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Asymmetric Hydrogenation of 3,4-Methylenedioxy- α -acetamidocinnamic Acid Using Newly Developed Silica Gel-Supported Chiral Rhodium(I)-Phosphine Complexes

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The asymmetric hydrogenation of 3,4-methylenedioxy- α -acetamidocinnamic acid was carried out in the presence of a chiral Rh(I)-complex of (2*S*,4*S*)-*N*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM) adsorbed on hydrophobic silica gel in MeOH-H₂O solvents. Excellent conversions (100%) and a high optical yield (85%) were attained with [Rh(COD)BPPM]⁺ClO₄⁻ on methylated silica gel. The adsorption of the complex was improved by introducing a stearyl group instead of the butoxycarbonyl group of BPPM. When the recovered catalysts were reused three times, the optical yields decreased gradually from 85 to 69%.

Keywords—asymmetric hydrogenation; rhodium complex; 3,4-methylenedioxy- α -acetamidocinnamic acid; L-DOPA; solid catalyst; silica gel

L- β -(3,4-Dihydroxyphenyl)alanine(L-DOPA), a specific drug for Parkinson's disease, is produced by the optical resolution of the cinchonine salts from racemic DOPA.¹⁾ Since chiral Rh(I)-complexes were first found, the asymmetric hydrogenation of 3,4-methylenedioxy- α -acetamidocinnamic acid (MACA), a precursor of L-DOPA, has been studied extensively.²⁾ In the asymmetric hydrogenation, reuse of the complex catalyst is essential; these catalysts are composed of a rare metal, Rh, and chiral phosphines obtained by complex synthetic procedures. Therefore, in the preparation of the solid phosphine catalysts, two types of supports for the Rh(I)-complexes have been proposed, organopolymers such as methyl methacrylate polymers,³⁾ and inorganic powders such as graphite⁴⁾ or mineral clays.⁵⁾ Charcoal has also been used as a support, and the asymmetric hydrogenation of acetamidocinnamic acid was carried out repeatedly.⁶⁾

Recently, 3,4-diphenylphosphinopyrrolidine has been found to be bound chemically on silica gel by the method of Merrifield and the complex has been used as a solid catalyst.⁷⁾ We have conveniently prepared a solid catalyst of chiral Rh(I)-complexes adsorbed on hydrophobic silica gel and used it for the asymmetric hydrogenation of MACA.

Results and Discussion

Asymmetric Hydrogenation of MACA with Rh(–)-2,3-Dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) and Rh-(2*S*,4*S*)-*N*-Butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM)

The asymmetric hydrogenation of MACA was carried out in the presence of Rh(I)-complexes adsorbed on a highly methylated silica gel. As chiral phosphine compounds, we used DIOP, BPPM, and (2*S*,4*S*)-*N*-stearyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (SPPM), which was prepared from BPPM in two steps. First, the reaction

TABLE I. Asymmetric Hydrogenation of α -Acetamido-3,4-methylenedioxcinnamic Acid with Rh-BPPM on Methylated Silica Gel

Entry	Catalyst	Substrate (g)	Temp. (°C)	H ₂ (kg/cm ²)	Conv. (%)	O.y. ^{d)} (%)
1	Rh-BPPM ^{a)}	1.0	50	20	100	84
2	Rh-DIOP ^{b)}	1.0	50	20	100	61
3	Rh-BPPM-mSiO ₂	1.0	50	20	100	89
4	Rh-DIOP-mSiO ₂	0.5	50	20	100	51
5	Rh-BPPM-mSiO ₂	0.5	80	20	100	84
6	Rh-BPPM-mSiO ₂	0.5	100	20	100	79
7	Rh-BPPM-mSiO ₂	0.5	50	40	100	84
8	Rh-BPPM-mSiO ₂	0.5	50	20	100	88
9	Recovered cata. of entry 8	0.5	50	20	68	52
10	Recovered cata. of entry 9	0.5	50	20	49	30
11	Rh-BPPM ⁺ ClO ₄ ⁻ -mSiO ₂ ^{c)}	0.5	50	20	100	85
12	Recovered cata. of entry 11	0.5	50	20	100	77
13	Recovered cata. of entry 12	0.5	50	20	100	69

