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Homogeneous Asymmetric Hydrogenation Using a Chiral Phosphinite Derivative of Carbohydrates as Ligand

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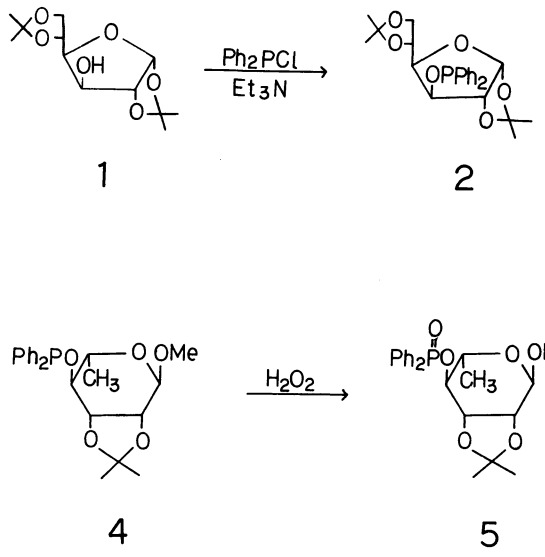
Diphenylphosphinite derivatives of sugars were conveniently synthesized by the reaction of diphenylphosphinous chloride–triethylamine with sugar derivatives. Homogeneous asymmetric hydrogenations of several prochiral olefins, i.e., (*Z*)-α-acetylaminocinnamic acid, (*Z*)-α-benzoylaminocinnamic acid, itaconic acid, tiglic acid, and their esters, were carried out using rhodium(I) catalysts with the tervalent chiral phosphorus derivative of sugars. The highest optical yields for all the prochiral substrates investigated were obtained when di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and methyl 2,3-*O*-isopropylidene-4-*O*-(diphenylphosphino)-α-L-rhamnopyranoside were used.

Homogeneous catalytic hydrogenation of olefins have been widely investigated since Wilkinson's work on chlorotris(triphenylphosphine)rhodium(I) was published.[1,2] Monosaccharides have several chiral carbon atoms in their skeletons, however, their application to homogeneous asymmetric hydrogenation of prochiral materials are found only in a few papers.[3–7] Bis-phosphinite of cellulose was used as a chiral ligand for a rhodium catalyst because of the more rigid conformation of the oxacylohexane ring than the cyclohexane ring of cyclohexane-1,2-diol.[8]

In our preceding paper we reported the asymmetric hydrogenation of a prochiral unsaturated acid such as (*Z*)-α-acetylaminocinnamic acid to afford the corresponding saturated acid in an optical yield of up to 67%, where 1,2:3,4-di-*O*-isopropylidene-6-*O*-(diphenylphosphino)-α-D-galactopyranose was revealed to be a good ligand.[9] The result suggested that the *O*-diphenylphosphino derivative of the carbohydrate afforded a higher optical yield than did the *C*-diphenylphosphino. In general, it is known that the nearer the chiral center is located to the ligand center the higher will be the optical yield on homogeneous asymmetric hydrogenation. Hence the synthesis of a dinuclear phosphorus ligand is more difficult than that of a mononuclear phosphorus ligand.[10,11] On the basis of the above standpoint much attention has been focussed on phosphinite derivatives of carbohydrate. The present paper deals with the facile synthesis of carbohydrates having a carbon–oxygen–phosphorus linkage on the hemiacetal ring and their successful application for asymmetric hydrogenation of olefins as an efficient ligand for the rhodium(I) catalyst.

Results and Discussion

Synthesis of Chiral Phosphinite Ligand from Carbohydrates. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(diphenylphosphino)-α-D-glucofuranose (**2**) was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) by treatment with diphenylphosphinous chloride in the presence of triethylamine in 73% yield. Methyl 2,3-*O*-isopropylidene-4-*O*-(diphenylphosphino)-α-L-rhamnopyranoside (**4**) was synthesized by a reported method,[9] and was oxidized with hydrogen peroxide giving oxide **5** in quantitative yield (Scheme 1) for the purpose of confirmation of compound **4**.



