Synthesis of Efficient Chiral Bisphosphine Ligands, Modified DIOPs, (4*R*,5*R*)-4-(Diaryl- or dialkylphosphino)methyl-5-(diarylphosphino)methyl-2,2-dimethyl-1,3-dioxolanes, and Their Use in Rhodium(I)-Catalyzed Asymmetric Hydrogenations¹⁾

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Modified DIOPs, (4*R*,5*R*)-4-(diaryl- or dialkylphosphino)methyl-5-(diarylphosphino)methyl-2,2-dimethyl-1,3-dioxolanes, were prepared on the basis of our design concept, and used as ligands for the rhodium(I)-catalyzed asymmetric hydrogenations of ketopantolactone, itaconic acid, dimethyl itaconate, and β -aryl-substituted itaconic acid derivatives. A neutral rhodium(I)-complex of (4*R*-*trans*)-dicyclohexyl[[5-[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]phosphine (DIOCP) bearing both a dicyclohexylphosphino group and a diphenylphosphino group was found to be a more efficient catalyst than the original DIOP in the asymmetric hydrogenation of ketopantolactone. Modified DIOPs bearing electron-donating groups at their *para* positions were efficient ligands for the rhodium(I)-catalyzed asymmetric hydrogenations of itaconic acid and its derivatives; in particular, (4*R*-*trans*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis[bis(4'-methoxy-3',5'-dimethylphenyl)phosphine] (MOD-DIOP) bearing both a *p*-methoxy group and two *m,m'*-methyl groups on each phenyl group showed much higher enantioselectivity and catalytic activity than DIOP.

Keywords asymmetric hydrogenation; bisphosphine ligand; rhodium(I) catalyst; modified DIOP; asymmetric catalyst; enantioselectivity

A chiral bisphosphine ligand, DIOP,²⁾ which has a dioxolane framework, is easily obtainable *via* several steps from L-tartaric acid,^{3a,4)} and has been one of the most successful ligands for several types of transition metal-catalyzed asymmetric reactions.⁵⁾ Since the ligand, DIOP, was first synthesized and used for the rhodium(I)-catalyzed asymmetric hydrogenation of (*Z*)- α -acylaminoacrylic acids by Kagan *et al.*,³⁾ it has been widely employed as a ligand for catalytic asymmetric hydrogenations of various kinds of prochiral olefins and ketones, in some of which considerably high enantioselectivities (>80% ee) have been achieved.⁶⁾ However, DIOP-rhodium(I) catalyst did not show excellent enantioselectivity or high catalytic activity in some other asymmetric hydrogenations.^{5,7)} Previously, two groups reported the preparation of (–)-Cy-DIOP⁸⁾ bearing trialkyl-type phosphines,^{8,9)} the neutral rhodium(I) complex of which was found to show much higher catalytic activity than that of the original DIOP for the asymmetric hydrogenation of prochiral carbonyl compounds, such as the amide derivatives of α -keto acids. However, the enantioselectivity was not higher than that of DIOP. Therefore, it was a major target of research to develop modified bisphosphine ligands which would endow their transition metal complexes with both higher catalytic activity and higher enantioselectivity.

In our studies on the development of new efficient ligands for catalytic asymmetric hydrogenations, we proposed the "respective control concept,"^{10,11)} and reported in several communications the syntheses and applications of efficient

chiral bisphosphine ligands, such as BCPM and its derivatives,¹²⁾ DIOCP (1),¹⁰⁾ modified DIOPs,^{13–18)} modified BPPMs,¹⁹⁾ and modified Degphos,²⁰⁾ each of which has at least one electron-rich phosphino group needed for exhibiting the higher catalytic activity as well as better enantioselectivity of the rhodium(I) complex catalysts. A possible key-intermediate in the asymmetric hydrogenation of ketopantolactone using a neutral rhodium(I) complex of BCPM is depicted in Fig. 2, where

Fig. 2

Fig. 3

Fig. 1

the prochiral carbonyl group is oriented *trans* to the dicyclohexylphosphino group at C₄ of the pyrrolidine ring and *cis* to the diphenylphosphino group on the methylene group at C₂. The former (*trans*) phosphino group is an electron-rich one which is considered to have a rate-accelerating function since the interaction of the highest occupied molecular orbital (HOMO) of Rh (d) and the lowest unoccupied molecular orbital (LUMO) of H₂ (σ^*) is important in the oxidative addition of a hydrogen molecule to the rhodium.²¹⁾ The latter (*cis*) is considered to have enantioselecting function since the prochiral carbonyl group is situated near the phosphino group and the stereochemistry of the prochiral carbonyl group coordinated to the Rh is strongly affected by the chiral environment formed by the face and the edge of the diphenyl groups on the phosphino group. A more favorable transition state of oxidative addition of hydrogen was estimated as I in Fig. 3 by calculation of the energy levels of I and II on the basis of the extended Hückel molecular orbital (EHMO).²²⁾

We describe here in detail the syntheses of DIOCP (1) and modified DIOPs (13–17, 25) designed on the basis of our concept, and their use in rhodium(I)-catalyzed asymmetric hydrogenations of ketopantolactone, itaconic acid and its ester, and its β -aryl-substituted analogs; all the hydrogenation products are useful optically active building blocks for the synthesis of various physiologically active compounds.

