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Asymmetric Hydrogenation of α-Acetamidocinnamic Acid with Chiral Rhodium Complexes of DIOP and BPPM on Charcoal

MASAMI INOUE,*,[a] KENJI OHTA,[a] NAOYASU ISHIZUKA[b] and SABURO ENOMOTO[a]

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University,[a] 2630 Sugitani, Toyama 930–01, Japan and Central Research Laboratories, Nihon Iyakuhin Kogyo, Co., Ltd.,[b] 350–1 Harihara, Toyama 931, Japan

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Chiral rhodium(I) complexes of (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) and (2*S*,4*S*)-*N*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM) were fixed on charcoal which had been pretreated with metal acetates and triethylamine, and the hydrogenation of α-acetamidocinnamic acid was performed in an ethanol–H_2O (1 : 1) mixture. L-*N*-Acetyl-(*R*)-phenylalanine was obtained in optical yields of 70.5% with RhCl(COD)-DIOP-charcoal catalyst and 86.5% with RhCl(COD)-BPPM-charcoal catalyst. The optical yields were affected by hydrogen pressure, reaction temperature, the concentration of the substrate, and the composition of the solvent. The recovered catalyst retained its activity well and could be re-used repeatedly for enantioface-differentiating hydrogenation, provided that it was kept under a nitrogen atmosphere throughout.

Keywords——asymmetric hydrogenation; DIOP; BPPM; RhCl(COD)-DIOP-charcoal catalyst; RhCl(COD)-BPPM-charcoal catalyst; α-acetamidocinnamic acid; L-*N*-acetyl-(*R*)-phenylalanine

Among medicines and pesticides, one enantiomer often exhibits the biological activity, whereas the other frequently has undesirable side-effects. Recently, the development of catalysts for asymmetric synthesis has been investigated by many workers. As regards the asymmetric hydrogenation of olefins, Knowles *et al.*[1] have found that chiral Rh(I) complexes are effective for the hydrogenation of various cinnamic acid derivatives which are possible precursors of L-β-(3,4-dihydroxyphenyl)alanine (L-DOPA), a specific drug for Parkinsonism. Many kinds of chiral phosphine derivatives have been prepared for this purpose.[2] From the practical standpoint, a heterogeneous catalytic system is useful since the separation of reaction products is easily performed by filtration. In connection with this, it has been demonstrated that cross-linked organopolymers are good supports for RhCl(1,5-cyclooctadiene)-((−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane[3] [RhCl(COD)-DIOP] and RhCl(1,5-cyclooctadiene)-((2*S*,4*S*)-*N*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine)[4] [RhCl(COD)-BPPM] for asymmetric hydrogenation.[5,6] Also, mineral clays have been used for the support of

$RhClO_4$ (1,5-cyclooctadiene)-*N*,*N*′-bis(*R*(+) or *S*(−)-α-methylbenzyl)-*N*,*N*′-bis(diphenylphosphino)ethylenediamine[7] [Rh(COD)-PNNP(+ or −)$^+ClO_4^-$]. We selected the chiral Rh(I) complexes RhCl(COD)-DIOP and Rh(COD)-BPPM on active charcoal for the asymmetric hydrogenation of α-acetamidocinnamic acid to L-*N*-acetyl-(*R*)-phenylalanine and obtained an optical yield close to those obtained in homogeneous systems. These catalysts can be used repeatedly. This paper deals with the properties of chiral Rh(I) complexes on charcoal and presents reaction conditions suitable for the asymmetric hydrogenation of α-acetamidocinnamic acid with these catalysts.

Experimental

Reagents——GR-grade α-acetamidocinnamic acid (mp 190—192 °C, *z* form) (Tokyo Kasei Co., Ltd.) was used as a substrate. Bone charcoal as a carrier was purchased from Wako Pure Chemicals Co., Ltd. Other charcoals were used after being passed through a 65 mesh sieve before use. (−)-DIOP was obtained from Strem Chemicals Co., Inc., $[\alpha]_D^{22}$ −12.2° (*c*=1, benzene), lit.,[8] $[\alpha]_D^{22}$ −12.3° (*c*=4.57, benzene). BPPM was prepared according to the method of Achiwa *et al.*,[4] $[\alpha]_D^{20}$ −38.6° (*c*=1, benzene), lit.,[4] $[\alpha]_D^{20}$ −36° (*c*=0.6, benzene).