Asymmetric Hydrogenation of Prochiral Olefins. Asymmetric hydrogenation of prochiral olefins such as (*Z*)-α-acetylaminocinnamic acid, methyl (*Z*)-α-acetylaminocinnamate, (*Z*)-α-benzoylaminocinnamic acid, itaconic acid, dimethyl itaconate, and tiglic acid were carried out. The hydrogenation using glucose derivative **2** as the chiral ligand for di-μ-chloro-bis(cyclooctadiene)dirhodium(I) complex proceeded in 100% chemical yield for such a substrate as (*Z*)-α-acetylaminocinnamic acid to afford *N*-acetylphenylalanine. However, the optical yield was 10% with the *R* configuration, which did not improve over the previous work.[9] The results are shown in Table 1. The complex was not effective enough for the asymmetric hydrogenation.

The asymmetric hydrogenation of prochiral olefins

in the presence of di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and rhamnose **4** gave the good results summarized in Table 2. Pure dimethyl (*S*)-methylsuccinate was prepared from dimethyl itaconate. Therefore, **4** should be a better ligand for the asymmetric hydrogenation than **2**. The asymmetric hydrogenation of (*Z*)-α-benzoylaminocinnamic and itaconic acids by chloro-bis(cyclooctene)rhodium(I) in the presence of chiral ligand **4** afforded the hydrogenation product in lower optical yields than

Table 1. Asymmetric Hydrogenation of Prochiral Olefins with $[(C_8H_{12})RhCl_2Rh(C_8H_{12})]$–Ligand **2**[a]

Substrate	Product	Chemical yield/%	$[\alpha]_D^{14}$/° (Solvent)	Optical yield/%	Configuration
(*Z*)-α-Acetylaminocinnamic acid	*N*-Acetylphenylalanine	100	−4.50 (*c* 1.0, EtOH)	10	(*R*)
Methyl (*Z*)-α-Acetylaminocinnamate	*N*-Acetylphenylalanine methyl ester	100	−1.60 (*c* 1.0, MeOH)	7	(*R*)
(*Z*)-α-Benzoylaminocinnamic acid	*N*-Benzoylphenylalanine	100	−4.29 (*c* 1.0, MeOH)	11	(*S*)
Itaconic acid	Methylsuccinic acid	100	−3.60 (*c* 1.0, EtOH)	21	(*S*)
Tiglic acid	2-Methylbutyric acid	100	−2.70 (*c* 1.0, EtOH)	14	(*R*)

a) The ratios of substrate to Rh(I) complex and of ligand **2** to Rh(I) complex were 25:1 and 4:1, respectively. All hydrogenations were carried out in 10 ml of benzene–ethanol (1:1, v/v) in the presence of 0.2 ml of triethylamine at room temperature under atmospheric pressure of hydrogen for 24 h.

Table 2. Asymmetric Hydrogenation of Prochiral Olefins with $[(C_8H_{12})RhCl_2Rh(C_8H_{12})]$–Ligand **4**[a]

Substrate	Product	Chemical yield/%	$[\alpha]_D^{14}$/° (Solvent)	Optical yield/%	Configuration
(*Z*)-α-Acetylaminocinnamic acid	*N*-Acetylphenylalanine	100	−22.1 (*c* 1.0, EtOH)	48	(*R*)
Methyl (*Z*)-α-Acetylaminocinnamate	*N*-Acetylphenylalanine methyl ester	96	− 8.70 (*c* 1.0, MeOH)	41	(*R*)
(*Z*)-α-Benzoylaminocinnamic acid	*N*-Benzoylphenylalanine	100	+31.1 (*c* 1.0, MeOH)	78	(*R*)
Itaconic acid	Methylsuccinic acid	100	−11.6 (*c* 4.3, EtOH)	68	(*S*)
Dimethyl itaconate	Dimethyl methylsuccinate	100	−17.0 (*c* 1.0, EtOH)[b]	100	(*S*)
Tiglic acid	2-Methylbutyric acid	100	−12.5 (*c* 1.0, EtOH)	65	(*R*)

a) The ratios of substrate to Rh(I) complex and of ligand **4** to Rh(I) complex were 25:1 and 4:1, respectively. All hydrogenations were carried out in 10 ml of benzene–ethanol (1:1, v/v) in the presence of 0.2 ml of triethylamine at room temperature under atmospheric pressure of hydrogen for 24 h. b) The value is for methylsuccinic acid, the hydrolysis product of dimethyl methylsuccinate.