Results and Discussion

A new C₂-unsymmetrical DIOP derivative, (4*R*-*trans*)-dicyclohexyl[[5-[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]phosphine {or (4*R*,5*R*)-4-

Fig. 4

(dicyclohexylphosphino)methyl-5-(diphenylphosphino)-methyl-2,2-dimethyl-1,3-dioxolane}, abbreviated as (4*R*, 5*R*)-DIOCP (1), bearing both a dicyclohexylphosphino group and a diphenylphosphino group, was designed as a modification of the original DIOP in order to attain both higher catalytic activity and better enantioselectivity in the rhodium(I)-catalyzed asymmetric hydrogenation. The synthetic route to 1 starting from 2,3-isopropylidene-L-threitol (3) is outlined in Chart 1. The diol 3 was obtained by acetonization of L-tartaric acid ester followed by reduction with lithium aluminum hydride. *O*-Monobenzoylation of 3 was carried out by selective benzylation of its sodium alcoholate with benzyl bromide in the presence of tetrabutylammonium iodide (TBAI) as a phase transfer catalyst. The *O*-monobenzoylated product (4) was isolated in 63% yield by fractional distillation from a small amount of recovered 3 and the *O*,*O'*-dibenzoylated by-product. The remaining free hydroxyl group of 4 was tosylated with tosyl chloride in pyridine to yield 5 quantitatively. Phosphination of 5 was carried out with sodium diphenylphosphide in a mixed solvent of dioxane and tetrahydrofuran (THF), giving the corresponding monophosphino compound (6), which was not isolated but directly oxidized with hydrogen peroxide in methanol. The monophosphine oxide (7) was isolated by column chromatography in 55% overall yield from 5. Several attempts to cleave the benzyl group of 7 by using hydrogenolysis with palladium on carbon were unsuccessful. Fortunately, both debenzoylation of the *O*-benzyl group and hydrogenation of the diphenyl groups on the phosphinyl group were found to proceed smoothly by using Raney nickel catalyst under 70 atm pressure of hydrogen at 70 °C for 20 h to give the dicyclohexylphosphinyl compound (8) in 75% yield. Mesylation of 8 with methanesulfonyl chloride in pyridine gave the mesylate (9) in 82% yield. Subsequent phosphination of 9 was carried out by reaction with lithium diphenylphosphide, affording the phosphinyl compound (10), which was isolated in 50% yield by column chromatography on neutral aluminum oxide. Reduction of the phosphine oxide of 10 was achieved by heating with trichlorosilane in the presence of triethylamine in benzene under an argon atmosphere followed by treatment with aqueous sodium hydroxide. (4*R*,5*R*)-DIOCP (1) was isolated in 43% yield by careful silica gel column chromatography. Since the product was relatively unstable to air-oxidation in a hot organic solvent, the recrystallization

Fig. 5. A New Design Concept for Developing Highly Efficient Chiral Bisphosphine-Rhodium Catalysts

TABLE I. Asymmetric Hydrogenation of Ketopantolactone (**11**) Catalyzed by a Rhodium(I) Complex with (4*R*,5*R*)-DIOCP (**1**) or DIOP

Ligand	[Rh]/[subst.]	atm/ $^{\circ}$ C/h	Convsn./% ^{a)}	$[\alpha]_D^{21-23}$ / ^{c)} (H ₂ O)	Opt. yield/%ee ^{b)} (Confign.)
1	10^{-3}	50/50/45	100	-36.3	72 (<i>R</i>)
	10^{-4}	50/50/45	67	-29.0 ^{c)}	57 (<i>R</i>)
	10^{-3}	15/50/70	100	-37.9	75 (<i>R</i>)
DIOP	10^{-2}	50/50/45	100	-26.5	52 (<i>R</i>)
	10^{-3}	50/50/45	45	-18.5 ^{c)}	37 (<i>R</i>)
Cy-DIOP ^{d)}	2×10^{-3}	15/r.t./12	100	-21.2	45 (<i>R</i>)

a) Determined by GLC analysis. b) Calculated on the basis of the reported value $[\alpha]_D^{20} - 50.7^{\circ}$ ($c=2.05$, H₂O) for pure (*R*)-(-)-pantolactone [E. T. Stiller *et al.*, *J. Am. Chem. Soc.*, **62**, 1785 (1940)]. c) Corrected on the basis of the ratio of the product to the remaining substrate. d) K. Yamamoto *et al.*, *Chem. Lett.*, **1984**, 1603.

was carried out from ethanol under an argon atmosphere to give analytically pure (4*R*,5*R*)-(-)-DIOCP (**1**).

Asymmetric hydrogenation of ketopantolactone (**11**) was chosen as a model reaction for evaluation of the capability of DIOCP (**1**) in comparison with DIOP and Cy-DIOP. The hydrogenation was carried out in THF at 50 $^{\circ}$ C under 15–50 atm pressure of hydrogen using the neutral rhodium(I) complex catalyst (molar ratio: Rh/substrate (subst.) = 10^{-4} – 10^{-2}) prepared just prior to use by mixing chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh(COD)Cl]₂) and DIOCP (**1**) (or DIOP) in a molar ratio of 1:2.4 under an argon atmosphere. The results summarized in Table I indicated that DIOCP (**1**)-Rh (subst./Rh = 10^3 , 72% ee) showed higher catalytic activity than DIOP-Rh (subst./Rh = 10^2) and better enantioselectivity than DIOP-Rh (52% ee) and Cy-DIOP-Rh (45% ee, under a milder reaction condition). Although the rate enhancement ($\times 10$) of DIOCP (**1**) compared to DIOP was considerably weaker than that ($\times 10^2$) of BCPM compared to BPPM, these facts suggest that the prochiral keto group

Fig. 6

orients selectively *trans* to the dicyclohexylphosphino group of DIOCP (**1**) in the rate-determining step, and also *cis* to the diphenylphosphino group in the enantioselecting step. Therefore, as one of the possible mechanisms for the asymmetric hydrogenation of ketopantolactone (**11**) cata-

lyzed by bisphosphine-neutral rhodium(I) complexes, the oxidative addition of a hydrogen molecule to the catalyst-substrate complexes seems to be the most important rate-determining and enantioselecting step. Thus, we have shown for the first time that loss of the symmetry of C_2 -symmetric type ligand such as DIOP could improve not only the catalytic activity but also the enantioselectivity of its rhodium complex. Thus the respective control concept for the design of highly efficient chiral bisphosphine ligands was recognized to have general utility, being capable of improving even C_2 -symmetric bisphosphine ligands.

