[Chem. Pharm. Bull. 33(12)5284—5293(1985)]

Syntheses of Novel Sugar Phosphine Derivatives, and Homogeneous Hydrogenation Reactions with Their Rhodium Complexes

SETSUO SAITO, YUSHIN NAKAMURA, and YUTAKA MORITA*

Faculty of Pharmaceutical Sciences, Josai University, Sakado, Saitama 350-02, Japan

(Received May 9, 1985)

Optically active diphenylphosphine derivatives, (1*R*,3*R*,4*S*,5*R*,6*R*)-6-cyano-5-diphenylphosphino-3,4-*O*-isopropylidene-2-oxabicyclo[3.2.0]heptane-3,4-diol (**15**) and its reduction product (**17**), were prepared by the cyclization of **12** or **13**, which was obtained from a common sugar, D-glucose. These phosphines were used as ligands in the rhodium complex-catalyzed asymmetric hydrogenation of prochiral olefins. The rhodium complex catalyst which was constructed with 2 mol of **15** and 1 mol of rhodium(cyclooctene)$_2$Cl (**20**) worked efficiently for the asymmetric hydrogenation of α-acetamidocinnamic acid (**18**) and itaconic acid (**24**) with 91.6% ee-(*S*) and 69.6% ee-(*R*), respectively. On the other hand, the rhodium complex constructed with 1 mol of **17** and 1 mol of **20** was less effective than that of **15**, giving 39.0% ee-(*R*) in the reaction with **18**. Methyl esters of **18** and **24** were also hydrogenated using the complex of **15**.

Keywords——D-glucose; (1*R*,3*R*,4*S*,5*R*,6*R*)-6-cyano-5-diphenylphosphino-3,4-*O*-isopropylidene-2-oxabicyclo[3.2.0]heptane-3,4-diol; cyclobutane ring formation; chiral phosphine ligand; rhodium complex; asymmetric hydrogenation, enantioselectivity

Asymmetric catalytic hydrogenation of amino acid precursors and other prochiral olefins using soluble diphosphine–rhodium complexes[1-10] has nearly reached a level of refinement where the enantioselection rivals that of enzymatic reactions. The mechanism of these reactions has been almost completely clarified and the structures of intermediates in these reactions have also been discussed.[3]

Nowadays, more than a dozen chelating chiral ligands have been developed, including those from naturally occurring chiral compounds such as lactic acid,[4b] tartaric acid,[1] menthol,[5] camphor,[5] 4-hydroxyproline,[6] and D-glucose.[7,8] Chiral ligands such as **1**,[7] **2**,[8] and

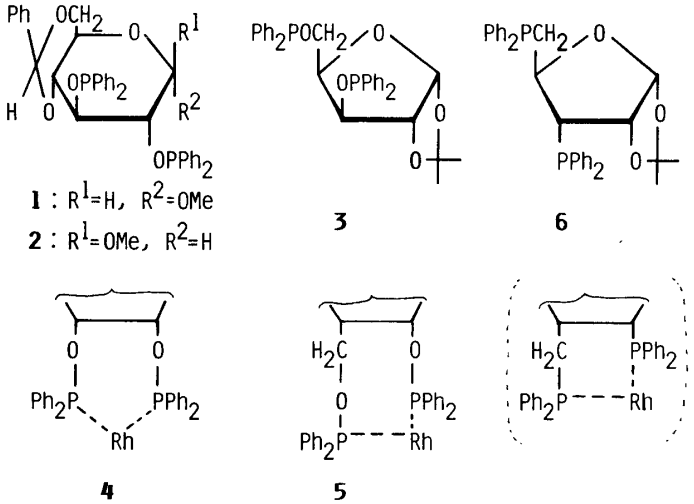


Fig. 1. D-Glucose-Derived Ligands

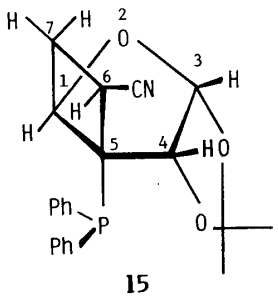


Fig. 2. The Absolute Structure of **15**

3[8] from D-glucose are known to be readily susceptible to hydrolysis because of their C–O bondings. Moreover, the rigidity of rhodium complexes derived from these can not be high, because of the seven-(**4**) or eight-(**5**) membered ring size (Fig. 1).

During our attempts to synthesize sugar bisdiphenyl phosphine ligands such as **6**, which has C–P bondings and forms a six-membered ring complex with rhodium metal,[9] we have obtained a compound **15** with a novel skeleton, assigned as (1*R*,3*R*,4*S*,5*R*,6*R*)-6-cyano-5-diphenylphosphino-3,4-*O*-isopropylidene-2-oxabicyclo[3.2.0]heptane-3,4-diol on the basis of X-ray analysis (Fig. 2).[11]

In this paper, we wish to report syntheses of novel sugar phosphines, **15** and **17**, and their application in the asymmetric hydrogenation of prochiral olefins by complexing with rhodium metal.

Results and Discussion

Attempted Preparation of 3,5-Dideoxy-3,5-bis(diphenylphosphino)-1,2-*O*-isopropylidene-α-D-ribose (6)

The synthesis of the target sugar diphenylphosphine (**6**) was unsuccessful. Namely, when 1,2-*O*-isopropylidene-3,5-di-*O*-tosyl-α-D-xylofuranose (**7**) was treated with sodium diphenylphosphide,[1] two products **8** (mp 127—128 °C) and **9** (mp 134—135 °C) were obtained. Compound **8** showed a band at 3400—3500 cm^{-1} (OH) in the infrared (IR) spectrum, and gave signals of aromatic protons (10H) at δ 7.33 and of H-3 at 4.07 ppm in the proton magnetic resonance (^{1}H-NMR) spectrum (60 MHz). Compound **9** gave no OH band in the IR, and gave signals of aromatic protons (12H; δ 7.00—7.14, 10H of diphenylphosphine protons and 2H of tosylphenyl protons, and 2H; 7.33, tosylphenyl protons) and of H-3 (4.68 ppm) in the ^{1}H-NMR spectrum (60 MHz), showing that the substitution of the tosyl group took place at C-3. Therefore, compounds **8** and **9** were assigned the 5-deoxy-5-diphenylphosphino-1,2-*O*-isopropylidene-α-D-xylofuranose and 5-deoxy-5-diphenylphosphino-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-xylofuranose structures, respectively.