Preparation of the Catalysts——Bone charcoal (0.4 g) was added to a 0.3% aqueous solution of metal acetate (40 ml), and dispersed. The mixture was stirred for 12 h at room temperature and then centrifuged. The supernatant was separated and the charcoal was washed three times with 40 ml each of distilled water. The charcoal was then treated with 5% triethylamine aqueous solution (40 ml) for 2 h at room temperature and washed three times with distilled water.

An ethanol solution of the complex (10 ml) prepared *in situ* from weighed amounts of 5 mg (0.01 mmol) of $[RhCl(COD)]_2$ and 0.022 mmol of the chiral phosphine was added to the pretreated charcoal. The mixture was stirred for 2 h, then the catalyst was washed twice with water and immediately used for the hydrogenation.

A Typical Hydrogenation Procedure——The hydrogenation of α-acetamidocinnamic acid was carried out in a 100 ml stainless steel autoclave (SUS 32) equipped with a magnetic stirrer. The substrate, the catalyst and an ethanol–H_2O (1 : 1 v/v) mixture were added to a glass tube (2.6 cm i.d. × 10 cm in length). The tube was placed in the autoclave, and hydrogenation was carried out under an H_2 pressure of 5—80 kg/cm^2, at 30—100 °C, with stirring at 100—200 rpm for 4—12 h. After the reaction, the catalyst was separated from the products by centrifugation.

Analysis of the Products——The hydrogenated products were treated according to the method of Kagan *et al.*[6] The solvent was evaporated off, and one portion (0.3 g) of powdered product was dissolved in 0.5 N NaOH. The solution was filtered and acidified with 1 N HCl, and the product was extracted with ether. The solvent was evaporated off and the conversion was estimated by ultraviolet (UV) spectrometry at 270 nm in ethanol. The optical yield was determined with respect to the value of $[\alpha]_D^{20}$ −46.5° (*c*=1, ethanol) for pure L-*N*-acetyl-(*R*)-phenylalanine[9] by means of a digital polarimeter (Union Giken Co., Ltd., PM-101).

Results and Discussion

Effect of the Pretreatment of Charcoal in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid with RhCl(COD)-DIOP and RhCl(COD)-BPPM

The hydrogenation of α-acetamidocinnamic acid was carried out with hydrogen in an ethanol–H_2O (1 : 1) mixture in the presence of RhCl(COD)-DIOP and RhCl(COD)-BPPM on a variety of charcoals such as bone charcoal and active charcoals from coal and palm. In our system, the hydrogenation was completed in 12 h at 50 °C. The results of asymmetric hydrogenation by the supported complexes together with those obtained with the homogeneous complexes are shown in Table I. The asymmetric Rh-complexes of DIOP and BPPM on charcoal catalysts gave L-*N*-acetyl-(*R*)-phenylalanine in optical yields of 43.0 and 66.7%, respectively. In contrast, the homogeneous hydrogenations in the presence of RhCl(COD)-DIOP and RhCl(COD)-BPPM gave higher optical yields of 64.1 and 78.7%, respectively. It seems probable that the lower optical yield given by the heterogeneous catalysts is due to the presence of partially dissociated rhodium species on the charcoal. In fact, 2% $RhCl_3$ on charcoal showed enough activity to reduce α-acetamidocinnamic acid under the same reaction conditions. Based on these results, we examined the modification of charcoals in order to prevent the dissociation of the complexes. It had been reported that zinc acetate-modified

TABLE I. Effect of the Treatment of Charcoal in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid in the Presence of Rh-Complexes on Charcoal

Catalyst	Reaction temp. (°C)	Time (h)	H_2 (kg/cm^2)	Treatment of charcoal	Optical yield (%)
Rh-DIOP	50	12	10	—	64.1
Rh-DIOP-charcoal	50	12	20	—	43.0
	50	12	20	AcONa	49.9
	50	12	20	$(AcO)_3Cr$	55.5
	50	12	20	Triethylamine	55.9
	50	12	20	AcONa, triethylamine	61.9
	50	12	10	$(AcO)_3Cr$, triethylamine	70.5
Rh-BPPM	50	12	20	—	78.7
Rh-BPPM-charcoal	80	4	20	—	66.7
	80	4	20	AcONa	83.9
	80	4	20	$(AcO)_3Cr$	67.5
	80	4	20	Triethylamine	83.9
	80	4	20	AcONa, triethylamine	84.3
	80	4	20	$(AcO)_3Cr$, triethylamine	86.5[a]