A molar ratio of the substrate to the Rh(I)-complexes of 1600, MeOH-H₂O (1 : 1, v/v), (30 ml/1 g-substrate), and methylated silica gel (mSiO₂ C; 3%) (0.2 g/1 g-substrate) were used. Ethanol was used as the solvent for the hydrogenation in entries 1 and 2. Reaction time, 12 h. a) RhCl(COD)BPPM. b) RhCl(COD)DIOP. c) [Rh(COD)BPPM]⁺ClO₄⁻ on mSiO₂. d) Optical yield (configuration, R).

Chart 1

conditions giving good conversion and optical yield were studied by comparing the activities of homogeneous and heterogeneous catalyst systems in the presence of Rh-DIOP or BPPM. The results are shown in Table I. It has been reported by Achiwa⁸⁾ that an optical yield of 83% was achieved under homogeneous reaction conditions with Rh-BPPM. Under our reaction conditions, the optical yield of the *R*-isomer reached 84% for Rh-BPPM and 61% for Rh-DIOP at 50 °C. To heterogenize the catalyst, several types of supports were examined, and methylated silica gel (mSiO₂) was found to be suitable; Rh(I)-complexes were adsorbed tightly on the support in a MeOH-H₂O (1 : 1, v/v) solvent as described later. With this pale-yellow solid catalyst, the hydrogenation was carried out at 50 °C for 12 h. In the MeOH-H₂O solvent, almost the same optical yield as that in the homogeneous Rh(I)-complex system in ethanol was obtained. When the reaction temperature was increased from 50 to 100 °C, the optical yield decreased from 89 to 79%. However, at lower temperature, the hydrogenation was retarded considerably and a part of the substrate remained insoluble.

On our solid catalyst, the hydrogen pressure hardly affected the optical yield up to 40 kg/cm². Therefore, the hydrogenation was carried out under a hydrogen pressure of 20 kg/cm² as the standard procedure. The recovered catalyst was very sensitive to air; on exposure to air for 5 h, it lost almost all activity. Thus, such procedures as separation of the catalyst and charging of substrates were carried out under an N₂ stream. In the hydrogenation, a cation-type Rh-catalyst [Rh(COD)BPPM]⁺ClO₄⁻ gave higher optical yields than a neutral-type complex

(RhCl(COD)BPPM). A sufficient activity was obtained by using one molecule of the complex per 1600 molecules of the substrate. After the reaction, the catalyst was recovered by centrifugation and used again. However, the color of the solid catalyst gradually changed from yellow to gray; the Rh(I) ion seemed to be reduced to Rh metal during the hydrogenation. Therefore, it was considered that milder reaction conditions might allow better retention of the activity.

Adsorption of Chiral Rh(I) Complexes on mSiO₂

The adsorption of Rh-BPPM on mSiO₂ was studied in various compositions of MeOH-H₂O solvent (Fig. 1). Finely powdered silica gel (Aerosil R 972) adsorbed Rh-BPPM (a cation type) in a water-rich solvent. However, methylated silica gel (Nipsil ss-10), which is hydrophobic in nature, adsorbed the Rh(I)-complex even in the MeOH-H₂O (1:1, v/v) solvent. Then, the effect of the composition of MeOH and H₂O on the adsorption of Rh-BPPM on methylated silica gel (C; 3%) was examined. With increasing ratio of water to MeOH, the amount of Rh(I)-complex adsorbed was increased and reached saturation at MeOH-H₂O (2:3, v/v). At this point, 1.25×10^{-3} mmol of [Rh(COD)BPPM]⁺ClO₄⁻ was adsorbed on 0.1 g of silica gel. The color of the silica gel became pale yellow after the adsorption of the Rh(I)-complexes. Such high adsorption was not observed with unmodified silica gel. When an excess amount (2.5×10^{-3} mmol) of [Rh(COD)BPPM]⁺ClO₄⁻ was added to mSiO₂ (0.1 g), a constant amount (1.25×10^{-3} mmol) was adsorbed at 30 °C. The Rh(I)-complex once adsorbed was not desorbed even by washing three times with MeOH-H₂O (1:1, v/v), as checked by ultraviolet (UV) spectroscopy.