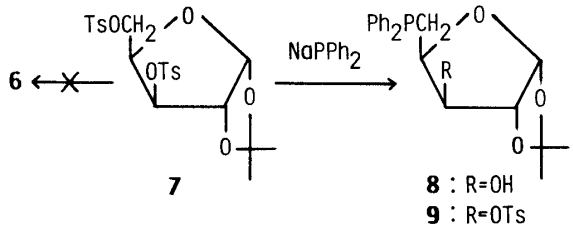


Chart 1. The Synthetic Route to **8** and **9** from **7**

Syntheses of (1*R*,3*R*,4*S*,5*R*,6*R*)-6-Cyano-5-diphenylphosphino-3,4-*O*-isopropylidene-2-oxabicyclo[3.2.0]heptane-3,4-diol (15) and Its Reduction Product (17)

As we anticipated that the attack of diphenylphosphide ion on C-3 from the α-side of the furanose ring might not be feasible because of the greater steric hindrance, we tried to synthesize olefins such as **12** and **13** as intermediates for the preparation of **14**, according to Chart 2.

Oxidation of 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylose (**10**) with P_2O_5–dimethyl sulfoxide[12] gave the corresponding ketone (**11**), which in turn was treated with $Ph_3P{=}CHCN$, a Wittig reagent, to give two olefins, **12** (66.8%) and **13** (23.7%). In the ^{1}H-NMR spectra (270 MHz), the protons of C-4 and C-5 of **12** (δ 5.19, H-4 and 4.30, 2H-5) were shifted to lower field than those of **13** (4.98, H-4 and 4.18 ppm, 2H-5). On the other hand, the proton at C-2 of **12** (δ 5.05) was shifted to higher field than that of **13** (5.16 ppm). These results suggested

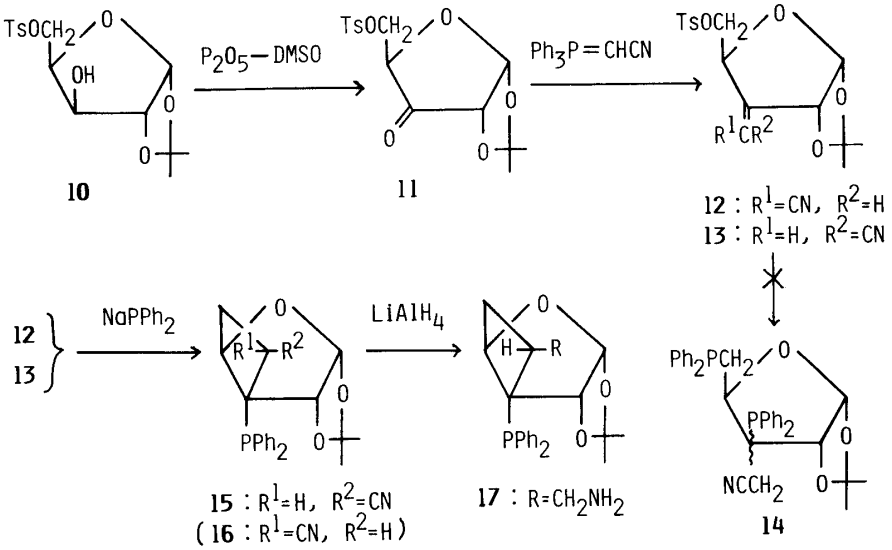


Chart 2. The Synthetic Route to **15** and **17**

that the nitrile group in **12** has *trans*-configuration with respect to C-2, and that in **13** has *cis*-configuration. When **12** or **13** was treated with sodium diphenylphosphide, both gave the same major product **15**. The ^{1}H-NMR spectrum (270 MHz) of **15** showed the hydrogen signals of only one diphenylphosphine (δ 7.30—7.60 ppm, 10H) and showed no signals due to cyanomethylene group and tosyl group protons. These results showed that the product obtained here was not like **14**, but was **15** or **16**, having a cyclobutane ring fused with the furanose ring. The structure of the compound has been established as **15** by ^{1}H-NMR and X-ray analyses.[11]

Reduction of **15** with $LiAlH_4$ gave the corresponding amine (**17**) which showed signals of H-7's at δ 1.17 as a two-proton multiplet and aminomethylene at 3.73 ppm as a 2H doublet among others in the ^{1}H-NMR (60 MHz). Signals of H-7's in **15** appeared at δ 1.33—1.42 and 1.82 ppm, separated by the anisotropic effect of the nitrile. The reduction of nitrile to aminomethylene caused higher field shifts of both H-7's. Judging from the observed shifts, the anisotropic effect of the nitrile group shielding at H-7a was not so marked, but deshielding of H-7b was relatively large, causing the lower field shift ($\Delta_{\delta a,b}$ 0.4—0.5 ppm) in **15**.

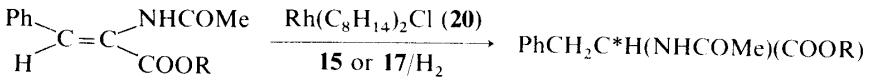
Asymmetric Hydrogenation Using 15– and 17–Rhodium Complexes

As shown in Tables I and II, the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid (**18**) and its methyl ester (**19**) by the use of the neutral Rh-complex, which was generated from $Rh(cyclooctene)_2Cl$ (**20**) and the ligand **15** or **17**, was carried out under various conditions. In the reaction of **18** with **15**–rhodium complex, the optical yield was higher (91.6%) with the complex consisting of 1 mol of **20** and 2 mol of **15** than that (30.7%) with the complex consisting of 1 mol of **20** and 1 mol of **15**. It appears that the ligand **15** acted as a monodentate ligand. However, when the ligand **17** was used in an amount of either 1 or 2 mol with respect to **20**, the resulting optical yield was nearly the same, 39.0 or 34.8%, respectively. The ligand **17** could be a bidentate ligand.