$[RhCl(COD)]_2$ 0.01 mmol, DIOP and BPPM 0.022 mmol, solvent ethanol–H_2O (1 : 1) 15 ml, bone charcoal 0.4 g, substrate 3 g or *a*) 6 g. Acetate (50 mg) and triethylamine (2 ml) were used.

charcoal regulates the adsorption of acetylene in vinyl acetate synthesis.[10] In aqueous solution, bone charcoal was treated with various metal acetates, and RhCl(COD)-DIOP or RhCl(COD)-BPPM was mounted on the charcoal. Using 4.2% RhCl(COD)-DIOP on the modified charcoal, α-acetamidocinnamic acid was hydrogenated under an H_2 pressure of 20 kg/cm^2 at 50 °C. After 12 h, the hydrogenation was completed. Optical yields obtained varied widely depending on the kinds of acetates used; 70.5% for Cr^{3+}, 63.2% for Ni^{2+}, and La^{3+}, 61.9% for Na^+, 61.1% for Ba^{2+} and Zn^{2+}, 59.8% for K^+, 58.4% for Bi^{3+}, 58.1% for Li^+, 57.2% for Tl^{3+}, 55.5% for Ag^+, 54.2% for Ca^{2+}, 52.5% for Co^{2+}, 44.7% for Cu^{2+}, 42.6% for Sn^{2+}, 25.3% for Hg^{2+}, and 23.7% for Mn^{2+}. Organic amines, particularly triethylamine, showed a similar improving effect on the optical yield from 43 oy% for raw charcoal to 55.9 oy% for the modified charcoal under the same reaction conditions. The use of RhCl(COD)-DIOP on bone charcoal which had been treated with both chromium acetate and triethylamine gave the highest optical yield of 70.5%. In the case of RhCl(COD)-BPPM, the optical yield was increased from 66.7 to 86.5%.

Effect of the Reaction Conditions in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid

It is well known that both hydrogen pressure and reaction temperature affect asymmetric hydrogenation in a homogeneous system. These effects were estimated for the heterogenized systems. The effect of hydrogen pressure on optical yield is shown in Fig. 1. A lower hydrogen pressure tended to improve the optical yield; under 5 kg/cm^2, optical yields reached 66.2% in the presence of RhCl(COD)-DIOP and 82.6% in the presence of RhCl(COD)-BPPM. On the other hand, a higher hydrogen pressure (80 kg/cm^2) gave a poor optical yield. However, optical yields obtained under atmospheric pressure and ambient temperature were not as good as was expected (82% oy% with the Rh-BPPM complex). Lower reaction temperature afforded higher optical yields, as shown in Fig. 2. The rhodium complexes of DIOP and BPPM on charcoal both gave good optical yields of 59.8 and 83.0% at 50 °C, respectively. The Rh-BPPM-charcoal catalyst was less sensitive to the reaction temperature and an optical yield of 77.4% was obtained even at 80 °C. Usually, we used a reaction temperature of 50—80 °C since the substrate was only partly soluble in ethanol–H_2O (1 : 1) mixture at room

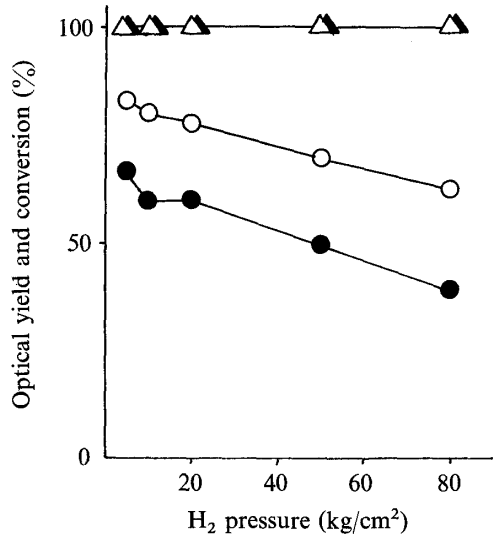

Fig. 1. Effect of H_2 Pressure in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid

$[RhCl(COD)]_2$ 0.01 mmol, DIOP and BPPM 0.022 mmol, solvent ethanol–H_2O (1 : 1) (15 ml), bone charcoal 0.4 g, substrate 3 g. —○—, BPPM; reaction temperature 80 °C, reaction time 4 h. —●—, DIOP; reaction temperature 50 °C, reaction time 12 h. —△— and —▲—, conversion. Bone charcoal was treated with AcONa (50 mg).

