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Asymmetric hydrogenation of enamides in aqueous media with a new water-soluble chiral rhodium-α,α-trehalose-derived phosphine–phosphinite catalyst

Kouichi Ohe,* Kiyoharu Morioka, Koji Yonehara and Sakae Uemura*

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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Abstract—A new chiral rhodium catalyst with α,α-trehalose-derived phosphine–phosphinite (α,α-TREHAPPN) ligand, [(TREHAPPN)Rh(cod)]BF_4 **8** has been prepared. This catalyst is soluble in water and is an effective chiral catalyst for asymmetric hydrogenation of *N*-acyldehydroamino acids in aqueous media to give enantiomerically enriched α-amino acid derivatives with *R* configuration. The simple decantation allows retrieval of the catalyst from the reaction mixture, the recovered catalyst being re-used without marked loss of enantioselectivity.

1. Introduction

The enantioselective hydrogenation of *N*-acyldehydroamino acids and their esters constitutes a standard tool for the synthesis of optically active amino acids. In particular, rhodium catalysis has been well investigated, and a plethora of efficient chiral ligands has been developed for this purpose.[1] While the majority of the development in this area involves bidentate phosphine, phosphite, and phosphinite ligands, or mixed phosphine–phosphite[2] ligands, the corresponding phosphine–phosphinite ligands have only rarely been exploited.[3] A wide range of carbohydrate-derived phosphinites and phosphines have been prepared and successfully applied to homogeneous catalysis in several enantioselective syntheses.[4,5] On the basis of our studies pursuing water-soluble and recyclable chiral catalysts, we have developed carbohydrate scaffolding phosphorus ligands.[6] We found that diphosphinite ligand **1a** (α,α-TREHAP), derived from the naturally occurring disaccharide α,α-trehalose, is an effective ligand for rhodium-catalyzed enantioselective hydrogenation of enamides in aqueous media (Scheme 1).[6a,b] We also demonstrated that the analogous diphosphinite **1b** (1β,1′β-anomer, β,β-TREHAP) prepared from β,β-trehalose was a much more effective ligand than compound **1a** for the same enantioselective hydrogenation.[6a,b] The high water-solubility of rhodium catalysts bearing **1a** and **1b** as ligands allows the catalytic reaction to be completed under aqueous conditions and recycling of the catalyst by decantation after one cycle. On the other hand, diphosphine **2**, also prepared from α,α-trehalose, is less soluble in water despite having the same number of hydroxy moieties in this molecule like **1a** and **1b**.[7] Thus, its applicability was restricted to non-aqueous conditions. Our continuous efforts to prepare new water-soluble ligands have been based upon the use of α,α-trehalose as a readily available chiral source, and herein, we wish to report a new water-soluble ligand, 2-(diphenylphosphino)-2-deoxy-3-*O*-(diphenylphosphino)trehalose **3** derived from α,α-trehalose. This approach widens the utility of α,α-trehalose as a chiral source with a hydrophilic function, and allows the synthesis of (*R*)-α-amino acids from enamides by rhodium-catalyzed asymmetric hydrogenation in aqueous media. Additionally, catalyst recovery and re-use is possible.

2. Results and discussion

A preparative method for the novel water-soluble rhodium complex **8**, having an α,α-trehalose-derived phosphine–phosphinite ligand **3** is shown in Scheme 2. Initially, partial protection of the 4,6:2′,3′:4′,6′-positions of α,α-trehalose with isopropylidene followed by purification (acylation and hydrolysis) provided 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-α-D-glucopyranoside **4**[8] in 35% yield. In the sec-

* Corresponding authors.

