

Efficient Asymmetric Hydrogenations of (Z)-2-Acetamidoacrylic Acid Derivatives with the Cationic Rhodium Complex of (2S,4S)-MOD-BPPM¹⁾

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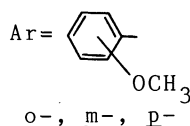
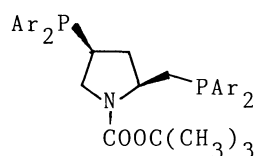
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The preparation of (2S,4S)-MOD-BPPM ((2S,4S)-N-(t-butoxycarbonyl)-4-[[bis(4'-methoxy-3',5'-dimethylphenyl)]phosphino]-2-[[[bis(4'-methoxy-3',5'-dimethylphenyl)]phosphino]methyl]pyrrolidine) and its application to highly effective asymmetric hydrogenations of (Z)-2-acetamidoacrylic acid derivatives are described.

Recently, we have prepared the methoxy-substituted BPPM ((2S,4S)-N-(t-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine)²⁾ analogues and clarified the effects of the methoxy groups on catalytic activities and enantioselectivities in the hydrogenation of (Z)-2-acetamidocinnamic acid catalyzed by the rhodium complexes of them.³⁾ When p-methoxy-BPPM (**4**) was used as a ligand, the hydrogenation proceeded smoothly with a very high substrate to catalyst ratio due to the electron donating factor of the p-methoxy group. The catalytic activity of m-methoxy-BPPM (**3**)-rhodium complex is lower than the other ones by the electron attracting factor of the m-methoxy group. o-Methoxy-BPPM (**2**) gave a much higher optical yield than the other ligands but accelerated the reaction rate less than p-methoxy-BPPM (**4**). This lesser activation of hydrogenation by o-methoxy-BPPM may be rationalized under the assumption that the steric factor of the o-methoxy group affects on the rate of the oxidative addition of molecular hydrogen to the rhodium.

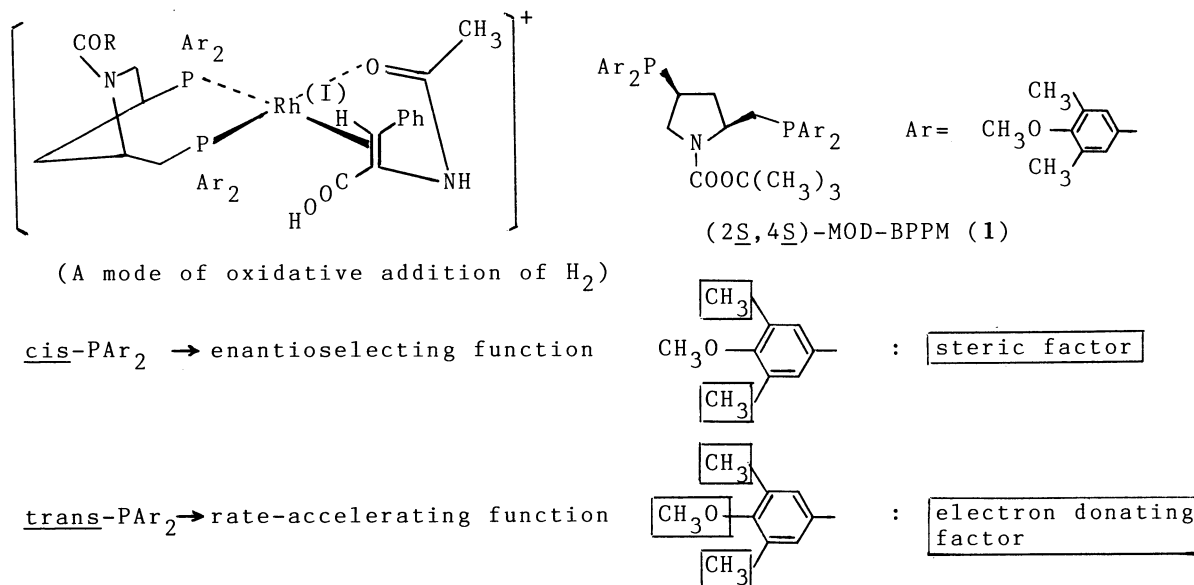
On the other hand, Kagan and co-workers have reported that m-methyl substituted DIOP ((2R,3R)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane) analogue gave a higher optical yield and accelerated the reaction rate slightly more than DIOP in the hydrogenation of (Z)-2-acetamidocinnamic acid.⁴⁾