Table 3. Asymmetric Hydrogenation of Prochiral Olefins with $[RhCl(C_8H_{14})_2]$–Ligand **4**[a]

Substrate	Product	Chemical yield/%	$[\alpha]_D^{14}$/° (Solvent)	Optical yield/%	Configuration
(*Z*)-α-Benzoylaminocinnamic acid	*N*-Benzoylphenylalanine	100	+3.40 (*c* 1.0, MeOH)	8	(*R*)
Itaconic acid	Methylsuccinic acid	100	−0.65 (*c* 4.3, EtOH)	4	(*S*)

a) The ratios of substrate to Rh(I) complex and of ligand **4** to Rh(I) complex were 25:1 and 2:1, respectively. All hydrogenations were carried out in 10 ml of benzene–ethanol (1:1, v/v) in the presence of 0.2 ml of triethylamine at room temperature under atmospheric pressure of hydrogen for 24 h.

that by di-μ-chloro-bis(cyclooctadiene)dirhodium(I) as shown in Table 3.

These results indicate that the efficiency of chiral phosphinite **4** is good enough for the asymmetric hydrogenation of prochiral olefins compared with the reported results using the ligand of carbohydrate derivatives.[9,12] This procedure seems to be a simple and efficient way for the asymmetric hydrogenation of prochiral olefins, especially for dimethyl itaconate, owing to the convenience in the ligand synthesis and to the improvement affording comparatively high optical yields.

Experimental

Measurements. ^{1}H-NMR spectra were measured on a Hitachi R-24 (60 MHz) spectrometer with tetramethylsilane as an internal standard, and IR spectra on a Japan Spectroscopic Co. Ltd. A-3 infrared spectrophotometer. Optical rotations were measured on Japan Spectroscopic Co. Ltd. DIP-4 digital polarimeter. Melting (measured by Yanagimoto micro melting apparatus) and boiling points are uncorrected.

Materials. The following materials were synthesized according to reported methods: (*Z*)-α-acetylaminocinnamic acid,[13] (*Z*)-α-benzoylaminocinnamic acid,[14] methyl (*Z*)-α-acetylaminocinnamate,[15] dimethyl itaconate,[15] 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**),[16] methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3**),[17] diphenylphosphinous chloride (bp 110 °C/0.5 mmHg[18]),[19] chloro-bis(cyclooctene)rhodium(I),[20] di-μ-chloro-bis(cyclooctadiene)dirhodium(I),[21] and methyl 2,3-*O*-isopropylidene-4-*O*-(diphenylphosphino)-α-L-rhamnopyranoside (**4**).[9]

Preparation of 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(diphenylphosphino)-α-D-glucofuranose (2). Reaction of diphenylphosphinous chloride (3.0 g) with glucose **1** (3.5 g) in triethylamine for 24 h at room temperature under nitrogen atmosphere followed by filtration and evaporation in vacuo gave compound **2** (4.4 g) in 73% yield. The purity was checked by TLC on silica gel (eluent; ethyl acetate:petroleum ether=1:1 v/v, R_f=0.77); $[\alpha]_D^{14}$=−12.9° (*c* 0.65, MeOH). ^{1}H-NMR ($CDCl_3$) δ=1.25, 1.30, 1.45, 1.50 (4s, 12H, 2CMe_2), 3.8—4.2 (m, 6H, $C_{2-6,6'}$-H), 6.00 (d, 1H, *J*=4.5 Hz, C_1-H), 7.1—7.9 (m, 10H, 2Ph); IR ν_{max}^{neat} (cm^{-1}) 1440 (P-Ph), 1040 (P-O-C); MS, *m/z*, 444 (M^+, $C_{24}H_{29}O_6P$).