As shown in the tables, although the reaction rates were accelerated under elevated pressure, the optical yields were the highest at 1 atm in both cases (**15**– and **17**–rhodium complexes). As compared with the case of DIOP (**23**),[1] the hydrogenation rates with **15**–rhodium complex were greatly delayed in the reaction at 1 atm. There was a marked contrast of chiral induction between **15** and **17**; (*R*)-configuration was obtained with **15** and (*S*)-configuration with **17** and **23**.

The asymmetric hydrogenations of itaconic acid (**24**), and its mono-(**25**) and di-(**26**)

TABLE I. Catalytic Hydrogenation of **18** and **19** with **15**-Rh-Complex[a]



18: R=H
19: R=Me

21: R=H
22: R=Me

Substrate	[15]/[20]	Pressure (atm)	Conversion (%)	Reaction time (h)	Optical yield (% ee)[b]	Product config.
18	2/1	1	83.7	72	91.6[c]	
	1/1	1	100	1 week	30.7	**21**-(*S*)
	2/1	15	100	10	85.6	
	2/1	30	100	10	60.1	
19	2/1	1	51.4	72	70.6[d]	
	2/1	15	100	10	53.8	**22**-(*S*)
	2/1	30	100	10	42.9	

a) The hydrogenation reactions were carried out under the following conditions; substrate/Rh = 50, [**20**] = 1.07×10^{-4} mol, 20 ml of C_6H_6–MeOH (1 : 4) as the solvent, at ambient temperature. *b*) The optical rotations of the pure saturated adducts are as follows: **21**-(*S*), $[\alpha]_D^{26}$ +46.0 (*c* = 1.0, EtOH)[11] and **22**-(*S*), $[\alpha]_D^{20}$ +16.4 (*c* = 2.0, MeOH).[3c] *c*) (−)-DIOP(**23**)–Rh complex (*cf.* Fig. 3) gave 75% ee **21**-(*R*) under the same conditions as in *a*), [**23**]/[**20**] = 1, and at 1 atm with 100% conversion in 8 h. *d*) The **23**–Rh complex gave 53% ee **22**-(*R*) under the same conditions as in *c*) with 100% conversion in 16 h.

TABLE II. Catalytic Hydrogenation of **18** and **19** with **17**-Rh-Complex[a]

Substrate	[17]/[20]	Pressure (atm)	Conversion (%)	Reaction time (h)	Optical yield (% ee)	Product config.
18	1/1	1	100	72	39.0	
	2/1	1	100	72	34.8	**21**-(*R*)
	1/1	15	100	10	14.8	
19	1/1	1	100	72	15.5	
	1/1	15	100	10	5.3	**22**-(*R*)

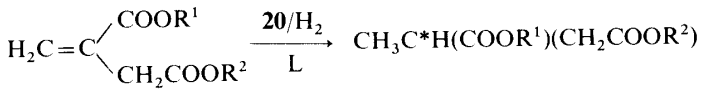
a) The conditions were the same as in *a*) of Table I.

methyl esters with **15**- and **23**-complexes were carried out, and the results are shown in Table III. Optical yields in the reactions of **24** and **25** were higher than that in the case of **26** with both **15**- and **23**-complexes.

Enantioselectivity in the Hydrogenation Reaction with Rhodium Complexes of Diphenylphosphine Derivatives

Previously reported studies on asymmetric hydrogenation have shown that the highest optical yields are obtained when chelating bisphosphine rhodium complexes are employed in the reduction of olefins carrying polar functionalities, especially enamides. A considerable range of structure variations in the ligand has been tested, most being based on Ph_2P-X-PPh_2 where X represents an unspecified asymmetric group. Few guiding principles have been derived from the reported data, although it appears that bisphosphines forming 5-ring chelate complexes are superior to those forming 6- or 7-ring chelate complexes because of their greater conformational rigidity. Asymmetric induction arises from chirality or induced chirality at phosphorus involving preferred P-phenyl rotamers. It has been shown that the

TABLE III. Catalytic Hydrogenation of **24**, **25**, and **26** with **15**- and **23**-Complexes[a]



24: $R^1=R^2=H$ **27**: $R^1=R^2=H$
25: $R^1=H$, $R^2=Me$ **28**: $R^1=H$, $R^2=Me$
26: $R^1=R^2=Me$ **29**: $R^1=R^2=Me$

L	Substrate	Conversion (%)	Reaction time (h)	Optical yield (% ee)[b]	Product config.
15	**24**	100	18	69.6	**27**-(*R*)
	25	84.2	72	89.7[c]	**28**-(*R*)
	26	66.7	72	6.4	**29**-(*R*)
23	**24**	100	1	45.1	**27**-(*S*)
	25	100	12	23.9[c]	**28**-(*S*)
	26	100	18	6.8	**29**-(*S*)

a) [**15**]/[**20**]=2/1, [**23**]/[**20**]=1/1. Other conditions were the same as in *a*) of Table I at 1 atm. *b*) The optical rotations of the pure saturated adducts are as follows: **27**-(*R*), $[\alpha]_D^{20}$ +17.09° (*c*=4.41, EtOH) and **29**-(*R*), $[\alpha]_D^{20}$ +6.11° (neat).[13] *c*) Converted into the diester to determine ee.