From these asymmetric hydrogenation findings, here we wish to report the asymmetric hydrogenation of (Z)-2-acetamidoacrylic acid derivatives (**5**) with high catalytic activity and enantioselectivity leading to optically active N-acetyl- α -amino acid (**6**) catalyzed by cationic rhodium complex of (2S,4S)-MOD-BPPM ((2S,4S)-N-(t-butoxycarbonyl)-4-[[bis(4'-methoxy-3',5'-dimethylphenyl)]phosphino]-2-[[[bis-

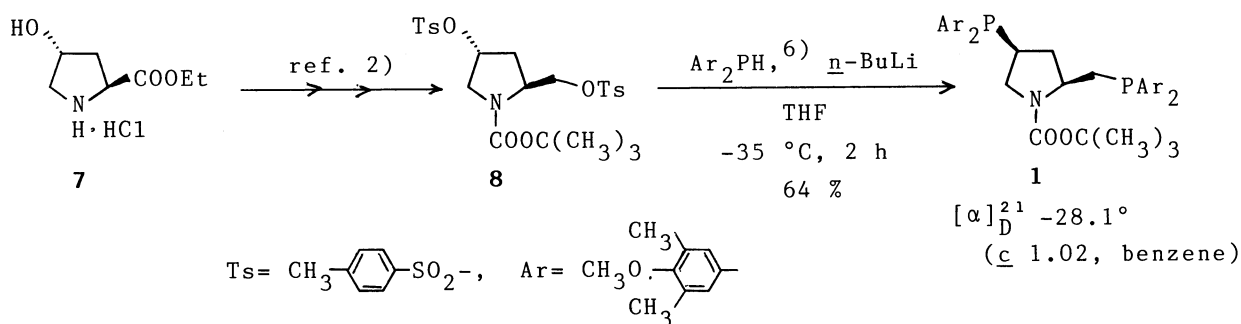
o-methoxy-BPPM (**2**)m-methoxy-BPPM (**3**)p-methoxy-BPPM (**4**)

(4'-methoxy-3',5'-dimethyl)]phosphino]methyl]pyrrolidene) (**1**) which has been designed on the respective control concept⁵⁾ to develop efficient chiral catalysts for asymmetric hydrogenations. As shown in Scheme 1, m-dimethyl groups on the diphenylphosphine of **1** oriented cis to the prochiral group of substrate was expected to enhance the enantioselectivity of asymmetric hydrogenation, and p-methoxy and m-dimethyl groups on the other diphenylphosphine oriented trans to the prochiral group were also expected to accelerate its reaction rate in comparison with those of BPPM.

The (2*S*,4*S*)-MOD-BPPM (**1**) was prepared easily from the ditosylate²⁾ (**8**) by the similar method reported previously³⁾ as indicated in Scheme 2.



Scheme 1.

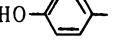
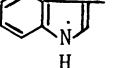
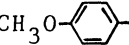
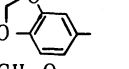
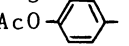


Scheme 2.

The results of asymmetric hydrogenations of **5a-1** are summarized in Table 1. Typical hydrogenations were carried out in the presence of a cationic rhodium catalyst (0.5-0.01 mol%) prepared in situ by mixing $[Rh(NBD)_2]ClO_4$ and **1** in a ratio of 1 : 1.2 and triethylamine ($[Et_3N]/[Rh]=50$) at 50 °C for 20 h in ethanol under the initial hydrogen pressure of 20 atm, unless otherwise noted.

Table 1 shows that high enantioselectivities are generally obtained. N-Acetyl-(R)-phenylalanine derivatives (**6f-g**, **6j-l**) were given with high optical yields. In particular, (2*S*,4*S*)-MOD-BPPM-rhodium complex was found to give (R)-**6f**

Table 1. Asymmetric Hydrogenations of (Z)-2-Acetamidoacrylic Acid Derivatives^{a)}