Oxidation of Compound 4. Oxidation of compound **4** (0.11 g) with 30% hydrogen peroxide (0.034 ml) in chloroform (2 ml)–methanol (1 ml) overnight at room temperature followed by work-up with sodium thiosulfate afforded methyl 2,3-*O*-isopropylidene-4-*O*-(diphenylphosphinyl)-α-L-rhamnopyranoside (**5**, 0.12 g) in quantitative yield. The purity was confirmed by HPLC (eluent; chloroform:methanol=20:1, retention time 6.5 min). ^{1}H-NMR ($CDCl_3$) δ=1.24 (d, 3H, *J*=5.4 Hz, C_5-Me), 1.41, 1.51 (2s, 6H, CMe_2), 3.33 (s, 3H, OMe), 3.8—4.4 (m, 4H, C_{2-5}-H), 4.79 (s, 1H, C_1-H), 7.0—8.0 (m, 10H, 2Ph); IR ν_{max}^{neat} (cm^{-1}) 1442 (P-Ph), 1225 (P=O), 1030 (P-O-C).

Found: *m/z* 419.1661. Calcd for $C_{22}H_{28}O_6P$: M+1, 419.1622.

Asymmetric Hydrogenation of (*Z*)-α-Acetylaminocinnamic Acid with Di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and Ligand 4. Asymmetric hydrogenation of (*Z*)-α-acetylaminocinnamic acid (500 mg) in anhydrous benzene (5 ml)–absolute ethanol (5 ml) was carried out using di-μ-chloro-bis(cyclooctadiene)dirhodium(I) (49 mg) and ligand **4** (160 mg) as catalyst in the presence of triethylamine (0.2 ml) under atmospheric pressure of hydrogen at room temperature for 24 h. Removal of the catalyst by passage through a column packed with ion-exchange resin Amberlite IRC-50 (H^+), followed by decolorization with activated charcoal and removal of the solvent in vacuo, gave *N*-acetylphenylalanine (100% conversion). The identification of the product was performed by ^{1}H-NMR, whose spectrum was as follows: ^{1}H-NMR ($CDCl_3$) δ=2.06 (s, 3H, COMe), 3.15 (d, 2H, *J*=6.0 Hz, $PhC\underline{H}_2$), 4.75 (t, 1H, *J*=6.0 Hz, CH), 7.1—7.4 (m, 5H, Ph); MS, *m/z*, 207 (M^+). The product had $[\alpha]_D^{14}$=−22.1° (*c*, 1.0, EtOH), which showed 48% optical yield of the *R* configuration.[22]

Removal of the catalyst from the hydrogenation mixture with ion-exchange resin Dowex 50 W (H^+) gave *N*-acetylphenylalanine methyl ester (100% conversion), which was esterified with eluent methanol.

Asymmetric Hydrogenation of Methyl (*Z*)-α-Acetylaminocinnamate with Di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and Ligand 4. Asymmetric hydrogenation of methyl (*Z*)-α-acetylaminocinnamate (500 mg) was carried out by the same method as mentioned for (*Z*)-α-acetylaminocinnamic acid using ion exchange resine Dowex 50 W (H^+) gave *N*-acetylphenylalanine methyl ester (100% conversion); ^{1}H-NMR ($CDCl_3$) δ=2.07 (s, 3H, COMe), 3.15 (d, 2H, *J*=6.0 Hz, $PhC\underline{H}_2$), 3.75 (s, 3H, OMe), 4.6—4.9 (m, 1H, CH), 6.05 (bd, 1H, *J*=7.5 Hz, NH), 6.9—7.4 (m, 5H, Ph); MS, *m/z*, 221 (M^+, $C_{12}H_{15}NO_3$). The product showed $[\alpha]_D^{14}$=−8.70° (*c* 1.0, MeOH), which indicated 41% optical yield of the *R* configuration.[23]