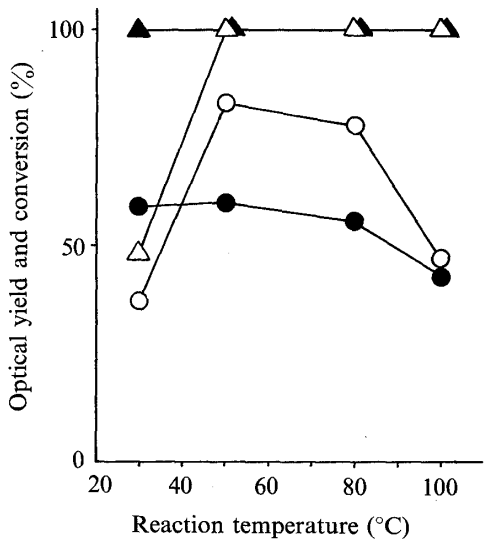

Fig. 2. Effect of Reaction Temperature in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid

$[RhCl(COD)]_2$ 0.01 mmol, DIOP and BPPM 0.022 mmol, solvent ethanol–H_2O (1 : 1) (15 ml), bone charcoal 0.4 g, substrate 3 g. —○—, BPPM; reaction time 4 h, H_2 pressure 20 kg/cm^2. —●—, DIOP; reaction time 12 h, H_2 pressure 20 kg/cm^2. —△— and —▲—, conversion. Bone charcoal was treated with AcONa (50 mg).

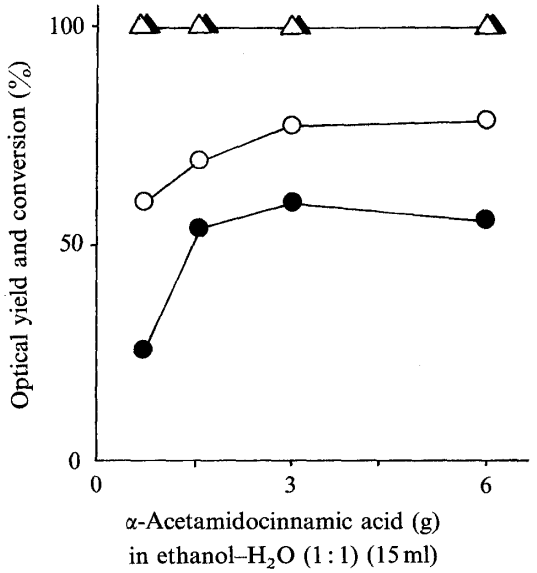

Fig. 3. Effect of Substrate Concentration in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid

$[Rh(COD)Cl]_2$ 0.01 mmol, DIOP and BPPM 0.022 mmol, bone charcoal 0.4 g. —○—, BPPM; reaction temperature 80 °C, reaction time 4 h, H_2 pressure 20 kg/cm^2. —●—, DIOP; reaction temperature 50 °C, reaction time 12 h, H_2 pressure 20 kg/cm^2. —△— and —▲—, conversion. Bone charcoal was treated with AcONa (50 mg).

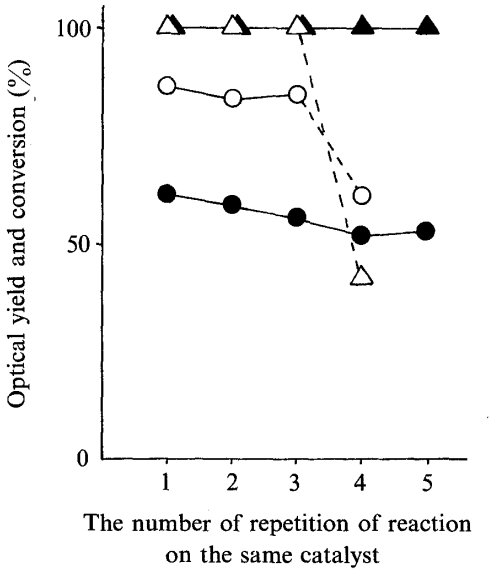

Fig. 4. Durability of Rh-Complex Catalysts in the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid

