C_2-Symmetric Bisphosphinobioxazoline as a Chiral Ligand. Highly Enantioselective Palladium-Catalyzed Allylic Substitutions and Formation of *P,N,N,P* Tetradentate Palladium (II) Complexes

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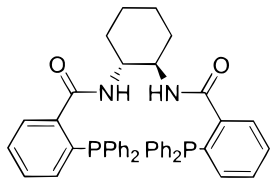
The C_2-symmetric bisphosphinobioxazoline [(*S,S*)-Phos-Biox] **4** was found to be a highly efficient chiral ligand for Pd-catalyzed enantioselective allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate and afforded enantioselectivities of up to 97% ee. Moderate enantioselectivities have been observed in Pd-catalyzed desymmetrizations of *cis*-1,4-bis(benzoyloxy)-cyclopent-2-ene (**12**) with dimethyl malonate (51−78% yield, 38−58% ee) and *N*-benzyl-*N*-methylamine (87% yield, 33% ee) nucleophiles and of biscarbamate **15** of *cis*-1,4-dihydroxycyclopent-2-ene (90% yield, 50% ee). A 1:1 molar mixture of (*S,S*)-Phos-Biox **4** with $Pd(CH_3CN)_2Cl_2$ and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ afforded the *P,N,N,P*-tetradentate Pd(II) complexes **19a** and **19b**, respectively. The structures of the complexes **19a**,**b** were determined by X-ray analysis. The complex **19a** also exhibited high enantioselectivity (86% yield, 92% ee) in allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

Introduction

The Pd-catalyzed asymmetric allylic substitution reactions have attracted considerable attention owing to its potential for the enantioselective formation of new covalent bonds such as carbon−carbon and carbon−nitrogen bonds. The stereochemical course of a metal-catalyzed reaction can be effectively controlled by an appropriate chiral ligand attached to the metal center. Therefore, the search for chiral ligands continues apace and a wide variety of chiral ligands have been developed for Pd-catalyzed allylic substitution reactions.[1] Notably, the C_2-symmetric *P,P*-bidentate phosphine ligands such as **1** or its analogues, derived from C_2-symmetric chiral *trans*-diamines, have been shown by Trost, to be very efficient in a number of examples.[2] The chirality of the chiral scaffold can effectively be transferred to the palladium metal through amide bond. Other interesting chiral ligands are phosphine-oxazoline hybrid ligands (**2**) reported by Pfaltz,[3a] Helmchen,[3b] and Williams[3c] independently. These phosphine-oxazoline hybrid ligands were designed based on the idea that a *P,N*-bidentate ligand



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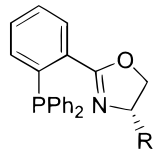

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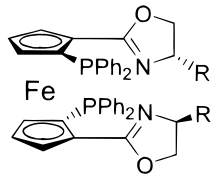

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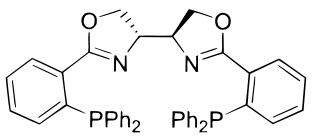

(*S,S*)-Phos-Biox **4**

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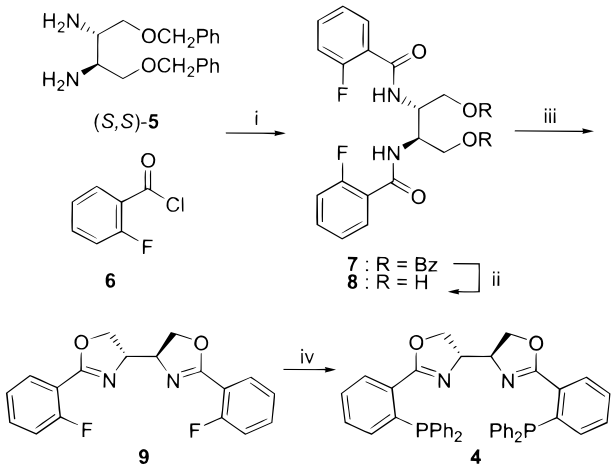
with two electronically different ligating groups could encourage a preferential attack at one of the two termini of the π-allyl complex, and demonstrated to be highly efficient in Pd-catalyzed allylic substitution of acyclic allylic acetate or carbonates.[3] Recently, ferrocene-based C_2-symmetric phosphine-oxazoline hybrid ligand **3**, which also exhibited excellent catalytic efficiency in Pd-catalyzed allylic substitutions, has been reported by Ikeda[4a] and Ahn.[4b] One of the interesting features of ligand **3** is complexation behaviors with Pd(II) metal. Among the several possible chelation modes, the ligand **3** gave a C_2-symmetric 1:2 *P*,*N*-chelate upon treatment with dichlorobis(acetonitrile)palladium(II).[4a] However, it has been found that the chelation mode of ligand **3** with Pd(II) depends on the source of palladium. Thus, with $[(\eta^3\text{-}C_3H_5)PdCl]_2$, a *P*,*P*-chelated complex was obtained.[5]