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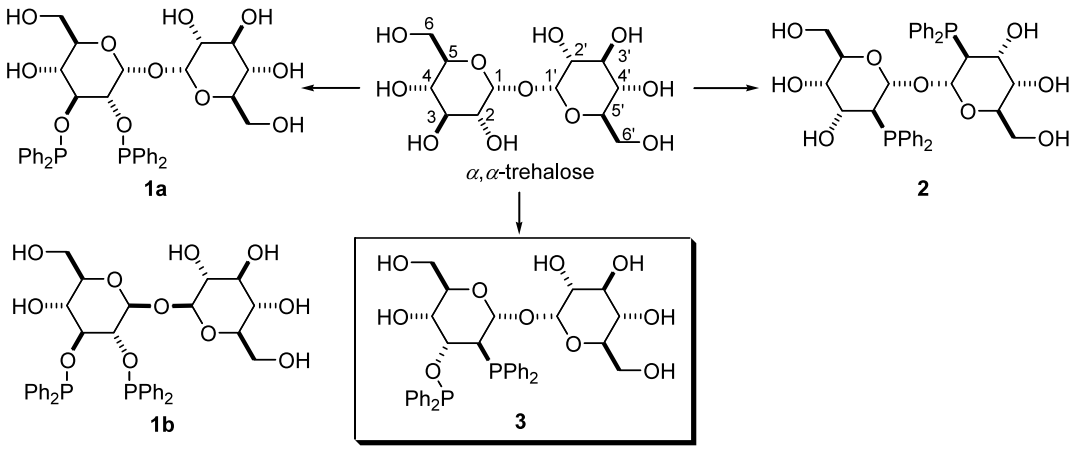
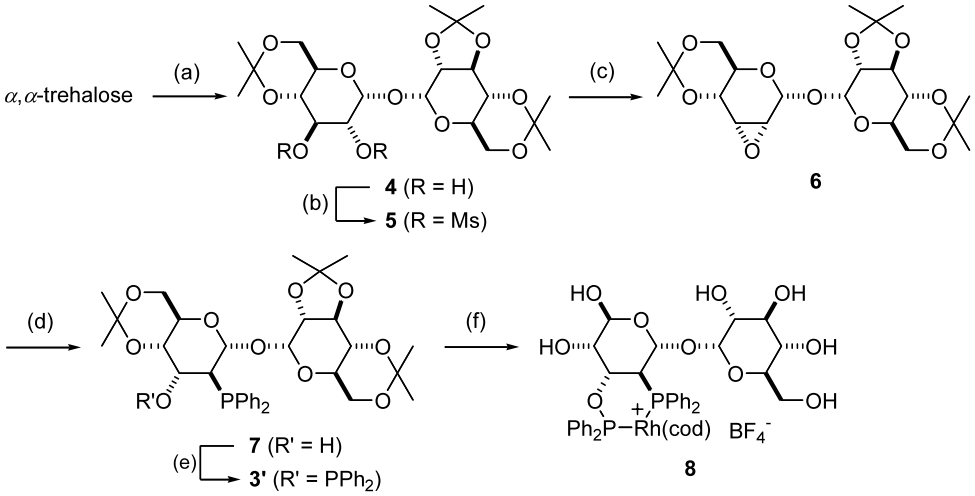


Scheme 1. Diphosphinite **1a**, **1b**, diphosphine **2**, and phosphine–phosphinite **3** derived from α,α-trehalose.

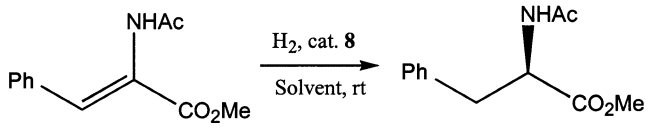


Scheme 2. *Reagents and conditions*: (a) (i) $Me_2C(OMe)_2$, cat. *p*-TsOH·H_2O, DMF, 90°C, 48 h; (ii) Ac_2O, C_5H_5N, rt, 8 h, 44% (two steps); (iii) K_2CO_3, MeOH, rt, 1 h, 80%. (b) MsCl, C_5H_5N, rt, 24 h, 92%. (c) Na/EtOH–2-PrOH, acetone, 10°C, 16 h, 75%. (d) $KPPh_2$, THF, rt, 2 h, 60%. (e) Ph_2PCl, cat. DMAP, Et_3N–THF, rt, 15 min, 47%. (f) (i) [Rh(acac)(cod)], THF, rt, 15 min; (ii) 40% aqueous HBF_4, rt, 1 h, 51% (two steps).