major source of discriminatory interaction is the chiral array of phenyl groups in reactions using (*S*,*S*)-CHIRAPHOS (**30**) and (*R*)-PROPHOS (**31**) as 5-ring chelate complexes,[4] and (*S*,*S*)-SKEWPHOS (**32**) and (*S*)-CHAIRPHOS (**33**) as 6-ring chelate complexes.[9] These phenyl groups, although capable of somewhat restricted rotation about the phosphorus–carbon bonds, present the prochiral substrates with a dissymmetric array of potential interactions which cause one face of the olefinic substrates to be preferentially coordinated by virtue of the interactions of the vinylic substituents with the phenyl groups. The ambiguity arises, in part, because the substrates may adopt a number of (unknown) rotameric conformations which will have varying degrees of diastereotopic interaction. The situation is even more complicated than would be expected just from the nature of the internal interactions, as has been shown in many experiments, since quite large solvent effects are observed. Thus, a complete description of the chiral discrimination would also require examination of the dissymmetry of the immediate solvation sphere as well as the solvent-incorporated coordination sphere. Recent studies[3m-q] have been aimed at improving our understanding of the reaction mechanism, by getting further detailed information on complexes formed in solution.

Despite many complications, however, the result that (−)-(*R*,*R*)-DIOP (**23**),[1] (*S*,*S*)-CHIRAPHOS (**30**),[4a,b] (*S*,*S*)-SKEWPHOS (**32**),[9] and BPPM (**34**)[3m,6a] gave (*R*)-*N*-acylamino acid in nearly all cases studied, irrespective of the geometry of the precursors,[10] suggests the existence of a common factor in these ligands, in contrast with (*S*)-*N*-acylamino acid production by (*R*)-PROPHOS (**31**),[4b] (+)-(*S*,*S*)-DIOP (**35**),[10a] (*R*,*R*)-DIPAMP (**36**),[3c,f,10b] and PPM (**37**)[6a] in the hydrogenation of α-acetamidocinnamic acid (Fig. 3).

As determined by X-ray crystallography, in the structures of various substrate- (or the second ligand-) bound rhodium or iridium complexes, the chelate ring assumes a conformation with one pair of axial and one pair of equatorial P-phenyl rings, and an *ortho*-hydrogen of each axial ring is in proximity to the rhodium at a pseudo-octahedral site orthogonal to the coordination plane in a particular manner in the Z-type group (**30**[3b,l] and **34**[3m]) of (*R*)-amino acid-forming complexes and differently in the S-type (**35**,[3a] **36**,[3c] and

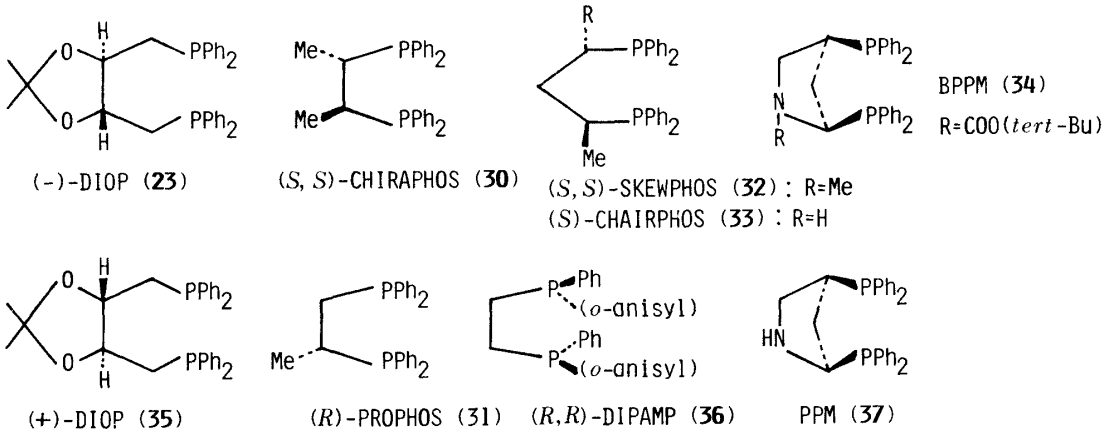


Fig. 3. Some Diphenylphosphine Ligands

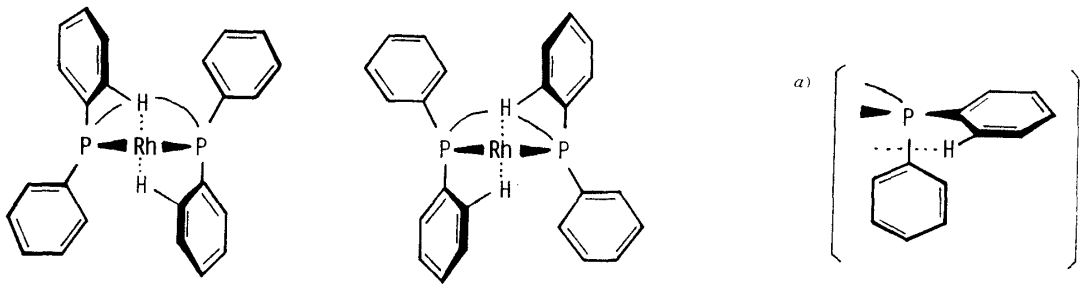


Fig. 4. Arrays of Diphenyl Groups in Rh-complexes
a) The right half in **34**- and **37**-complexes.

37[3i]) of (*S*)-amino acid-forming complexes as shown in Fig. 4.

Provided that any complex can be classified into one of these two types, the following statement can be made for prediction of the enantioselectivity of the complex used in the asymmetric hydrogenation. When a diphenylphosphine ligand gives the (*R*)-amino acid in the hydrogenation of α-acetamidocinnamic acid complexing with rhodium, the complex should have its phenyl groups in Z-type form, and *vice versa*.