The surface area occupied by one molecule of Rh(I)-complex was calculated from the specific surface area of mSiO₂ (87 m²/g) and the adsorbed amount of Rh-BPPM (1.25×10^{-3} mmol/0.1 g-mSiO₂). This value of 1.16×10^3 Å²/molecule was close to that estimated from a molecular model⁹⁾ (ca. 3×10^2 Å²). These results suggest that the Rh(I)-complexes were

Fig. 1. Effect of the Composition of MeOH-H₂O upon the Adsorption of [Rh(COD)-BPPM]⁺ClO₄⁻ on Silica Gel

[Rh(COD)BPPM]⁺ClO₄⁻ (1.25×10^{-3} mmol), silica gel (0.1 g), solvent (15 ml). The complex was adsorbed at 30 °C for 1 h.

○, mSiO₂ (Nipsil ss-10, C; 3%); ●, Aerosil (R 972).

Fig. 2. Effect of the Composition of MeOH-H₂O upon the Adsorption of RhCl(COD)-BPPM and [Rh(COD)SPPM]⁺ClO₄⁻ on Silica Gel

Rh(I)-complexes (1.25×10^{-3} mmol), silica gel (0.1 g), solvent (15 ml). The complexes were adsorbed at 30 °C for 1 h.

○, [Rh(COD)SPPM]⁺ClO₄⁻ on mSiO₂ (Nipsil ss-115, C; 4.5%); ●, RhCl(COD)BPPM on mSiO₂ (Nipsil ss-10, C; 3%).

TABLE II. Asymmetric Hydrogenation of α -Acetamido-3,4-methylenedioxycinnamic Acid with Rh-SPPM on a Highly Methylated Silica Gel

Entry		MeOH-H ₂ O (v/v)	Temp. (°C)	H ₂ (kg/cm ²)	Conv. (%)	O.y. ^{a)} (%)
1	Rh-BPPM	(1:1)	50	20	97	76
2	Rh-SPPM ⁺ ClO ₄ ⁻ -mSiO ₂	(2:1)	25	20	9	—
3	Rh-SPPM ⁺ ClO ₄ ⁻ -mSiO ₂	(2:1)	35	5	92	74

Substrate (1.5 g), solvent (22.5 ml), and mSiO₂ (C: 4.5%) (0.1 g) were used. The molar ratio of the substrate to Rh(I)-complex was 4800. Reaction time, 36 h. a) Optical yield (configuration R).

adsorbed on mSiO₂ as a monomolecular layer.

Activity of Rh-SPPM on a More Methylated Silica Gel

From the results in Table I, it was considered that mild reaction conditions, such as a lower reaction temperature, were important to obtain high optical yields and to increase the life of the catalyst. Thus, we modified (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (PPM) with stearoyl chloride to give SPPM, and Rh-SPPM was adsorbed on mSiO₂ in methanol-rich solvents. As shown in Fig. 2, Rh-SPPM was completely adsorbed on mSiO₂ (C: 4.5%) in the MeOH-H₂O (2:1, v/v) solvent. As a result, the solubility of the substrate was increased and the hydrogenation could be carried out at a lower reaction temperature (35 °C). On this catalyst, about 4500 molecules of the substrate were hydrogenated by one molecule of Rh-SPPM to give an optical yield of 74% (Table II).

In conclusion, the Rh(I)-complexes were heterogenized to make solid catalysts by adsorption of the complexes on methylated silica gel, and these catalysts were used for the asymmetric hydrogenation under mild reaction conditions. Further studies along these lines are in progress.

Experimental

Infrared (IR) spectra were taken on a Hitachi IR-260-30 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and the following abbreviation is used: m= multiplet. The optical yield was determined with respect to the value of $[\alpha]_D^{25} + 53.4^\circ$ (EtOH)¹¹ for (*R*)-*N*-acetyl-3-(3,4-methylenedioxyphenyl)alanine by means of a digital polarimeter (Union Giken Co., PM-101).