DIOCP (**1**) and BCPMs bearing both a dicyclohexylphosphino group and a diphenylphosphino group are unsymmetrical in the steric as well as electronic sense. Symmetric or unsymmetric *para*-substituted DIOPs were reported to give less change of the enantioselectivity in the hydrogenation of (*Z*)- α -acylaminoacrylic acids than *ortho*- or *meta*-substituted ones.^{3b,23,24} However, the net role of the electronic effects of the phosphino groups on the enantioselectivity in asymmetric hydrogenations has not been clarified. Therefore, we prepared *para*-substituted DIOP derivatives (**13**–**16**) in order to elucidate the electronic effects of the phosphino groups on the enantioselectivity and the catalytic activity of their rhodium(I) complexes. Since *para*-substituted DIOPs are sterically more C_2 -symmetric than DIOCP (**1**), the electronic effect of the phosphino groups on the enantioselectivity was expected to be more easily elucidated with less regard to the steric effect.

Symmetrically substituted DIOP derivatives, **13** and **14**, bearing *p*-dimethylamino groups and *p*-methoxy groups, respectively, were synthesized by the reaction of a ditosylate (**18**) with the lithium salt of the corresponding diarylphosphine, and unsymmetrically substituted ones, **15** and **16**, were prepared by the reaction with lithium diphenylphosphide, followed by the reaction with the corresponding lithium diarylphosphide (Chart 3).

Asymmetric hydrogenations of ketopantolactone (**11**), itaconic acid (**21**),²⁵ and dimethyl itaconate (**23**)²⁵ were selected for evaluation of the effects of the *p*-substituents on the catalytic activity and the enantioselectivity of the

rhodium(I) complex catalysts. The neutral rhodium(I) complex was prepared just prior to use by mixing $[\text{Rh}(\text{COD})\text{Cl}]_2$ and each modified DIOP (**13**, **14**, **15**, or **16**). All the hydrogenations were carried out in the presence of 0.1 mol% of the neutral rhodium(I) complexes of modified DIOPs (**13**–**16**). The hydrogenations of itaconic acid (**21**) and dimethyl itaconate (**23**) were run under atmospheric pressure of hydrogen at 30 °C for 20 h and for 4 h, respectively. The results summarized in Tables II and III show that the rhodium(I) complexes of **13**, **14**, **15**, and **16** have higher catalytic activities and better enantioselectivities than that of DIOP. In the hydrogenations of itaconic acid and dimethyl itaconate, dramatic effects of the *para*-dimethylamino and *para*-methoxy groups of the ligands (**13**–**16**) were observed on the activities and enantioselectivities of the catalysts.

The α -acylamino or α -acyloxy group of (*Z*)- α -acylaminoacrylic acids or enol esters is important for forming a rigid chelation ring with rhodium(I), and electronegative substituents at the α position to the olefin are also recognized to be significant for rigid coordination to rhodium(I).²⁶ The latter implies that the complex formation is controlled by back donation from the rhodium (d-orbital) to the olefin group (π^* -orbital).²⁷ Our results may imply that electron-rich phosphine is important for forming rigid chelation of electron-deficient olefins with rhodium(I) at the *trans* position to the phosphino group, resulting in higher enantioselectivity by the diarylphosphino group oriented *cis* to the prochiral groups, and is also significant for accelerating the oxidative addition of a hydrogen molecule to the rhodium(I), resulting in higher catalytic activity. Furthermore, these facts may suggest that in the use of the ligands, **15** and **16**, the prochiral olefin group orients predominantly *trans* to the more electron-rich

TABLE III. Asymmetric Hydrogenation of Itaconic Acid (**21**) and Dimethyl Itaconate (**23**) with (4*R*,5*R*)-DIOPs–Rhodium(I) Complex

Ligand	Substrate			
	Itaconic acid (21) ^a		Dimethyl itaconate (23) ^b	
	Convsn./% ^c	Opt. yield/%ee ^d	Convsn./% ^e	Opt. yield/%ee ^f
13	100	70 (S)	100	53 (S)
14	100	70 (S)	—	—
15	100 ^g	67 (S)	100	42 (S)
16	100	65 (S)	—	—
17	100	76 (S)	100	55 (S)
DIOP	7	—	30	7 (S) ^h

a) $[\text{NEt}_3]/[\text{subst.}] = 1$, 30 °C, 20 h. b) 30 °C, 4 h. c) Determined by ¹H-NMR analysis. d) Calculated on the basis of the optical rotation value of pure enantiomer, (*R*)-(+)-methylsuccinic acid; $[\alpha]_D^{20} + 16.88^\circ$ ($c = 2.16$, EtOH). e) Determined by GLC analysis. f) Calculated on the basis of the maximum optical rotation value for (*S*)-(–)-methylsuccinic acid dimethyl ester; $[\alpha]_D^{20} - 6.86^\circ$ (neat) determined by HPLC analysis. g) $[\text{NEt}_3]/[\text{subst.}] = 2$. h) Corrected on the basis of the ratio of the product to the remaining substrate.

TABLE II. Asymmetric Hydrogenation of Ketopantolactone (**11**) Catalyzed by Modified (4*R*,5*R*)-DIOPs–Rhodium(I) Complex

Ligand	Convsn./% ^a	Opt. yield/%ee ^b (Config.)
13	100	46 (R)
14	100	55 (R)
15	100	45 (R)
16	100	53 (R)
17	100	53 (R)
DIOP	55	37 (R)

a) Determined by GLC analysis. b) Calculated on the basis of the reported value $[\alpha]_D^{20} - 50.7^\circ$ ($c = 2.05$, H₂O) for pure (*R*)-(-)-pantolactone [E. T. Stillier *et al.*, *J. Am. Chem. Soc.*, **62**, 1785 (1940)].

Chart 4

phosphino group, and necessarily *cis* to the diphenylphosphino group in the rate-determining and enantioselecting step.

As an application of the concept to develop more efficient chiral ligands, we prepared another unsymmetrical ligand **17** bearing a bis(3-methylphenyl)phosphino group on one side in order to enhance enantioselectivity (Chart 3). The neutral rhodium(I) complex of **17** showed somewhat higher enantioselectivities than those of **13** and **15** and comparable catalytic activities in the hydrogenations of **21** and **23** (Table III).

Thus, we have demonstrated that electron-rich phosphines play an important role in enantioselectivity and catalytic activity of the rhodium(I) complex catalysts; the respective control concept (depicted in Fig. 5) is applicable to the *para*-substituted DIOP analogs that are sterically more C_2 -symmetrical than DIOCP (**1**), and the concept is potentially useful for developing highly efficient chiral biphosphine ligands from other C_2 -symmetrical ones bearing two diphenylphosphino groups.