According to the type classification mentioned above, **23** should belong to the Z-type, and **35** and **36** to the S-type, because **23** gave the enantiomeric amino acid to that obtained with **35** and **36** in the hydrogenation reaction. In the case of hydrogenation of itaconates to methyl succinates, the products formed by **23**[3p] and **34**[3m,6d] were of (*S*)-form, whereas those produced by **36**[3g,p,6f] were of (*R*)-form, in the enantiomeric form as expected, but with reversed sign compared with the case of hydrogenation of α-acetamidocinnamates to amino acids. Likewise, ammonium atropate, $H_2C=C(Ph)(COONH_4^+)$, was hydrogenated to α-phenylpropionate in (*S*)-form by **23**,[3g] but in (*R*)-form by **36**.[3p] The enantioselectivities of these Z- and S-type ligands seem to be substrate type-dependent as shown in Table IV. When the denticity of the substrate is assessed qualitatively by counting each O- and N-containing substituent and the olefin which is to be hydrogenated, acetamidocinnamate, itaconate, and atropate may be designated as tridentate (TD), tridentate (itaconate) (TDI), and bidentate (BD) substrates, respectively.

Using the above mentioned notation and classification, the following rule can be proposed, *viz.*, Z-type complex hydrogenates TD at the *si*-, TDI at the *re*-, and BD at the *re*-face. In the case of S-type complex, the attack face is reversed, *viz.*, TD at *re*, TDI at *si*, and

TABLE IV. The Complex Type, the Preferred Attack Face, and the Substrate Denticity in the Hydrogenation of Prochiral Olefins

Denticity of substrate	Tridentate (TD)	Tridentate (Itaconate) (TDI)	Bidentate (BD)	
Example substrate	α-Acetamido-cinnamates	Itaconates	Atropates	
Complex type Z-Type	*si*	*re*	*re*	Attack face Config. of
(**23**, **30**, **32**, **34**, **17**)	*R*	*S*	*S*	product from example subst.
S-Type	*re*	*si*	*si*	Attack face Config. of
(**35**, **31**, **36**, **37**, **15**)	*S*	*R*	*R*	product from example subst.

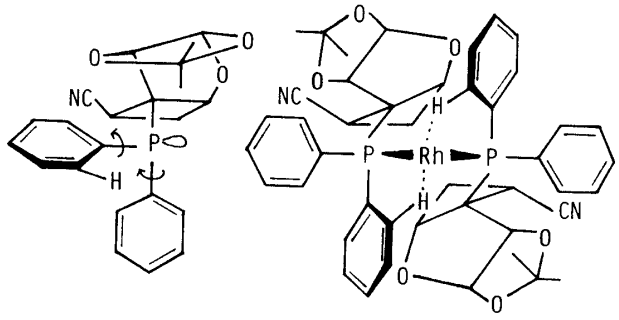
BD at *si* (Table IV).

Previously reported data are consistent with the rule postulated here. Enolacetate of pyruvate, $H_2C=C(COOEt)(OCOMe)$, which is TD, was hydrogenated to acyllactate in (*R*)-form with **30** (Z-type) by *si*-face attack and conversely in (*S*)-form with **31** (S-type) by *re*-face attack,[4b] according to the rule. The Z-type complex **23** gave (*S*)-form products in reactions with BD-substrates such as $H_2C=C(Ph)(R)$(R = $CONH_2$, $CONMe_2$, and NHCOMe) by *re*-face attack, and (*R*)-form products with TD-substrates such as $H_2C=C$(*o*-anisyl)(COR) (R = OH and NMe_2) by *si*-face attack.[3p] The triethylamine effect on the enantioselectivity was observed in the above cases, giving just the opposite enantiomers.

Unfortunately, there are no data for S-type complex on the same substrate as Z-type complex in the hydrogenation reaction. However, the following data may be relevant. The S-type complex **36** gave (*R*)-form products with BD-substrates such as (*E*)- and (*Z*)-(Ph)(H)C=C(Me)(R) (R = COOH and NHCOMe) by *si*-face attack, and (*S*)-form products with TD-substrates such as (*E*)- and (*Z*)-(Ph)(MeCONH)C=C(H)(COOEt), and (*Z*)-(Ph)(H)C=C(R)(R′) (R = CN, COOEt, and $CONH_2$; R′ = NHCOPh, NHCOOEt, NHC(S)OEt, and OCOMe) by *re*-face attack.[3c]

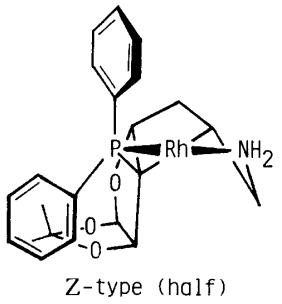
Unfortunately, there are some exceptions to the rule. The Z-type **23** hydrogenated $H_2C=C(Ph)(CH_2NHCOMe)$ to (*R*)-form product, possibly due to some effect of the 6-membered chelate ring,[3p] and the Z-type **34** hydrogenated (Me)(COOH)C=C(H)(COOH) to (*S*)-form product from (*Z*)-substrate and (*R*)-form product from (*E*)-substrate, influenced by the preferred chiral recognition, as Ojima *et al.* mentioned.[3m]

Although the rule is only a qualitative one, many substrates (or products) in the hydrogenation reaction fall into the scope of the rule (Table IV). As shown in Tables I and II, the (*S*)-form product with **15**-complex in the hydrogenation of α-acetamidocinnamate was enantiomeric to the (*R*)-form product with **17**-complex. The following discussion, based on the above rule, might explain the contrasting enantiomer production of these two ligands. The X-ray crystal structure of **15**[11] shows that the *o*-hydrogen of a phenyl ring is directed in parallel to the orbital lobe of P to which Rh may coordinate (Fig. 5a). In the hydrogenation reaction complexing with Rh, 2 mol of **15** were necessary for 1 mol of Rh to work as an effective catalyst, as shown above. Based on examination of Dreiding models, the least congested conformer constructed with 2 mol of **15** and 1 mol of Rh could be the one depicted in Fig. 5b (an S-type complex). To form the conformer, the axial phenyl groups should be