Asymmetric Hydrogenation of Dimethyl Itaconate with Di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and Ligand 4. Asymmetric hydrogenation of dimethyl itaconate (250 mg) in anhydrous benzene (5 ml)–absolute ethanol (5 ml) was carried out using di-μ-chloro-bis(cyclooctadiene)dirhodium(I) (32 mg) and ligand **4** (103 mg) as the catalyst in the presence of triethylamine (0.2 ml) under atmospheric pressure of hydrogen for 24 h at room temperature. Removal of the catalyst by passing a column packed with ion exchange resin Dowex 50 W (H^+), followed by decolorization with activated charcoal and removal of the solvent in vacuo, gave dimethyl methylsuccinate quantitatively, ^{1}H-NMR ($CDCl_3$) δ=1.15 (d, 3H, *J*=7.0 Hz, $C\underline{H}_3CH$), 2.1—3.3 (m, 3H, $CHCH_2$), 3.67 (s, 3H, $CHCO_2\underline{Me}$) 3.72 (s, 3H, CO_2Me). Alkaline hydrolysis of the ester at room temperature gave methylsuccinic acid, $[\alpha]_D^{14}$=−17.0° (*c* 1.0, EtOH), indicating 100% optical yield of the *S* configuration.[3,24] Treatment of methylsuccinic acid with diazomethane[25] in ether gave the dimethyl ester, $[\alpha]_D^{14}$=−6.1° (*c* 1.0, EtOH).[24]

Asymmetric hydrogenation of prochiral olefins with di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and ligand **4** gave the corresponding product as shown in Table 2. The optical yields of the products were calculated based on the reported values of optical rotation for *N*-acetyl-(*S*)-phenylalanine, $[\alpha]_D^{26}$ +46.0° (*c* 1.0, EtOH);[22] *N*-acetyl-(*S*)-phenylalanine methyl ester, $[\alpha]_D^{25}$ +21.4° (*c* 2.0, MeOH);[23] *N*-benzoyl-(*S*)-phenylalanine, $[\alpha]_D^{27}$=−40.3° (*c* 1.0, MeOH);[26] (*R*)-methylsuccinic acid, $[\alpha]_D^{18}$ +17.01° (*c* 4.41, EtOH);[3,24]

dimethyl (*R*)-methylsuccinate, $[\alpha]_D^{25}$ +6.11° (neat);[24] and (*S*)-2-methylbutyric acid, $[\alpha]_D$ +19.33°.[28]

Asymmetric Hydrogenation of (*Z*)-α-Acetylaminocinnamic Acid with Chloro bis(cyclooctene)rhodium(I) and Ligand 4. Asymmetric hydrogenation of (*Z*)-α-acetylaminocinnamic acid (500 mg) in anhydrous benzene–absolute ethanol (1:1 v/v, 10 ml) was carried out using chlorobis(cyclooctene)rhodium(I) (27 mg) and ligand **4** (60 mg) as the catalyst in the presence of triethylamine (0.2 ml) under atmospheric pressure of hydrogen at room temperature for 24 h. Removal of the catalyst and work-up as described for the asymmetric hydrogenation with di-μ-chloro-bis(cyclooctadiene)dirhodium(I) gave *N*-acetylphenylalanine (100% conversion); $[\alpha]_D^{14}$=+3.40° (*c* 1.0, MeOH), indicating an optical yield 8% of the *R* configuration.

Results for asymmetric hydrogenation with chlorobis(cyclooctene)rhodium(I) and ligand **4** were summarized in Table 3.

Asymmetric Hydrogenation of (*Z*)-α-Acetylaminocinnamic Acid with Di-μ-chloro-bis(cyclooctadiene)dirhodium(I) and Ligand 2. Asymmetric hydrogenation of (*Z*)-α-acetylaminocinnamic acid (500 mg) in anhydrous benzene–absolute ethanol (1:1 v/v, 10 ml) was carried out using di-μ-chloro-bis(cyclooctadiene)dirhodium(I) (49 mg) and ligand **2** (178 mg) as the catalyst in the presence of triethylamine (0.2 ml) under atmospheric pressure of hydrogen at room temperature for 24 h. Removal of the catalyst and work-up as mentioned for asymmetric hydrogenation using ligand **4** gave *N*-acetylphenylalanine (100% conversion); $[\alpha]_D^{14}$=−4.50° (*c* 1.0, EtOH), optical yield of 10% of the *R* configuration.

The results obtained for several prochiral olefins are shown in Table 1.

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