ond step of the synthesis, mesylation of **4** with MsCl ($MeSO_2Cl$) gave 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2,3-di-*O*-mesyl-α-D-glucopyranoside **5** in 92% yield. Treatment of **5** with Na/EtOH–^{i}PrOH[9] gave 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-2,3-anhydro-4,6-*O*-isopropylidene-α-D-allopyranoside **6**[10] in 75% yield and ring-opening of the epoxide moiety of **6** with $KPPh_2$ in tetrahydrofuran (THF) afforded 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2-(diphenylphosphino)-2-deoxy-α-D-altropyranoside **7**[11] in 60% yield. Reaction of **7** with Ph_2PCl then gave 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2-(diphenylphosphino)-2-deoxy-3-*O*-(diphenylphosphino)-α-D-altropyranoside **3′** in 47% yield. Finally, the reaction of **3′** with [Rh(acac)(cod)] followed by treatment with 40% aqueous HBF_4[12] afforded [Rh(α-D-glucopyranosyl-(1,1)-2-(diphenylphosphino)-2-deoxy-3-*O*-(diphenylphosphino)-α-D-altropyranoside)(cod)]BF_4 **8** bearing six free hydroxy groups in 51% yield. In the ^{31}P NMR spectrum of **8** resonance peaks of the two phosphorus nuclei as a doublet of doublet [δ 19.2 (dd, $J_{P-P}=49$, $J_{P-Rh}=147$ Hz) and 120.5 (dd, $J_{P-P}=49$, $J_{P-Rh}=165$ Hz) ppm] show that the phosphine–phosphinite **3** coordinates to rhodium in a bidentate fashion. Gratifyingly, complex **8** has good solubility in water (ca. 1 g/100 mL at 20°C) and polar organic solvents such as methanol, dichloromethane, 1,2-dichloroethane, and THF, while it is less soluble in non-polar organic solvents such as hexane or toluene.

Asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate **9a** as a test substrate was carried out using the water-soluble rhodium complex **8**. The effects of different reaction parameters, such as solvent and hydrogen pressure, on the efficiency of the catalyst were investigated. The results are summarized in Table 1. Enantioselective hydrogenation proceeded under atmo-

Table 1. Enantioselective hydrogenation of enamides **9a** using a catalyst **8**[a]



9a (*R*)

Entry	Solvent	**8** (mol%)	H_2 (atm)	Time (h)	Conv. (%)	ee (%)[b]
1	THF	1	1	4	77	63
2	CH_2Cl_2	1	1	1	100	37
3	$ClCH_2CH_2Cl$	1	1	0.5	100	69
4	$ClCH_2CH_2Cl$	1	50	2	88	33
5	H_2O	2.5	10	24	0	–
6	H_2O	2.5	30	24	100	13
7	H_2O	2.5	50	24	100	72
8	H_2O	2.5	70	24	100	62
9	MeOH	1	50	9	100	50
10	H_2O–AcOEt (1:1)	2	50	12 (24)[c]	100 (100)[d]	73 (70)[d]

[a] Reaction conditions: **9a** (0.1 mmol), solvent (2 mL) at room temperature.
[b] Enantiomeric excess of methyl *N*-acetylphenylalanate with (*R*)-configuration was determined by HPLC.
[c] Reaction time in the second cycle using recovered aqueous phase containing the catalyst.
[d] The value obtained from the second cycle.

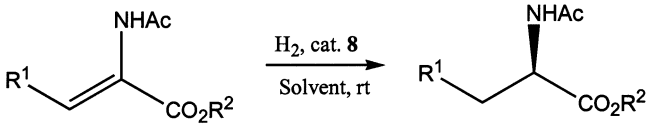
spheric pressure of hydrogen in THF, dichloromethane, and 1,2-dichloroethane to give (*R*)-methyl *N*-acetylphenylalanate with moderate enantioselectivities (37–69% ee, entries 1–3). Both the enantioselectivity and activity of the hydrogenation in 1,2-dichloroethane diminished when the hydrogen pressure was raised from 1 to 50 atm (entry 4). The hydrogenation of **9a** was sluggish in H_2O, no hydrogenated product being obtained at hydrogen pressures below 10 atm (entry 5). Interestingly, both the enantioselectivity and activity were notably enhanced when the hydrogen pressure was raised from 10 to 30 and 50 atm, respectively [13% ee (30 atm) and 72% ee (50 atm)] (entries 6 and 7). This contrasts with the usual decrease in enantioselectivity observed with bidentate ligands when the hydrogen pressure is raised.[13,14] Much higher pressure of H_2 (70 atm), on the other hand, decreased the enantioselectivity (62% ee, entry 8). Hydrogenation in MeOH instead of H_2O proceeded more smoothly and was complete within 9 h, but the enantioselectivity was lower (50% ee) than that in H_2O (entry 9). This result is in sharp contrast with the fact that the rhodium complexes with ligands **1a**,**b** afforded the best enantioselectivity when MeOH was used as a solvent or a cosolvent.[6a] In a biphasic system (1:1 H_2O–AcOEt), the reaction also took place to give the product with 73% ee (entry 10). In these aqueous systems, after the reaction was complete, the organic phase including the product was easily separated by decantation. The recovered aqueous phase containing the catalyst could be re-used in the second cycle hydrogenation to give almost the same enantiomeric excess (70% ee), although the prolonged reaction time (24 h) was required. In the third cycle, both enantioselectivity and activity for the hydrogenation were diminished, probably due to the catalyst decomposition (63% conv., 50% ee after 72 h).[15]