(a) (b) S-type

Fig. 5. The Conformation of **15** in the Crystal (a) and the Least Congested Conformation of **15**-Complex (b)



Z-type (half)

Fig. 6. The Conformation of **17**-Complex

rotated, as shown by arrows, from the conformer in the crystal state (Fig. 5a) to alleviate the steric interaction with the sugar moiety, with accompanying rotation of the equatorial phenyl rings. As a result, the edge-face array of phenyl groups in **15**-complex is just the reverse of that in **15** itself in the crystal state. The S-type conformation of **15**-complex coincides well with the (*S*)-amino acid production and (*R*)-methyl succinate production in the hydrogenation reaction. On the other hand, **17** forms a 1-to-1 complex with Rh, and could form only the complex in which the P-Rh containing ring has a boat conformation due to the *trans* relation of P and aminomethyl groups, as depicted in Fig. 6. In the conformation of **17**-complex shown in Fig. 6, *o*-hydrogen of the axial phenyl could be located in proximity to Rh as in the Z-type complex. The rotation of the equatorial phenyl is somewhat hindered by the sugar moiety. Although the enantio excess in the hydrogenation reaction using **17**-complex was less than that using **15**-complex, enantiomeric (*R*)-amino acid production was observed with **17**-complex as compared with the (*S*)-amino acid production by **15**-complex. The Z-type conformation of **17**-complex may explain its opposite enantioselectivity as compared with the S-type **15**-complex.

Experimental

^{1}H-NMR spectra of samples were recorded with a JEOL JNM-PMX60 (60 MHz) or GNX270 (270 MHz) NMR spectrophotometer in chloroform-*d* ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were obtained on a Shimadzu-LKB 9000 gas chromatograph-mass spectrometer with the direct inlet method at an ionizing energy of 70 eV. Optical rotations were measured in a 1-dm cell with a JASCO DIP-4 digital polarimeter. Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Thin layer chromatography (TLC) and preparative TLC were carried out on Kieselgel HF (Type 60; Merck), and spots were visualized by ultraviolet (UV) irradiation or by exposure to iodine. Columns for chromatography were prepared with Kieselgel 60 (Merck).

Reaction of 7 with Sodium Diphenylphosphide——A solution of sodium diphenylphosphide (1.34×10^{-2} mol) was generated by the reaction of sodium strips (620 mg, 2.7×10^{-2} mol) with triphenylphosphine (3.5 g, 1.34×10^{-2} mol) in liq. ammonia (50 ml). A solution of **7** (3.2 g, 6.7×10^{-3} mol) in abs. tetrahydrofuran (30 ml) was added to the resulting deep orange-red solution over a period of 30 min at 0 °C under a nitrogen atmosphere, and the mixture was stirred for another 1 h at room temperature, then evaporated to obtain a residue. Under a nitrogen flow, the residue was triturated with degassed ether and the ether solution was filtered. The filtrate was concentrated and chromatographed on silica gel (benzene–acetone, degassed with nitrogen, gradient up to 3%) to provide compounds **8** (530 mg, 22%) and **9** (23 mg, 6.6%). Compound **8**: 5-deoxy-5-diphenylphosphino-1,2-*O*-isopropylidene-α-D-xylofuranose, colorless needles from ether, mp 127—128 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400—3500 (OH), 1600 (benzene ring), 1540, 1400, 1380, 1370. ^{1}H-NMR (60 MHz) δ: 1.27 (3H, s, CH_3), 1.35 (3H, s, CH_3), 2.35 (1H, dd, $J=10$, 5 Hz, H-5), 2.67 (1H, dd, $J=10$, 2 Hz, H-5′), 4.07 (1H, d, $J=4$ Hz, H-3), 3.95—4.33 (1H, m, H-4), 4.47 (1H, d, $J=4$ Hz, H-2), 5.87 (1H, d, $J=4$ Hz, H-1), 7.33 (10H, s, aromatic protons). *Anal.* Calcd for $C_{20}H_{23}O_4P$: C, 67.03; H, 6.47. Found: C, 66.86; H, 6.32. Compound **9**: 5-deoxy-5-diphenylphosphino-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-xylofuranose, color-

less needles from ether–petroleum ether, mp 134—135 °C. ^{1}H-NMR (60 MHz) δ: 1.23 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.93 (1H, dd, J=13, 7 Hz, H-5), 2.37 (1H, dd, J=13, 7 Hz, H-5'), 2.37 (3H, s, tosyl CH_3), 3.83—4.33 (1H, m, H-4), 4.68 (1H, d, J=4 Hz, H-3), 4.82 (1H, d, J=3 Hz, H-2), 5.87 (1H, d, J=3 Hz, H-1), 7.00—7.13 (12H, protons of diphenyl group and A part of AB quartet of the tosyl group), 7.33 (2H, B part of AB quartet of the tosyl group). *Anal.* Calcd for $C_{27}H_{29}O_6PS$: C, 63.27; H, 5.70. Found: C, 63.32; H, 5.64.

3-Deoxy-1,2-*O*-isopropylidene-3-oxo-5-*O*-tosyl-α-D-xylofuranose (11)——Phosphorus pentoxide (5 g) was added to a stirred solution of **10** (7 g) in dimethylsulfoxide (10 ml) at 0 °C. The reaction mixture was stirred at 50—60 °C for a further 2 h, then poured into ice-water (200 ml), and the resulting suspension in water was extracted with dichloromethane (100 ml × 3). The extracts were combined and washed successively with saturated aqueous sodium bicarbonate and water, dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to give an oily residue, which was chromatographed on silica gel (benzene–acetone, gradient up to 3%) to give 4.5 g (65%) of **11** as a colorless oil giving a single spot on TLC. ^{1}H-NMR (60 MHz) δ: 1.43 (3H, s, CH_3), 2.47 (3H, s, tosyl CH_3), 4.03—4.57 (4H, m, H-2, 4, 5, and 5'), 6.07 (1H, d, J=4 Hz, H-1), 7.40—7.78 (4H, AB quartet of tosyl aromatic protons).