On the basis of the above results, electron-donating groups on the diphenylphosphino group were considered to enhance the catalytic activity and the enantioselectivity of the rhodium(I) complex, and in addition *meta*-methyl groups having a small electron-donating effect were expected to increase the enantioselectivity sterically and electronically. We considered that the introduction of both an electron-donating group at the *para* position and two methyl groups at the *meta* positions on each phenyl group of DIOP would provide efficient biphosphine ligands having better enantioselectivity and higher catalytic activity in the rhodium(I)-catalyzed asymmetric hydrogenations. Therefore, we designed a new modified DIOP (**25**) bearing a *p*-methoxy group and *m,m'*-dimethyl groups on each phenyl group (Fig. 7).

The modified biphosphine ligand, (4*R*-*trans*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis[bis(4'-methoxy-3',5'-dimethylphenyl)phosphine] {or (4*R*,5*R*)-4,5-bis[[bis(4'-methoxy-3',5'-dimethylphenyl)phosphino]-methyl]-2,2-dimethyl-1,3-dioxolane}, abbreviated as (4*R*,5*R*)-MOD-DIOP (**25**) was prepared by the reaction of

trans: [PAr₂] → electron-donating factor *cis*: [PAr₂] → steric factor

Fig. 7

Chart 5

a ditosylate **18** with lithium bis(4-methoxy-3,5-dimethylphenyl)phosphide formed *in situ* from bis(4-methoxy-3,5-dimethylphenyl)phosphine and *n*-butyllithium in THF (Chart 3).

A preliminary asymmetric hydrogenation was carried out with itaconic acid (**21**) and dimethyl itaconate (**23**) in the presence of 0.1 mol% of the rhodium(I) complex of **25** in methanol under the conditions shown in Table IV. The rhodium(I) complexes of **25** were found to show much better enantioselectivity and higher catalytic activity than those of DIOP, and the cationic rhodium (Rh⁺) complex showed somewhat higher enantioselectivity.

The analogs (**26a—d**) of itaconic acid half-ester bearing β -aryl groups were also hydrogenated in similar manners, as shown in Chart 5 and Table V. The rhodium(I) complex of **25** showed very high enantioselectivity, giving rise to

TABLE IV. Asymmetric Hydrogenation of Itaconic Acid (**21**) and Dimethyl Itaconate (**23**) with (4*R*,5*R*)-MOD-DIOP (**25**)-Rhodium(I) Complex

Substrate	Rh ^{a)}	Convsn./%	Opt. yield/%ee
Itaconic acid (21)	Rh ^N	100 ^{b)}	86 (S)
	Rh ⁺	100 ^{c)}	91 (S)
Dimethyl itaconate (23)	Rh ^N	100 ^{d)}	41 (S)
	Rh ⁺	100 ^{d)}	79 (S)

a) Rh^N = 1/2[Rh(COD)Cl]₂ + MOD-DIOP (**25**); Rh⁺ = [Rh(COD) (**25**)]⁺BF₄⁻.

b) 30 °C, 20 h. c) 30 °C, 2 h. d) 30 °C, 4 h.

TABLE V. Asymmetric Hydrogenation of Arylidene succinic Acid Monomethyl Esters (**26a—d**) with (4*R*,5*R*)-MOD-DIOP (**25**)-Rhodium(I) Complex

Substrate	Convsn./%	Product		
Ar	% ^{a)}	[α] _D ²²⁻²³ (MeOH)	ee/% ^{b)}	Confign.
(26a)	100	27a -26.3° (c=2.00)	90 (86) ^{e)}	S
	100 ^{d)}	-27.3° (c=2.02)	94 (90) ^{e)}	S
(26b)	100	27b -26.2° (c=1.10)	91 (90) ^{e)}	S
(26c)	100	27c -28.8° (c=1.14)	94	(S) ^{g)}
(26d)	100 ^{f)}	27d -40.1° (c=2.01)	78	(S) ^{g)}

a) Determined by ¹H-NMR analysis. b) Determined by HPLC analysis of its

morpholine amide derivative, O=C(NC₄H₈)CH₂CH(CH₂Ar)CO₂Me, on Chiralcel OC

(Daicel). c) Calculated on the basis of the maximum rotation [α]_D²⁰ -30.5° (c=1.35, methanol) for the pure *S*-enantiomer [E. Brown and A. Daugan, *Tetrahedron Lett.*, **26**, 3997 (1985)]. d) [Rh] = 1/2[Rh(COD)Cl]₂ + (4*R*,5*R*)-MOD-DIOP (**25**).

e) Calculated on the basis of the maximum optical rotation [α]_D²⁰ -29° (c=1.1, methanol) for the pure *S*-enantiomer [E. Brown and A. Daugan, *Tetrahedron Lett.*, **27**, 3719 (1986)]. f) [Rh]/[subst.] = 4 × 10⁻³. g) The absolute configuration was

considered as *S* based on a comparison of the optical rotation (levorotatory) with those of the other analogs.

(*S*)-arylmethyl-substituted succinic acid half-esters (**27a—c**) in high optical yields (90–94% ee), except for the 1-naphthyl-substituted one (**27d**). The hydrogenation products **27a—b** are useful intermediates for the synthesis of the “non-natural” antipode of lignan lactones. Since the antipode of **25** is easily obtainable from *D*-tartaric acid, the present method allows a simple, efficient, and large-scale preparation of the key intermediates for various naturally occurring, optically active lignan derivatives.^{15–17,28}

Conclusion

We modified DIOP in an attempt to develop highly efficient asymmetric catalysts on the basis of our design concept, and found that 1) DIOCP (**1**) bearing both a dicyclohexylphosphino group and a diphenylphosphino group was a very efficient ligand for rhodium(I)-catalyzed asymmetric hydrogenation of ketopantolactone; 2) DIOP derivatives (**13—17**) bearing *p*-electron-donating groups were better ligands than the original DIOP in the hydrogenations of electron-deficient olefins such as itaconic acid and its ester; 3) MOD-DIOP (**25**) bearing both a *p*-methoxy group and *m,m'*-dimethyl groups was a very efficient ligand for the rhodium(I)-catalyzed asymmetric hydrogenation of itaconic acid and its derivatives. The present methodology may be useful for developing highly efficient chiral bisphosphine ligands from many other ligands bearing diphenylphosphino groups.