Next, the asymmetric hydrogenation of several *N*-acyldehydroamino acids and their esters **9b**–**g** was carried out in H_2O or a mixed solvent of H_2O and EtOAc under H_2 (50 atm). The results are shown in Table 2. Hydrogenation of enamides (entries 1–4) in a biphasic system (1:1 H_2O–AcOEt) under identical conditions to those used for methyl (*Z*)-α-acetamidocinnamate gave the corresponding α-amino acid derivatives in good yield with fair to good enantioselectivities (50–67% ee). The addition of MeOH was required for the hydrogenation of dehydro *N*-acetyl-3-(1-naphthyl)alanine methyl ester **9e** because of the low solubility of the substrate in H_2O–EtOAc (entry 4). Hydrogenation of α-*N*-acetamidoacrylic acid **9f** and its methyl ester **9g** took place in aqueous media but with very low enantioselectivity for each substrate (entries 5 and 6).

Results summarized in Tables 1 and 2 show that the catalyst **8** having a (2*S*,3*R*)-2-deoxyaltropyranoside backbone provides α-amino acids with *R* configuration predominantly. In general, one of the perceived limitations of natural products as chiral sources is the scarcity of one of the enantiomers. Thus, it is worth noting that the present transformation to the catalyst **8** from α,α-trehalose complementarily compensates for the reverse selectivity of our previous catalyst having **1a** as a ligand[16] in asymmetric hydrogenation of enamides.

In the previous study, we have found that some surfactants notably enhance the enantioselectivity in the hydrogenation of enamides and itaconic acid in water using rhodium catalysts involving ligands **1a**,**b**.[6b] Therefore, we examined the effect of surfactants, such as sodium dodecyl sulfate (SDS), cetyltrimethylammonium hydrogensulfate (CTA–HSO_4), and Brij 58 on enantioselectivity in hydrogenation of **9a** in water using

Table 2. Enantioselective hydrogenation of enamides **9** using catalyst **8**[a]



Entry	9	R^1	R^2	Solvent	Conv. (%)	ee (%)[b]	Config.[c]
1	**b**	Ph	H	H_2O–EtOAc (1:1)	100	50[d]	*R*
2	**c**	4-$MeOC_6H_4$	Me	H_2O–EtOAc (1:1)	71	66	*R*
3	**d**	3-ClC_6H_4	Me	H_2O–EtOAc (1:1)	100	67	*R*
4	**e**	1-Naphthyl	Me	H_2O–MeOH–EtOAc (0.6:0.4:1)	100	51	*R*
5	**f**	H	H	H_2O	100	10[d]	*R*
6	**g**	H	Me	H_2O–EtOAc (1:1)	100	18	*R*

[a] Reaction conditions: enamide (0.1 mmol), catalyst **8** (0.2×10^2 mmol), H_2 (50 atm), solvent (2 mL), rt, 24 h.
[b] Determined by HPLC.
[c] Determined by comparing with authentic samples.
[d] Determined as its methyl ester.

the catalyst **8**. Each surfactant accelerated the rate of hydrogenation, but the observed enantioselectivities were lower (0% ee with SDS, 5% ee with CTA–HSO_4, and 21% ee with Brij 58) than in the absence of surfactants.

In conclusion, we have developed a novel water-soluble cationic rhodium complex **8** having a phosphine–phosphinite (α,α-TREHAPPN) ligand derived from α,α-trehalose. This complex was found to be an effective catalyst for the enantioslective hydrogenation of dehydroamino acids and their esters in aqueous media. Since the catalyst can be immobilized in the aqueous phase, the aqueous phase containing the catalyst can be recovered by simple phase separation and re-used for the next cycle. We have also demonstrated that the ligand **3**, derived from α,α-trehalose, afforded unnatural types of α-amino acid derivatives with the opposite sense of enantioselectivity to ligand **1**.