Wittig Reaction of Compound 11——A mixture of **11** (4.5 g) and Wittig reagent, PPh_3=CHCN (4.2 g), in dry benzene (200 ml) was refluxed for 14 h under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to give an oily residue, which provided two compounds, **12** (3.1 g, 66.8%) and **13** (1.1 g, 23.7%), after chromatography on silica gel with benzene–acetone (97 : 3). Compound **12**: 3-[(*E*)-cyanomethylene]-3-deoxy-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose, colorless needles from ether, mp 113—115 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2215 (CN). ^{1}H-NMR (60 MHz) δ: 1.40 (6H, s, 2 × CH_3), 2.47 (3H, s, tosyl CH_3), 4.30 (2H, J=2 Hz, H-5 and 5'), 5.03 (1H, m, H-2), 5.16 (1H, m, H-4), 5.68 (1H, t, J=1 Hz, =CHCN), 5.90 (1H, d, J=4 Hz, H-1), 7.33—7.75 (4H, AB quartet of tosyl aromatic protons). *Anal.* Calcd for $C_{17}H_{19}NO_6S$: C, 55.87; H, 5.24; N, 3.85. Found: C, 55.60; H, 5.20; N, 3.47. Compound **13**: 3-[(*Z*)-cyanomethylene]-3-deoxy-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose, colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2215 (CN). ^{1}H-NMR (60 MHz) δ: 1.38 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.43 (3H, s, tosyl CH_3), 4.10 (2H, d, J=4 Hz, H-5 and 5'), 4.93 (1H, m, H-4), 5.10 (1H, m, H-2), 5.40 (1H, t, J=1 Hz, =CHCN), 5.80 (1H, d, J=4 Hz, H-1), 7.33 and 7.72 (4H, AB quartet of tosyl aromatic protons). *Anal.* Calcd for $C_{17}H_{19}NO_6S$: C, 55.87; H, 5.24; N, 3.85. Found: C, 55.65; H, 5.21; N, 3.44.

Reaction of 12 with Ph_2PNa——1) A solution of **12** (1.3 g, 3.56×10^{-3} mol) in abs. tetrahydrofuran (20 ml) was added to a stirred solution of sodium diphenylphosphide (9.5×10^{-3} mol) in abs. tetrahydrofuran (50 ml) over a period of 45 min at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for a further hour at room temperature, then filtered. The filtrate was concentrated and the residue was loaded on preparative TLC plates (*n*-hexane–acetone 8 : 2) in chambers filled with nitrogen. This procedure yielded **15**, (1*R*,3*R*,4*S*,5*R*,6*R*)-6-cyano-5-diphenylphosphino-3,4-*O*-isopropylidene-2-oxabicyclo[3.2.0]heptane-3,4-diol, as colorless needles (148 mg, 11.0%), mp 174—176 °C (recrystallized from ether). $[\alpha]_D^{28}$ +141° (c=2.5, benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2215 (CN). ^{1}H-NMR (60 MHz) δ: 1.23 (1H, m, H-7a), 1.33 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.73 (1H, m, H-7b), 3.13 (1H, br q, H-6), 4.70 (1H, br t, H-1), 5.25 (1H, d, H-4), 6.33 (1H, d, H-3), 7.33—7.47 (10H, aromatic protons); (270 MHz) δ: 1.33—1.42 (1H, m, H-7a), 1.36 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.82 (1H, ddd, J_1=13.9, J_2=5.1, J_3=5.1 Hz, H-7b), 3.16 (1H, dddd, J_1=8.8, J_2=5.1, J_3=2.1, J_4=0.5 Hz, H-6), 4.72 (1H, dddd, J_1=5.1, J_2=5.1, J_3=2.1, J_4=1.5 Hz, H-1), 5.29 (1H, d, J=3.7 Hz, H-4), 6.37 (1H, d, J=3.7 Hz, H-3), 7.30—7.60 (10H, m, aromatic protons). MS *m/z* (relative intensity): 379 (M^+, 83), 321 (6), 292 (100), 268 (98). *Anal.* Calcd for $C_{22}H_{22}NO_3P$: C, 69.64; H, 5.84; N, 3.71. Found: C, 69.56; H, 5.82; N, 3.52.

2) A solution of **12** (1 g, 2.74×10^{-3} mol) in abs. tetrahydrofuran (15 ml) was added to a solution of sodium diphenylphosphide (3.5×10^{-3} mol) in abs. tetrahydrofuran (20 ml). The procedure described in method 1) was followed to obtain **15** (120 mg, 11.5%).

Reaction of 13 with Ph_2PNa——A solution of **13** (1 g, 2.74×10^{-3} mol) in abs. tetrahydrofuran (29 ml) was added to a stirred solution of sodium diphenylphosphide (3.5×10^{-3} mol) in abs. tetrahydrofuran (50 ml) at 0 °C over a period of 45 min under nitrogen. The procedure described in 1) was followed to obtain **15** (110 mg, 10.6%).