Experimental

All melting points and boiling points are uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectrometers employed in this study were Hitachi R-24 (60 MHz) and JEOL FX-90Q (90 MHz) instruments. Chemical shifts were recorded in δ values with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Gas-liquid chromatography (GLC) analyses were conducted on a Hitachi 163 gas chromatograph equipped with a 1 m $\times$ 3 mm column of 10% Poly(ethylene glycol) (PEG) 20M or 10% Silicone GE SE-30 supported on Chromosorb W (AW-DMCS) (80–100 mesh). Chiral high-performance liquid chromatography (HPLC) analyses for the determination of enantiomeric excess were carried out with a JASCO HPLC assembly consisting of a JASCO Trirotar-V HPLC pump, a JASCO Uvidec-100-V UV spectrophotometer, equipped with a Shimadzu Chromatopack C-R6A integrator using a chiral stationary phase column, Chiralcel OC (Daicel Chemical Industries, Ltd.).

Materials THF was purified by distillation from sodium benzophenone ketyl immediately prior to use. All other solvents and reagents were obtained commercially in high purity and were used without further purification unless otherwise indicated. Ketopantolactone (**11**) (Fuji Chemical Industries, Ltd.) and itaconic acid (**21**) (Wako Pure Chemical Industries, Ltd.) were purified by recrystallization. Dimethyl itaconate (**23**) (Tokyo Chemical Industry Co., Ltd.) was distilled prior to use. Arylidene succinic acid monomethyl esters (**26a—d**) were prepared by the condensation of dimethyl succinate with the corresponding substituted benzaldehydes and 1-naphthaldehyde in the presence of sodium methoxide or lithium methoxide according to the previous method (Stobbe condensation),²⁹ and were purified by recrystallization. Column chromatography was carried out on silica gel, Merck Kieselgel 60 (70–230 mesh) or Wakogel C-200 (100–200 mesh) unless otherwise indicated.

2,3-O-Isopropylidene-L-threitol (3) This compound was prepared from diethyl L-tartrate according to the reported method^{4,30}; bp 150–152 °C/1 mmHg, $[\alpha]_D^{25} -8.2^\circ$ ($c=8.14$, methanol) (Lit.,⁴) bp 88–90 °C/0.02 mmHg).

(4*S*,5*S*)-4-(Benzyloxy)methyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (4) Sodium hydride (ca. 60% content, suspension in oil) (1.14 g, 35.3 mmol) was washed three times with hexane by decantation, and suspended in dry THF (50 ml). To the stirred suspension was added dropwise a solution of **3** (5.16 g, 32 mmol) in dry THF (50 ml), and the mixture was heated under reflux for 1 h. Then the mixture was cooled in an ice bath, and tetrabutylammonium iodide (0.6 g) was added. A solution

of benzyl bromide (5.99 g, 35 mmol) in dry THF (50 ml) was added dropwise, and the whole mixture was stirred at room temperature overnight. The resulting precipitates were filtered off, and the filtrate was concentrated *in vacuo*. The residue was extracted several times with ether. The combined extracts were washed with brine, and dried over anhydrous MgSO₄. Evaporation of the solvent left a yellow oil. GLC analysis (column, SE 30) showed the presence of two components (*O*-monobenzyloxy and *O,O'*-dibenzyloxy products) in a ratio of ca. 5:2. The oily mixture was fractionally distilled to give **4** (5.05 g, 63%); bp 155 °C/4 mmHg (bulb-to-bulb), $[\alpha]_D^{25} +8.2^\circ$ ($c=1.00$, chloroform). *Anal.* Calcd for C₁₄H₂₀O₄: C, 66.65; H, 7.99. Found: C, 66.58; H, 7.99. ¹H-NMR (CDCl₃) δ : 1.40 (6H, s), 2.54 (1H, brs), 3.42–3.79 (4H, m), 3.80–4.19 (2H, m), 4.56 (2H, s), 7.31 (5H, brs).

(4*S*,5*S*)-4-(Benzyloxy)methyl-2,2-dimethyl-5-[(4'-methylphenyl)sulfonyloxy]methyl-1,3-dioxolane (5) Compound **4** (3.12 g, 12.4 mmol) was dissolved in dry pyridine (5 ml) and chilled to –30 °C. To the stirred solution, *p*-toluenesulfonyl chloride (3.53 g, 18.5 mmol) was added in three portions, and the stirring was continued at –30 °C overnight. The reaction mixture was poured into ice water, and extracted twice with dichloromethane. The combined extracts were washed successively with saturated NaHCO₃ and brine, and dried over anhydrous MgSO₄. After removal of the solvent, the resulting oily residue was purified by silica gel column chromatography using benzene–ethyl acetate (9:1) as the eluent to afford **5** (4.92 g, 98%); $[\alpha]_D^{25} -9.8^\circ$ ($c=1.10$, chloroform). *Anal.* Calcd for C₂₁H₂₆O₆S: C, 62.05; H, 6.44. Found: C, 62.47; H, 6.51. ¹H-NMR (CDCl₃) δ : 1.33 (3H, s), 1.36 (3H, s), 2.42 (3H, s), 3.40–3.73 (2H, m), 3.85–4.32 (4H, m), 4.53 (2H, s), 7.31 (5H, brs), 7.29 (2H, d, $J=8.4$ Hz), 7.76 (2H, d, $J=8.4$ Hz).