3. Experimental

3.1. General

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl under argon. Dichloromethane, triethylamine, and *N*,*N*-dimethylformamide were distilled from calcium hydride. Methanol was distilled over $Mg(OMe)_2$. Analytical thin-layer chromatographies (TLC) were performed with silica gel 60 Merck F-254 plates or aluminum oxide 60 Merck F-254. Column chromatographies were performed with Merck silica gel 60 or ICN Alumina Akt I (neutral). NMR spectra were measured on JEOL EX-400, AL-300, and JNM-GSX-270 spectrometers for solutions in $CDCl_3$ or CD_3OD with Me_4Si as an internal standard (^1H and ^{13}C) or with $P(OMe)_3$ as an external standard (^{31}P): the following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Optical rotations were recorded at 589 nm. Enantiomeric ratios were determined by HPLC with Daicel Chiralcel OJ or OD column (4.6×250 mm) (at 254 or 210 nm) at 40°C except for an *N*-acetylalanine methyl ester. Melting points are uncorrected. Mass spectra (FAB LRMS or HRMS) were obtained with a JEOL JMX-SX 102A spectrometer. 2,3:4,6-Di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-α-D-glucopyranoside **4** was prepared according to the reported procedure.[8] α,α-Trehalose dihydrate was purchased from Hayashibara Corporation.

3.2. 2,3:4,6-Di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2,3-di-*O*-mesyl-α-D-glucopyranoside, 5

To a solution of **4** (0.90 g, 1.95 mmol) in pyridine (50 mL) was added methanesulfonyl chloride (0.56 g, 4.85 mmol) at 0°C, and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice-water (50 mL) and extracted with $CHCl_3$ (3×50 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under vacuum and the orange residue was subjected to column chromatography on SiO_2 with hexane–EtOAc (v/v = 1:1) as an eluent to give the title compound **5** (1.11 g, 1.79 mmol, 92%) as a white solid: mp 102.0–103.0°C; $[\alpha]_D^{23} = +103.0$ (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 3.12 (s, 3H), 3.19 (s, 3H), 3.57 (dd, $J = 2.9$, 9.3 Hz, 1H), 3.70–3.86 (m, 4H), 3.89–4.05 (m, 4H), 4.14 (t, $J = 9.3$ Hz, 1H), 4.67 (dd, $J = 3.9$, 9.8 Hz, 1H), 4.88 (t, $J = 9.8$ Hz, 1H), 5.36 (d, $J = 2.9$ Hz, 1H), 5.40 (d, $J = 3.9$ Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.2, 19.3, 26.1, 26.8, 28.9, 38.8, 38.8, 61.8, 61.9, 63.7, 66.3, 72.0, 73.3, 73.7, 75.1, 76.2, 77.8, 94.4, 94.6, 99.6, 100.0, 111.9 ppm. HRMS (FAB) calcd for $C_{23}H_{39}O_{15}S_2$ ($M+H^+$): 619.1730. Found: 619.1719.

3.3. 2,3:4,6-Di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-2,3-anhydro-4,6-*O*-isopropylidene-α-D-allopyranoside, 6

To a solution of **5** (1.11 g, 1.79 mmol) in acetone (50 mL) was added a mixture of sodium alkoxides generated from Na (0.23 g, 10 mmol) in 2-PrOH and EtOH

(v/v = 3:1, 40 mL) at 10°C. The mixture was stirred at the same temperature for 16 h. After removing the solvent under vacuum, water (20 mL) was added and then the product was extracted with $CHCl_3$ (3×20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed under vacuum and the orange residue was subjected to column chromatography on SiO_2 with petroleum ether–EtOAc (v/v = 3:2) as an eluent to give the title compound **6** (0.60 g, 1.35 mmol, 75%) as a white solid: mp 76.4–77.5°C; $[\alpha]_D^{23} = +73.8$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 6H), 1.46 (s, 3H), 1.51 (s, 3H), 1.52 (s, 3H), 1.55 (s, 3H), 3.40 (m, 1H), 3.48 (dd, J = 2.9, 9.3 Hz, 1H), 3.54 (dd, J = 2.9, 9.3 Hz, 1H), 3.63–3.72 (m, 2H), 3.81–3.91 (m, 3H), 3.93 (t, J = 9.3 Hz, 1H), 4.00–4.02 (m, 2H), 4.18 (t, J = 9.8 Hz, 1H), 5.24 (d, J = 2.9 Hz, 1H), 5.44 (d, J = 2.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.9, 19.1, 26.2, 26.8, 29.0, 50.7, 52.8, 61.1, 62.1, 62.3, 65.9, 70.2, 73.4, 73.8, 76.5, 91.0, 94.1, 99.7, 100.0, 111.7 ppm. HRMS (FAB) calcd for $C_{21}H_{33}O_{10}$ ($M+H^+$): 445.2074. Found: 445.2061.

