rhodium complexes[6)].



3a: R= $(CH_3)_3CCO$- (PPPM-Rh^+) 3c: R= HCO- (FPPM-Rh^+)
3b: R= C_6H_5CO- (BZPPM-Rh^+) 3d: R= $(CH_3)_3COCO$- (BPPM-Rh^+)

In a typical experiment, the asymmetric hydrogenation of (Z)-1 (2 mmole) was run with [Rh(1,5-cyclooctadiene)(BPPM)]$^+ClO_4^-$ (BPPM-Rh^+) (4×10^{-2}mmole) in ethanol under an initial hydrogen pressure of 50 atom at 80°C for 45 h. The resulting reaction mixture was purified on preparative TLC (Silicagel, n-hexane-ether (1:2) as a developing solvent) to give 2, mp 75.0-76.5°C, $[\alpha]_D^{20}$ +14.6° (c 1.42, ethanol) in a 92.2% isolated yield. The absolute configuration and optical purity of 2 were determined by converting (+)-2 ($[\alpha]_D$ +14.6°(ethanol) into threo-(2R,3R)-β-methylaspartic acid[8,9)], $[\alpha]_D^{20}$-7.8° (c 1.001, 5N-HCl); $[\alpha]_D^{20}$+7.2° (c 0.528, H_2O), on 6N-HCl hydrolysis. Therefore, the specific rotation of pure threo-(2R,3R)-2 was calculated to be $[\alpha]_D$ +25.1°(ethanol).

Table I. Asymmetric hydrogenation of diethyl (Z)-2-acetamido-3-methylfumarate[a)]

Chiral reagent (R)		Solvent	Condition Temp.(h)	Conversion[b)] (%)	Threo[b)] (%)	Opt.y. (%)	(conf.)[c)]
$(CH_3)_3COCO-$	(BPPM-Rh)	EtOH	80°(45)	55	97	19.5	(2R,3R)
$(CH_3)_3COCO-$	(BPPM-Rh^+)	EtOH	80°(45)	100	>99	58.2	(2R,3R)
$(CH_3)_3COCO-$	(BPPM-Rh^+)	THF	70°(45)	100	>99	56.2	(2R,3R)
HCO-	(FPPM-Rh^+)	EtOH	80°(45)	100	>99	56.6	(2R,3R)
C_6H_5CO-	(BZPPM-Rh^+)	EtOH	80°(45)	100	>99	54.2	(2R,3R)
$(CH_3)_3CCO-$	(PPPM-Rh^+)	EtOH	80°(45)	100	>99	52.6	(2R,3R)

a) All hydrogenations were carried out with 2 mmole of substrate and 0.04 mmole of [Rh(1,5-cyclooctadiene)(bisphosphine)]$^+ClO_4^-$ (3) or 0.02 mmole of [Rh(1,5-cyclooctadiene)Cl]$_2$ and 0.048 mmole of bisphosphine in 4 ml of solvent under an initial hydrogen pressure of 50 atom.
b) Vpc analysis.
c) $[\alpha]_D$ +25.1°(EtOH) was used for pure threo-(2R,3R)-2. See the Text.

Table I shows clearly that the cationic pyrrolidinephosphine-rhodium complexes gave stereospecifically the threo-product in almost quantitative chemical yields, whereas the neutral complex afforded the threo-product with 97% diastereoselectivity in a 55% chemical yield. These facts indicate that the homogeneous asymmetric hydrogenations of (Z)-1 proceed with complete stereoselectivity of cis-addition to give only the threo-isomer, even at the temperature of 80°C , especially when the cationic complexes were employed as the catalysts.

Further investigations for the chiral induction of adjacent two asymmetric carbon atoms using chiral pyrrolidinephosphine-metal complexes are actively under way.

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