(4*S*,5*R*)-4-(Benzyloxy)methyl-5-(diphenylphosphinyl)methyl-2,2-dimethyl-1,3-dioxolane (7) A mixture of sodium metal (566 mg, 24.6 mmol) and chlorodiphenylphosphine (2.17 g, 9.84 mmol) in dry degassed 1,4-dioxane (30 ml) was stirred and heated for 3 h under an argon atmosphere, resulting in a yellow suspension. After cooling, the reaction mixture was diluted with dry THF (10 ml) and chilled on an ice-bath. A solution of **5** (2.00 g, 4.92 mmol) in dry THF (20 ml) was added and the whole mixture was stirred at ice-bath temperature for 2 h, and then at room temperature overnight. The resulting mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was extracted twice with ethyl acetate, and the combined extracts were washed successively with water and brine, and dried over anhydrous MgSO₄. Removal of the solvent gave an oily residue containing the diphenylphosphination product (**6**), which was dissolved in methanol (30 ml) and chilled on an ice-bath. To the stirred solution was added dropwise aqueous hydrogen peroxide (10%) (6.70 g), and the mixture was stirred for 30 min. After removal of the organic solvent, the residue was poured into water (50 ml), and extracted twice with dichloromethane. The combined extracts were dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was subjected to column chromatography using ethyl acetate–ethanol (95:5) as the eluent to afford **7** (1.19 g, 55%) as a white solid. Recrystallization from ethanol–isopropyl ether gave fine needles; mp 91–92 °C, $[\alpha]_D^{25} +1.90^\circ$ ($c=3.00$, chloroform). *Anal.* Calcd for C₂₆H₂₉O₄P: C, 71.55; H, 6.70. Found: C, 71.65; H, 6.70. ¹H-NMR (CDCl₃) δ : 1.28 (3H, s), 1.31 (3H, s), 2.54–2.85 (2H, m), 3.48–3.71 (2H, m), 3.91–4.36 (2H, m), 4.51 (2H, s), 7.28 (5H, brs), 7.21–8.01 (10H, m).

(4*S*,5*R*)-5-(Dicyclohexylphosphino)methyl-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (8) Raney nickel (R-205, slurry in water, Nikko Rika Co., Ltd.) (4.00 g) was washed three times with ethanol by decantation. The catalyst slurry was poured into an autoclave (100 ml) with ethanol (25 ml), and compound **7** (2.00 g, 4.58 mmol) was placed in it. The hydrogenation was carried out under 70 atm pressure of hydrogen at 70 °C for 20 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate–ethanol, 4:1) to give **8** (1.23 g, 75%) as needles; mp 81–82 °C, $[\alpha]_D^{25} +22.2^\circ$ ($c=1.00$, chloroform). *Anal.* Calcd for C₁₉H₃₅O₄P: C, 63.66; H, 9.84. Found: C, 63.79; H, 9.94. ¹H-NMR (CDCl₃) δ : 1.38 (3H, s), 1.40 (3H, s), 0.99–2.46 (24H, m), 3.56–3.95 (3H, m), 4.05–4.42 (1H, m), 5.00–5.35 (1H, br).

(4*S*,5*R*)-5-(Dicyclohexylphosphinyl)methyl-2,2-dimethyl-4-(methylsulfonyloxy)methyl-1,3-dioxolane (9) A solution of **8** (927 mg, 2.59 mmol) in dry pyridine was chilled on an ice bath. Methanesulfonyl chloride (1.48 g, 12.9 mmol) was added dropwise to the stirred solution. The mixture was allowed to warm to room temperature and stirred overnight, then poured into ice water (50 ml), and extracted twice with ethyl acetate. The combined extracts were washed successively with saturated NaHCO₃ and brine, and dried over anhydrous MgSO₄. After removal of the solvent,

the residue was subjected to column chromatography (ethyl acetate–ethanol, 4:1) to give **9** (932 mg, 82%) as a solid, which was further purified by recrystallization from isopropyl ether; mp 91.5–92.5 °C. ¹H-NMR (CDCl₃) δ: 1.43 (6H, s), 1.06–2.16 (24H, m), 3.08 (3H, s), 3.93–4.41 (2H, m), 4.41–4.58 (2H, m).

(4*R*,5*R*)-4-(Dicyclohexylphosphinyl)methyl-5-(diphenylphosphino)-methyl-2,2-dimethyl-1,3-dioxolane (10) Diphenylphosphine (597 mg, 3.31 mmol) was dissolved in dry THF (10 ml) under an argon atmosphere, and the solution was stirred and chilled to –30 °C. *n*-Butyllithium (1.6 M in hexane, 2.2 ml, 3.5 mmol), was added, and the mixture was stirred at –30 °C for 15 min. To the resulting red solution was added dropwise a solution of **9** (693 mg, 1.59 mmol) in dry THF (10 ml). After stirring at –30 °C for 1 h and then at ice-bath temperature for 30 min, the reaction mixture was concentrated *in vacuo*. The residue was subjected to column chromatography on neutral aluminium oxide (70–230 mesh, Merck) using benzene–ethyl acetate (1:1) as the eluent to afford **10** (418 mg, 50%) as a white solid, which was appreciably sensitive to air in solution (the compound was partly oxidized during isolation by column chromatography). Since the product was determined to be almost pure by thin layer chromatography (TLC) and ¹H-NMR analysis, it was used in the succeeding reaction without further purification. ¹H-NMR (CDCl₃) δ: 1.28 (3H, s), 1.35 (3H, s), 1.01–2.19 (24H, m), 2.44 (2H, d, *J* = 5.9 Hz), 3.53–3.85 (1H, m), 3.98–4.36 (1H, m), 7.16–7.64 (10H, m).

(4*R*,5*R*)-4-(Dicyclohexylphosphino)methyl-5-(diphenylphosphino)-methyl-2,2-dimethyl-1,3-dioxolane [(4*R*,5*R*)-DIOCP, **1]** A solution of the compound **10** (287 mg, 0.55 mmol) and triethylamine (550 mg, 5.44 mmol) in dry benzene (10 ml) was cooled in an ice bath. A solution of trichlorosilane (368 mg, 2.72 mmol) in dry benzene (2 ml) was added, and the mixture was heated under reflux for 2 h in an argon atmosphere. Then the reaction mixture was cooled in an ice-bath and diluted with benzene (10 ml). Aqueous 25% NaOH (20 ml) was added cautiously to the cooled mixture in small portions with vigorous stirring, and the whole was heated at 80 °C under an argon atmosphere until the two layers became clear. The organic layer was separated, washed successively with water, brine, and saturated NaHCO₃, and dried over MgSO₄. After removal of the solvent, the residue was subjected to column chromatography using benzene–ethyl acetate (98:2) as the eluent to give DIOCP (**1**) (120 mg, 43%) as a viscous oil, which was kept in a refrigerator overnight to afford a white solid. Recrystallization from ethanol under an argon atmosphere gave fine needles; mp 52.5–54 °C, $[\alpha]_D^{25} -24.1^\circ$ (*c* = 0.80, benzene). Anal. Calcd for C₃₁H₄₄O₂P₂: C, 72.92; H, 8.68 Found: C, 72.78; H, 8.48. ¹H-NMR (CDCl₃) δ: 1.37 (3H, s), 1.38 (3H, s), 0.80–1.93 (24H, m), 2.19–2.78 (2H, m), 3.56–4.14 (2H, m), 7.13–7.62 (10H, m).