3.4. 2,3:4,6-Di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2-(diphenylphosphino)-2-deoxy-α-D-altropyranoside, 7

To a solution of **6** (0.20 g, 0.45 mmol) in degassed THF (10 mL) was added dropwise a solution of 0.5 M potassium diphenylphosphide (1.35 mL, 0.68 mmol) in THF at −78°C. The mixture was stirred at room temperature for 2 h under Ar. To the reaction mixture was added NH_4Cl (1.0 g) and the mixture was stirred for 0.5 h. After removal of excess NH_4Cl insoluble in THF, the solvent was removed under vacuum, and the residue was subjected to column chromatography on SiO_2 with $CHCl_3$–AcOEt (v/v = 1:3) as an eluent to give the title compound **7** (0.17 g, 0.27 mmol, 60%) as a white solid: mp 104.3–106.0°C; $[\alpha]_D^{23} = +78.9$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.48 (s, 3H), 1.52 (s, 6H), 3.22–3.34 (m, 2H), 3.42–3.53 (m, 2H), 3.66 (t, J = 10.7 Hz, 1H), 3.82–3.91 (m, 4H), 4.07 (t, J = 9.3 Hz, 1H), 4.17 (m, 2H), 4.87 (d, J = 5.5 Hz, 1H), 5.32 (d, J = 3.3 Hz, 1H), 7.37–7.87 (m, 10H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.1, 19.2, 26.2, 26.7, 29.0, 29.1, 44.6 (d, J = 16.1 Hz), 59.6, 61.8, 62.4, 65.9, 66.9 (d, J = 16.1 Hz), 69.6 (d, J = 7.3 Hz), 73.4, 73.7, 75.8, 92.2, 94.0 (d, J = 21.8 Hz), 99.6, 99.9, 111.8, 128.8, 128.9, 129.0, 129.0, 129.6, 130.0, 130.6, 130.7, 132.8 (d, J = 21.8 Hz), 133.5 (d, J = 21.8 Hz), 134.9 (d, J = 13.0 Hz), 135.3 (d, J = 14.5 Hz); ^{31}P NMR (161.9 Hz, $CDCl_3$) δ −20.5 ppm. HRMS (FAB) calcd for $C_{33}H_{44}O_{10}P$ ($M+H^+$): 631.2672. Found: 631.2692.

3.5. 2,3:4,6-Di-*O*-isopropylidene-α-D-glucopyranosyl-(1,1)-4,6-*O*-isopropylidene-2-(diphenylphosphino)-2-deoxy-3-*O*-(diphenylphosphino)-α-D-altropyranoside, 3′

To a solution of **7** (0.11 g, 0.18 mmol), 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (2.0 mg, 0.24 mmol), and triethylamine (1.0 mL, 7.1 mmol) in degassed THF (1.0 mL) was slowly added chlorodiphenylphosphine (0.03 mL, 0.20 mmol) and the reaction mixture was stirred at room temperature for 15 min under Ar. The solvent was removed under vacuum, and the white residue was subjected to column chromatography on Al_2O_3 with $CHCl_3$ as an eluent to give the title compound **3′** (0.069 g, 0.085 mmol, 47%) as a white solid: mp 90.3–92.0°C; $[\alpha]_D^{23} = +40.4$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.07 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.53 (s, 3H), 1.54 (s, 3H), 3.25 (s, 1H), 3.29–3.34 (m, 1H), 3.39 (dd, J = 4.9, 10.5 Hz, 1H), 3.49 (dd, J = 3.2, 9.0 Hz, 1H), 3.63 (t, J = 10.5 Hz, 1H), 3.72 (t, J = 10.5 Hz, 1H), 3.82–3.89 (m, 2H), 4.06–4.10 (m, 2H), 4.29 (m, 1H), 4.46 (m, 1H), 4.84 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 2.9 Hz, 1H), 7.13–7.71 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 19.2, 26.1, 26.8, 28.5, 29.2, 59.4, 60.0, 62.0, 62.3, 65.5, 70.0 (d, J = 4.4 Hz), 73.7, 74.0, 76.3, 77.2, 92.2, 93.4, 94.0 (d, J = 24.9 Hz), 99.7, 111.6, 127.8–135.6 (22 carbons), 143.7, 143.9; ^{31}P NMR (161.9 Hz, $CDCl_3$) δ −18.3, 117.9 ppm. HRMS (FAB) calcd for $C_{45}H_{53}O_{10}P_2$ ($M+H^+$): 815.3114. Found: 815.3122.