Reduction of 15 with $LiAlH_4$——A solution of **15** (120 mg) in dry ether (25 mg) was treated with lithium aluminum hydride (70 mg) and the mixture was refluxed for 7 h. After cooling, the reaction mixture was treated with a saturated aqueous Rochelle salt solution and extracted with dichloromethane (30 ml × 3). The combined dichloromethane solution was washed with water, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by preparative TLC with benzene–acetone (8 : 2). The separated colorless oil (90 mg, 74%) was crystallized by trituration with ether. Recrystallization from ether afforded colorless needles **17**, mp 125—127 °C. $[\alpha]_D^{28}$ +90° (c=0.6, benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH_2), 1480, 1400, 1380, 1370. ^{1}H-NMR (60 MHz) δ: 1.17 (2H, m, H-7 and 7'), 1.32 (3H, s, CH_3), 1.60 (3H, s, CH_3), 2.33—3.00 (1H, m, H-6), 3.73 (2H, br d, J=8 Hz, aminomethyl CH_2), 4.73 (1H, m, H-1), 5.33 (1H, d, J=4 Hz, H-4), 6.17 (1H, d, J=4 Hz, H-3), 7.33 (10H, aromatic protons). MS *m/z* (relative intensity): 383 (M^+, 23.9), 353 (31.5), 325 (10.6), 295 (100), 268 (27.7). *Anal.* Calcd for $C_{22}H_{26}NO_3P$: C, 68.92; H, 6.83; N, 3.65. Found: C, 68.73; H, 7.04; N, 3.22.

References

1) T. P. Dang and H. B. Kagan, *J. Chem. Soc., Chem. Commun.*, **1971**, 481; H. B. Kagan and T. P. Dang, *J. Am.*

Chem. Soc., **94**, 6429 (1972); N. Langlois, T. P. Dang, and H. B. Kagan, *Tetrahedron Lett.*, **1973**, 4865; T. P. Dang, J. C. Poulin, and H. B. Kagan, *J. Organomet. Chem.*, **91**, 105 (1975); G. Gelbard, H. B. Kagan, and R. Stern, *Tetrahedron*, **32**, 233 (1976).

2) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *J. Chem. Soc., Chem. Commun.*, **1972**, 10; W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2567 (1975); T. Hayashi, T. Mise, S. Mitachi, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, **1976**, 1133; C. Fischer and H. S. Mosher, *ibid.*, **1977**, 2487; T. Hayashi, M. Tanaka, and I. Ogata, *ibid.*, **1977**, 295; K. Yamamoto, A. Tomita, and J. Tsuji, *Chem. Lett.*, **1978**, 3.

3) *a*) S. Brunie, J. Mazan, N. Langlois, and H. B. Kagan, *J. Organomet. Chem.*, **114**, 225 (1976); *b*) R. G. Ball and N. Payne, *Inorg. Chem.*, **16**, 1187 (1977); *c*) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **99**, 5946 (1977); *d*) A. S. C. Chan, J. J. Pluth, and J. Halpern, *J. Inorg. Chim. Acta*, **37**, L477 (1979); *e*) J. M. Brown and P. A. Chaloner, *J. Chem. Soc., Chem. Commun.*, **1979**, 613; *f*) J. M. Brown, P. A. Chaloner, R. Glaser, and S. Geresh, *Tetrahedron*, **36**, 815 (1980); *g*) J. M. Brown and D. Parker, *J. Chem. Soc., Chem. Commun.*, **1980**, 342; *h*) J. M. Brown and P. A. Chaloner, *ibid.*, **1980**, 344; *i*) Y. Ohga, Y. Iitaka, and K. Achiwa, *Chem. Lett.*, **1980**, 861; *j*) A. S. C. Chan and J. Halpern, *J. Am. Chem. Soc.*, **102**, 838 (1980); *k*) J. M. Brown and P. A. Chaloner, *ibid.*, **102**, 3040 (1980); *l*) A. S. C. Chan, J. J. Pluth, and J. Halpern, *ibid.*, **102**, 5959 (1980); *m*) I. Ojima, T. Kogure, and N. Yoda, *J. Org. Chem.*, **45**, 4728 (1980); *n*) K. Achiwa, P. A. Chaloner, and D. Parker, *J. Organomet. Chem.*, **218**, 2499 (1981); *o*) P. S. Chua, N. K. Roberts, B. Bosnich, S. J. Okrasinski, and J. Halpern, *J. Chem. Soc., Chem. Commun.*, **1981**, 1278; *p*) J. M. Brown and D. Parker, *J. Org. Chem.*, **47**, 2722 (1982); *q*) J. M. Brown and P. A. Chaloner, *J. Chem. Soc., Perkin Trans. 2*, **1982**, 711.

4) *a*) M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977); *b*) *Idem, ibid.*, **100**, 5491 (1978); *c*) *Idem, ibid.*, **101**, 3040 (1979).

5) J. D. Morrison, W. F. Masler, and M. K. Neuberg, *Advances in Catalysis*, **25**, 81 (1976).

6) *a*) K. Achiwa, *J. Am. Chem. Soc.*, **98**, 8265 (1976); *b*) *Idem, Chem. Lett.*, **1977**, 777; *c*) *Idem, Tetrahedron Lett.*, **1977**, 3735; *d*) *Idem, ibid.*, **1978**, 1475; *e*) *Idem, Chem. Lett.*, **1978**, 561; *f*) W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.*, **101**, 4406 (1979).

7) W. R. Cullen and Y. Sugi, *Tetrahedron Lett.*, **1978**, 1635.

8) R. Jackson and D. J. Thompson, *J. Organomet. Chem.*, **159**, C-29 (1978).

9) P. A. MacNeil, N. K. Roberts, and B. Bosnich, *J. Am. Chem. Soc.*, **103**, 2273 (1981).

10) *a*) C. Detellier, G. Gelbard, and H. B. Kagan, *J. Am. Chem. Soc.*, **100**, 7556 (1978); *b*) K. E. Koenig and W. S. Knowles, *ibid.*, **100**, 7561 (1978).

11) S. Saito, T. Kato, Y. Morita, and H. Miyamae, *Chem. Pharm. Bull.*, **33**, 3092 (1985).

12) T. Okuda, S. Saito, and Y. Shiobara, *Carbohydr. Res.*, **39**, 237 (1975); T. Okuda, S. Saito, and K. Watanabe, *ibid.*, **65**, 183 (1976).

13) R. Rossi, P. Diversi, and G. Ingrosso, *Gazz. Chim. Ital.*, **98**, 1391 (1968).