$ \begin{array}{ccc} \begin{array}{c} \text{R}^2 \\ \diagup \\ \text{R}^1 - \text{C} = \text{C} - \text{COOR}^3 \\ \diagdown \\ \text{NHCOCH}_3 \end{array} & \xrightarrow[\text{[Et}_3\text{N]}/[\text{Rh}]=50]{\begin{array}{c} \text{H}_2 \\ \text{[Rh(NBD)}_2\text{]ClO}_4, (2\text{S}, 4\text{S})\text{-MOD-BPPM} \\ 20 \text{ atm, } 50^\circ\text{C, } 20 \text{ h in ethanol} \end{array}} & \begin{array}{c} \text{R}^2 \\ \diagup \\ \text{R}^1 - \text{C}^* - \text{COOR}^3 \\ \diagdown \\ \text{NHCOCH}_3 \end{array} \\ \text{5a-i} & & \text{6a-i} \end{array} $								
Entry	Substrates			[Subst.]/[Rh]	Products ^{b)}			Confign.
	R ¹ -	R ² -	R ³ -		%ee ^{c)}			
1	5a	H-	H-	1000	6a	95.0		<u>R</u>
2	5b	H-	CH ₃ -	1000	6b	81.6		<u>R</u>
3	5c	(CH ₃) ₂ CH-	H-	1000	6c	89.8		<u>R</u>
4 ^{d)}	5d	CH ₃ SCH ₂ -	H-	500	6d	69.0		<u>R</u>
5 ^{e)}	5e	CH ₃ -	CH ₃ -	1000	6e	58.6		<u>R</u>
6	5f		H-	1000	6f	97.8		<u>R</u>
7	5f		H-	10000	6f	98.0		<u>R</u>
8 ^{f)}	5f		H-	2000	6f	98.6		<u>R</u>
9	5g		H-	1000	6g	85.1		<u>R</u>
10	5h		H-	1000	6h	79.6		<u>R</u>
11	5i		H-	1000	6i	89.2		<u>R</u>
12	5j		H-	1000	6j	88.6		<u>R</u>
13	5k		H-	1000	6k	91.7		<u>R</u>
14	5l		H-	1000	6l	91.3		<u>R</u>

a) All hydrogenations were carried out with [Substrate]=0.5 M in ethanol. b) The chemical yields were quantitative. The conversions were 100 %, which were determined by ¹H-NMR analysis. c) Calculated on the basis of the optical rotations of pure enantiomers: (R)-(+)-**6a** [α]_D²⁵ +66.5° (c 2.0, H₂O); (S)-(-)-**6b** [α]_D²⁵ -91.7° (c 2.0, H₂O); (S)-(-)-**6c** [α]_D²⁶ -32.2° (c 1.0, EtOH); (S)-(-)-**6d** [α]_D²⁰ -20.8° (c 4.0, MeOH); (S)-(+)-**6f** [α]_D²⁶ +46.0° (c 1.0, EtOH); (S)-(+)-**6g** [α]_D²⁵ +21.4° (c 1.9, MeOH); (S)-(+)-**6h** [α]_D²⁷ +51.5° (c 1.0, MeOH); (S)-(+)-**6i** [α]_D¹⁵ +25.0° (c 1.0, 95% EtOH); (S)-(+)-**6j** [α]_D²¹ +67.5° (c 5.0, EtOH); (S)-(+)-**6k** [α]_D¹⁸ +53.4° (c 1.8, EtOH); (S)-(+)-**6l** [α]_D²⁰ +40.7° (c 1.0, MeOH). d) Conditions: 20 atm, rt, 24 h. e) Reaction time: 45 h. The reduction product was converted to N-acetylvaline methyl ester with CH₂N₂ in ether and the optical yield was calculated using the optical rotation of pure methyl ester: N-acetyl-(S)-(-)-valine methyl ester [α]_D²⁵ -47.6° (c 7.8, H₂O). f) Conditions: 1 atm, rt, 45 h.

with very high enantioselectivity (98 %ee) as well as very high catalytic activity ([Substrate]/[Rh]=10000) in hydrogenation of **1f** (entry 7). It is noteworthy that asymmetric hydrogenation of sulfur containing or tetrasubstituted dehydroamino acid (**5d** or **5e**) also proceeded smoothly, although the catalytic activity and the enantioselectivity are relatively low (entries 4-5). Asymmetric hydrogenations of methionine and valine precursors catalyzed by (2*S*,4*S*)-BPPM-rhodium complex did not proceed smoothly and enantioselectivities were low.⁷⁾ In general, the hydrogenation catalyzed by MOD-BPPM-rhodium complex proceeded with higher enantioselectivities under milder conditions compared with that when BPPM-rhodium complex was used as a chiral catalyst.^{2,8)}

The MOD-BPPM-rhodium complex was found to be a very efficient catalyst for asymmetric hydrogenation of (*Z*)-2-acetamidoacrylic acid derivatives. These experimental findings offer practical synthetic method for optically active α -amino acids and their derivatives and the respective control concept is also useful for asymmetric hydrogenation of (*Z*)-2-acetamidoacrylic acids.

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