3.6. [Rh(α-D-glucopyranosyl-(1,1)-2-(diphenylphosphino)-2-deoxy-3-*O*-(diphenylphosphino)-α-D-altropyranoside)-(1,5-cyclooctadiene)]$^+BF_4^-$, 8

[Rh(acac)(cod)] (13.3 mg, 0.043 mmol) and **3′** (36 mg, 0.045 mmol) were dissolved in degassed dry THF (1.0 mL) under Ar and the mixture was stirred for 15 min. Aqueous 40% HBF_4 solution (0.2 mL) was added to the mixture and the reaction mixture was stirred at room temperature for 1 h. Degassed dry Et_2O (30 mL) was added, and then the yellow solid was precipitated. The supernatant solution was removed by syringe, and the title complex **8** (21.8 mg, 0.022 mmol, 51%) was obtained as yellow crystals: mp 230.0–231.5°C; ^{31}P NMR (161.9 Hz, CD_3OD) δ 19.2 (dd, J_{P-P} = 49, J_{P-Rh} = 147 Hz), 120.5 (dd, J_{P-P} = 49, J_{P-Rh} = 165 Hz) ppm. LRMS (FAB) m/z 905 (M^+-BF_4). HRMS (FAB) calcd for $C_{44}H_{52}O_{10}P_2Rh$ (M^+-BF_4): 905.2091. Found: 905.2096.

3.7. A typical procedure for the hydrogenation of dehydroamino acids in an aqueous/organic medium (H_2O–EtOAc) using the complex 8

The Rh complex **8** (2.0 mg, 0.20×10^{-2} mmol) was dissolved in degassed H_2O (1.0 mL), and the solution was injected into a stainless steel autoclave with glass container by a syringe under Ar. To this solution was added a solution of methyl α-acetamide (*Z*)-cinnamate (21.8 mg, 0.10 mmol) in degassed EtOAc (1.0 mL) by a syringe under Ar, and the mixture was stirred vigorously under H_2 pressure (50 atm). When the reaction was complete (as confirmed by GLC, TLC, or ^{1}H NMR) the organic layer was separated by decantation, and the removal of solvent under vacuum gave the crude product as a pale yellow oil. Purification of the crude product by column chromatography on SiO_2 with petroleum ether–EtOAc (v/v = 1:10) as eluent gave *N*-acetylphenylalanine methyl ester. The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OJ column [1.0 mL/min, 10% 2-PrOH/hexane; (*R*)

$t_1 = 10.0$ min, (*S*) $t_2 = 13.0$ min]. The separation of racemic mixtures under HPLC conditions is as follows: *N*-acetyl-3-(4-methoxyphenyl)alanine methyl ester (OJ, 1.0 mL/min, 10% 2-PrOH/hexane), (*R*) $t_1 = 16.0$ min, (*S*) $t_2 = 27.5$ min; *N*-acetyl-3-(3-chlorophenyl)alanine methyl ester (OJ, 1.0 mL/min, 10% 2-PrOH/hexane), (*R*) $t_1 = 10.2$ min, (*S*) $t_2 = 12.5$ min; *N*-acetyl-3-(1-naphthyl)alanine methyl ester (OJ, 0.5 mL/min, 10% 2-PrOH/hexane), (*R*) $t_1 = 27.8$ min, (*S*) $t_2 = 32.5$ min; *N*-acetylalanine methyl ester (OD, 1.0 mL/min, at 25°C, 1% 2-PrOH/hexane), (*R*) $t_1 = 53.5$ min, (*S*) $t_2 =$ 71.7 min.

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16. The ligands **1a** and **1b** having a (2*R*,3*S*)-glucopyranoside backbone provide (*S*)-α-amino acid derivatives in the asymmetric hydrogenation of enamides, although they form seven-membered complexes with rhodium, see: Ref. 6a.