(4*R*,5*R*)-2,2-Dimethyl-4,5-bis[(4'-methylphenyl)sulfonyloxy]methyl-1,3-dioxolane (18**)** Compound **18** was prepared according to the literature procedure; mp 92–92.5 °C (Lit.,⁴⁾ 91.5–92.5 °C).

(4*R*,5*S*)-4-(Diarylphosphino)methyl-2,2-dimethyl-5-[(4'-methylphenyl)sulfonyloxy]methyl-1,3-dioxolane (19**, **20**)** Preparation of compound **19** has been reported,²³⁾ but the product had not been purified. Bis(3-methylphenyl)phosphine was prepared according to the reported procedure.³¹⁾ We prepared **19** and **20** according to the reported method.²³⁾ Purification of the product was carried out by column chromatography (benzene–ethyl acetate, 98:2–98:5). **19**: a viscous oil. ¹H-NMR (CDCl₃) δ: 1.28 (3H, s), 1.38 (3H, s), 2.32–2.53 (2H, m), 2.43 (3H, s), 3.76–4.32 (4H, m), 7.29–7.90 (14H, m). **20**: a viscous oil; $[\alpha]_D^{22} -24.6^\circ$ (*c* = 1.11, benzene). Anal. Calcd for C₂₈H₃₃O₅PS: C, 65.61; H, 6.49. Found: C, 65.27; H, 6.45. ¹H-NMR (CDCl₃) δ: 1.23 (3H, s), 1.35 (3H, s), 2.30 (6H, s), 2.39 (3H, s), 2.23–2.51 (2H, m), 3.68–4.29 (4H, m), 7.02–7.41 (10H, m), 7.70 (2H, d, *J* = 8 Hz).

Synthesis of Modified DIOPs (13–17, 25) By a similar procedure to that described for the synthesis of **10**, modified DIOPs were prepared from **18**, **19**, or **20** and diarylphosphines. The diarylphosphines, bis[4-dimethylamino]phenyl]phosphine,³²⁾ bis(4-methoxyphenyl)phosphine,³¹⁾ bis(3-methylphenyl)phosphine,³¹⁾ and bis(4-methoxy-3,5-dimethylphenyl)phosphine,¹⁴⁾ were prepared according to the procedures described in the cited literature. The bisphosphine ligands **13**, **15**, and **17** were purified by column chromatography on neutral aluminium oxide (Merck) using toluene–ethyl acetate (50:1–25:1) as the eluent. The ligands **14**, **16**, and **25** were purified by column chromatography on silica gel (Wako gel) using benzene–ethyl acetate (95:5–90:10) as the eluent. Physical and analytical data for each modified DIOP were consistent with the structures. **13**: an amorphous solid, $[\alpha]_D^{24} +23.4^\circ$ (*c* = 1.8, benzene). Anal. Calcd for C₃₉H₅₂N₄O₂P₂: C, 69.83; H, 7.81, N, 8.35. Found: C, 69.97; H, 7.72; N, 8.06. ¹H-NMR (CDCl₃) δ: 1.35 (6H, s), 2.10–2.60 (4H, m), 2.94 (24H, s), 3.60–3.90 (2H, m), 6.56–6.81 (8H, m), 7.18–7.50 (8H, m). **14**: a

viscous oil. Anal. Calcd for C₃₅H₄₀O₆P₂: C, 67.95; H, 6.52. Found: C, 67.78; H, 6.41. ¹H-NMR (CDCl₃) δ: 1.32 (6H, s), 2.20–2.40 (4H, m), 3.60–4.00 (2H, m), 3.75 (12H, s), 6.80 (8H, d, *J* = 8 Hz), 7.18–7.50 (8H, m). **15**: a viscous oil; $[\alpha]_D^{20} -1.70^\circ$ (*c* = 3.2, benzene). Anal. Calcd for C₃₅H₄₂N₂P₂: C, 71.90; H, 7.24; N, 4.79. Found: C, 71.47; H, 7.10; N, 4.49. ¹H-NMR (CDCl₃) δ: 1.34 (6H, s), 2.10–2.70 (4H, m), 2.93 (12H, s), 3.70–4.00 (2H, m), 6.50–6.75 (4H, m), 7.10–7.60 (14H, m). **16**: a viscous oil. Anal. Calcd for C₃₃H₃₆O₄P₂: C, 70.96; H, 6.50. Found: C, 71.60; H, 6.57. ¹H-NMR (CDCl₃) δ: 1.25 (3H, s), 1.35 (3H, s), 2.20–2.45 (4H, m), 3.70–4.00 (2H, m), 6.85 (4H, d, *J* = 8 Hz), 7.20–7.70 (14H, m). **17**: a viscous oil, $[\alpha]_D^{20} +8.4^\circ$ (*c* = 1.1, benzene). Anal. Calcd for C₃₇H₄₆N₂O₂P₂: C, 72.53; H, 7.57; N, 4.57. Found: C, 72.75; H, 7.49; N, 4.56. ¹H-NMR (CDCl₃) δ: 1.35 (6H, s), 2.31 (6H, s), 2.04–2.51 (4H, m), 2.92 (12H, s), 3.59–3.97 (2H, m), 6.42–6.76 and 6.89–7.44 (16H, m). **25**: mp 128–129 °C (ethanol), $[\alpha]_D^{21} +14.4^\circ$ (*c* = 1.08, benzene). Anal. Calcd for C₄₃H₅₆O₆P₂: C, 70.67; H, 7.72. Found: C, 70.81; H, 7.62. ¹H-NMR (CDCl₃) δ: 1.36 (6H, s), 2.24 (24H, s), 1.90–2.58 (4H, m), 3.70 (12H, s), 3.48–3.96 (2H, m), 7.10 (8H, dd, *J* = 3.4, 7.6 Hz).