Reagents—MACA was synthesized according to the method of Yamada *et al.*¹¹ Rh(I)-cyclooctadienyl complex [RhCl(COD)]₂ was prepared from RhCl and cyclooctadiene in MeOH. BPPM was synthesized according to the method of Achiwa.⁸⁾ DIOP was obtained from Aldrich Chemical Co. Other reagents were of GR grade. Methylated silica gels, Nipsil ss-10 (C: 3%) and ss-115 (C: 4.5%), were kindly provided by Nippon Silica Co.

Preparation of SPPM—In a two-necked flask, BPPM (3.5 g) and trifluoroacetic acid (10 ml) were stirred at 5 °C for 5 h under an argon atmosphere. After the reaction, the solution was poured into ice-water (300 ml), neutralized with sodium carbonate, and extracted three times with ethyl acetate (80 ml). The ethyl acetate layer was washed with saturated aqueous sodium bicarbonate (50 ml) and dried on magnesium sulfate. By evaporation of the solvent under reduced pressure, an oily product, PPM (3.3 g), was obtained.

A benzene solution of stearoyl chloride (2.1 g, 7.0 mmol) was added to a benzene solution (30 ml) of PPM (3.3 g) and triethylamine (1.3 g, 12.5 mmol) at -5 °C under an argon atmosphere. The solution was stirred for 1.5 h at 5–10 °C. The reaction product was chromatographed on a column packed with Florisil (100–200 mesh, Wako Pure Chemical Co.). Elution with hexane-ethyl acetate (5:1, v/v) gave SPPM (3.5 g) (yield 75.8%) as an oil. *Anal.* Calcd for C₄₇H₆₃NOP₂: C, 78.41; H, 8.82; N, 1.95. Found: C, 78.62; H, 8.86; N, 1.9. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3050, 2920, 2850, 1640, 1430, 1410, 740, 700. NMR (CDCl₃): 0.7–2.5 (35H, m), 2.5–4.3 (8H, m), 7.0–7.8 (20H, m). $[\alpha]_D^{25} - 12.3^\circ$ ($c = 1.02$, benzene), -14.4° ($c = 0.92$, CHCl₃).

Pretreatment of mSiO₂ and Adsorption of Rh(I)-Complexes—Methylated silica gel (C: 3 or 4.5%) (0.1 g) was dispersed in MeOH-H₂O (1:1, v/v) (7.5 ml), then acetic acid (0.05 ml) was added, and the mixture was stirred for

30 min at room temperature. The silica gel was washed by centrifugation three times with the same solvent (7.5 ml each). A freshly prepared ethanol solution (1 ml) of Rh(I)-complex containing $[\text{Rh}(\text{COD})]^+\text{ClO}_4^-$ (0.39 mg, 1.25×10^{-3} mmol) and SPPM (0.89 mg, 1.25×10^{-3} mmol) was added to the pretreated support and the mixture was stirred for 1 h. Adsorption of the complex was carried out in the solvent for half an hour under magnetic stirring at room temperature. After centrifugation, the supernatant was decanted, leaving a pale yellow catalyst. The catalyst was washed three times with the same solvent (7.5 ml each).

Procedures for Asymmetric Hydrogenation—MACA and the catalyst were added to a glass tube (25×100 mm) with the solvent (15 ml). The tube was put into a stainless autoclave (100 ml), and hydrogenation was carried out under a hydrogen pressure of 20 kg/cm^2 . After the reaction, the catalyst was separated by centrifugation. The products were obtained by evaporation of the solvent. The conversion was determined from the UV absorption at 320 nm. The products were treated with 0.5 N NaOH followed by 1 N HCl, and extracted with ether according to the method of Kagan and Dang.¹⁰⁾ The separation of the catalyst and charging of the substrate were carried out in an N_2 (99.99%) stream, and the recovered catalyst was reused.

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