$[RhCl(COD)]_2$ 0.01 mmol, DIOP and BPPM 0.022 mmol, solvent ethanol–H_2O (1 : 1) (15 ml), bone charcoal 0.4 g. —○—, BPPM; reaction temperature 80 °C, reaction time 4 h, H_2 pressure 20 kg/cm^2, substrate 6 g, N_2 atmosphere. —●—, DIOP; reaction temperature 50 °C, reaction time 12 h, H_2 pressure 20 kg/cm^2, substrate 3 g, N_2 atmosphere. —△— and —▲—, conversion. Bone charcoal was treated with AcONa (50 mg).

temperature. In our heterogenized catalyst system, the optical yield also depends on the ratio of the substrate to the catalysts (Fig. 3); a substrate to Rh-complex-charcoal catalyst ratio of more than 3 g : 0.4 g in 15 ml of solvent gave good results. The ratio of Rh-complex to carrier affected the optical yield; a small amount of Rh-complex gave poor results presumably due to dissociation of the complex.

Durability of RhCl(COD)-DIOP on Charcoal Catalyst

The recovery of the catalyst activity was examined by repeating the hydrogenation. After hydrogenation, the RhCl(COD)-DIOP-charcoal catalyst was separated from the reaction solution by centrifugation (2000 rpm for 5 min), then α-acetamidocinnamic acid and the solvent were newly added, and further hydrogenation was carried out. Hydrogenation with Rh-DIOP-charcoal was performed in five batch reactions each at 50 °C for 12 h and with Rh-BPPM-charcoal at 80 °C for 4 h. Both complexes, particularly Rh-BPPM-charcoal, were sensitive to oxygen; when operations such as the separation of the catalyst and charging of the substrate were carried out in air, the conversion decreased considerably from 100% of initial value to 39.5% after four cycles. Furthermore, the enantioface-differentiating activity disappeared almost completely. However, when the treatment of the catalysts was performed in a nitrogen box (99.99% purity of N_2), α-acetamidocinnamic acid was reduced quantitatively and the optical yields were good, ranging from 86.5 to 83.4% (Fig. 4). Also, optical yields of 61.5 to 53.3% were obtained with Rh-DIOP-charcoal. Rapid decreases in conversion and optical yield took place when the recovered catalyst was treated in air (dashed lines in Fig. 4).

Analysis of Rhodium Complexes on Charcoal

The analysis of Rh-complexes fixed on the modified charcoal was carried out. The adsorption of the complexes on charcoal was influenced significantly by the ratio of ethanol to H_2O used in the solvent. Although ethanol is a widely used solvent for the hydrogenation with Rh-complexes, the brown complexes in this solvent were not adsorbed on charcoal. The Rh-complexes were barely soluble in water; the hydrogenation was retarded and the optical yield was poor. Therefore, a mixture of ethanol–H_2O (1 : 1) is a suitable solvent for the hydrogenation of acetamidocinnamic acid in the presence of the Rh-complex-charcoal catalysts.

The amount of complexes desorbed from bone charcoal into the ethanol–H_2O (1 : 1) mixture was examined. In the first place, the complex liberated from charcoal into the solvent was analyzed quantitatively by UV spectrometry. After RhCl(COD)-BPPM (0.01 mmol) had been adsorbed on charcoal (0.4 g) pretreated with AcONa and triethylamine as mentioned in the experimental section, the catalyst was washed three times with 20 ml of water and then dispersed in ethanol–H_2O (1 : 1) solvent (20 ml). The ratio of the desorbed amount of BPPM to the amount originally adsorbed decreased from 5% in the first wash to 1.5% in the third wash. Next, rhodium in solution was analyzed by the oxine complex formation method[11] in the presence of α-acetamidocinnamic acid. After the reaction, the catalyst was separated from the reaction solution. The solvent was evaporated off and the products were calcined in an electric furnace at 800 °C for 5 h. The residue was further reduced to rhodium metal in a stream of hydrogen at 500 °C for 1 h and dissolved in 4 N H_2SO_4. A yellow oxine complex was formed at pH 5—8 and extracted from 1 N H_2SO_4 with chloroform. The amount of rhodium was estimated from the absorbance at 424 nm. Initially, 5% of the rhodium was liberated from the Rh-BPPM-charcoal catalyst. However, the amount of rhodium in the liquid phase decreased to 2.1% after three repetitions of the hydrogenation; approximately 85% of rhodium initially added appeared to be well bound on the charcoal. These results indicate that the hydrogenation can be repeated many times on the supported complexes.

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