Catalytic Asymmetric Hydrogenations. General Procedure: Hydrogenation of Ketopantolactone (11) A solution of a neutral rhodium(I) complex catalyst was prepared by mixing [Rh(1,5-cyclooctadiene)Cl]₂ (Kanto Chemical Co., Ltd.) (2.5 mg, 5 × 10^{–3} mmol) and a modified DIOP (**1**, **13**–**17**) (1.2 × 10^{–2} mmol) in dry THF (1 ml) under an argon atmosphere. Ketopantolactone (**11**) (1.281 g, 10 mmol), dry THF (9 ml), and the catalyst solution prepared just prior to use were placed in a 100 ml autoclave. The hydrogenation was carried out under the conditions in Table I. The hydrogenations at other molar ratios of the catalyst to the substrate (10^{–2}–10^{–4}) were similarly performed. The conversion rate of the substrate was determined by GLC analysis (column, PEG 20 M). The product **12** was obtained by distillation (bulb-to-bulb) as a solid, whose optical rotation was measured in H₂O (*c* = ca. 2). The optical yield was calculated by using the maximum optical rotation value $[\alpha]_D^{20} -50.7^\circ$ (*c* = 2.05, H₂O) for pure (*R*)-(–)-pantolactone reported in the literature.³³⁾ The results are summarized in Tables I and II.

Hydrogenation of Itaconic Acid (21) To a solution of itaconic acid (**21**) (651 mg, 5.0 mmol) and triethylamine (506 mg, 5.0 mmol) in degassed methanol (8 ml) was added a solution of the neutral rhodium(I) complex (5 × 10^{–3} mmol) of modified DIOP (**13**–**17**, **25**) in methanol (2 ml), prepared in the same manner as described above. A cationic rhodium(I) complex of **25**, [Rh-(4*R*,5*R*)-MOD-DIOP (**25**)](1,5-cyclooctadiene)⁺BF₄[–], was prepared by the reaction of the neutral rhodium(I) complex with excess sodium tetrafluoroborate according to the reported method.³⁴⁾ When the cationic rhodium(I) complex (5 × 10^{–3} mmol) was used, the catalyst was added to a solution of the substrate and triethylamine in methanol (10 ml). The hydrogenation was carried out under 1 atm of hydrogen with vigorous stirring at 30 °C for 20 h. The reaction mixture was concentrated, and the residue was dissolved in aqueous NaOH (0.5 M, 5 ml) at ice-bath temperature. The insoluble materials were filtered off, and the filtrate was acidified with 6 N hydrochloric acid. After three extractions with ether, the combined extracts were dried over anhydrous MgSO₄, and concentrated *in vacuo* to give the hydrogenation product **22**. The conversion rate of the substrate was determined by ¹H-NMR analysis. The optical yield was calculated on the basis of the maximum optical rotation value $[\alpha]_D^{20} +16.88^\circ$ (*c* = 2.16, EtOH) for (*R*)-(+)-methylsuccinic acid reported in the literature.³⁵⁾ The results are summarized in Tables III and IV.

Hydrogenation of Dimethyl Itaconate (23) To a solution of dimethyl itaconate (**23**) (791 mg, 5.0 mmol) in degassed methanol (8 ml) was added a solution of the neutral rhodium(I) complex (5 × 10^{–3} mmol) of modified DIOP (**13**–**17**, **25**) in methanol (2 ml) prepared in the same manner as above. The hydrogenation was carried out under atmospheric pressure of hydrogen with vigorous stirring at 30 °C for 4 h. The conversion rate of the substrate was determined by GLC analysis (column, PEG 20 M). The hydrogenation product **24** was isolated by distillation (bulb-to-bulb), and the optical yield was calculated on the basis of the maximum optical rotation value $[\alpha]_D^{20} -6.86^\circ$ (neat) reported for (*S*)-(–)-dimethyl methylsuccinate.^{19b)} The results are summarized in Tables III and IV.

Hydrogenation of Arylidene succinic Acid Monomethyl Esters (26a–d) The cationic rhodium(I) complex (2.1 mg, 2.0 × 10^{–3} mmol) of **25** was added to a solution of one of the arylidene succinic acid monomethyl esters (**26a–d**) (1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in methanol (2 ml). The hydrogenation was carried out under atmospheric pressure of hydrogen with vigorous stirring at 30 °C for 40 h, then the reaction mixture was concentrated *in vacuo*. The concentrated residue was dissolved in cold aqueous NaOH (0.5 M, 2 ml), and extracted with

dichloromethane to remove the catalyst. The aqueous layer was acidified with 6M hydrochloric acid, and extracted twice with ether. The combined extracts were dried over anhydrous MgSO_4 , and concentrated. The conversion rate was determined by $^1\text{H-NMR}$ analysis. The absolute configuration and the optical yield of the products **27a–d** were determined by comparing the optical rotation value with the reported data.³⁶⁾ Furthermore, the corrected optical yields of the products were measured by HPLC analysis of the monomorpholine amide derivatives on a chiral column, Chiralcel OC (Daicel), using isopropyl alcohol–hexane (1:1) as the eluent. The results are summarized in Table V. The monomorpholine amide derivatives were prepared as follows. A solution of the hydrogenation product (**27a–d**) (0.5 mmol) in dichloromethane (1.5 ml) was stirred and chilled on an ice bath, and N,N' -dicyclohexylcarbodiimide (103 mg, 0.5 mmol) was added. After 15 min stirring, morpholine (44 mg, 0.5 mmol) was added, and the whole mixture was stirred for another 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (10 ml). The insoluble substances were filtered off, and the filtrate was concentrated to give the corresponding monoamide derivative.

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