During our studies on the development of new C_2-symmetric chiral ligands for asymmetric catalysis,[6] we prepared the new type of C_2-symmetric bisphosphinobioxazoline ligand [(*S*,*S*)-Phos-Biox **4**]. The structure of **4** looks similar with Trost's ligand **1** having bioxazoline chiral scaffold and dimeric form of the phosphinooxazoline **2**. The (*S*,*S*)-Phos-Biox **4** has conformationally rigid chiral bioxazoline ring which may restrict the flexibility of the ligand bound to a transition metal. Therefore, it was expected that the chirality of the bioxazoline backbone could be transferred effectively to the metal. Moreover, C_2-symmetry of **4** may provide an additional advantage, i.e., reduce the number of degrees of freedom in the chiral complexes. In a preliminary study for the application of **4** as a chiral ligand, it has exhibited excellent enantioselectivities of up to 97% ee in Rh(I)-catalyzed hydrosilylation of ketones.[6c] These results intrigued us to examine the chiral induction ability of Phos-Biox **4** for Pd-catalyzed asymmetric allylic substitution. Moreover, it is of interest which kinds of chelates are formed with Pd(II) among the several possible combinations such as *P*,*P*-, *P*,*N*-, *P*,*N*,*N*-, *P*,*P*,*N*-, or *P*,*N*,*N*,*P*-chelates. In contrast with **3**, the C_2-symmetric bisphosphinooxazoline ligand **4** formed *P*,*N*,*N*,*P*-tetradentate complex with Pd(II) regardless the source of palladium. Here we report synthesis of Phos-Biox **4**, Pd-catalyzed allylic substitution reactions using **4** as a chiral ligand, and its complexation behavior with Pd(II).

Scheme 1



i) Et_3N, CH_2Cl_2, 0 °C, 80%; ii) $Pd(OH)_2$-C, cyclohexene, EtOAc/EtOH, reflux, 98%; iii) MsCl/Et_3N,CH_2Cl_2, rt, 59%; iv) $KPPh_2$, THF, rt, 46%

Results and Discussion

As shown in Scheme 1, the Phos-Biox **4** has been synthesized straightforwardly from chiral diamine **5**, which was prepared by the reported procedures using L-tartaric acid as a starting material.[7]

The reaction of diamine **5** with 2.5 equiv of 2-fluorobenzoyl chloride in methylene chloride at room temperature afforded diamide **7** in 80% yield after chromatographic purification upon silica gel column (*n*-hexane: ethyl acetate = 6:1 eluent) or recrystallization from diethyl ether. Debenzylation of **7** using Pd−C (5% or 10% Pd) under an atmospheric pressure of H_2 was not accomplished efficiently. The increased hydrogen pressure (40 psi using Par hydrogenation reactor) did not change the reaction profile either. However, when the dibenzyl ether **7** was refluxed for 20 h in the presence of $Pd(OH)_2$-C/cyclohexene in ethyl acetate-methanol (1:1, v/v) solvent, the debenzylated diol **8** was obtained in quantitative yield. Among the various reported reaction conditions for the formation of bisoxazoline rings from bis(hydroxy)-amides,[8] the bis(*o*-fluorophenyl)bioxazoline **9** could be obtained efficiently by the reaction of diol **8** with methanesulfonyl chloride in the presence of triethylamine.[8j] The ring formation occurred simultaneously during mesylation in 59% yield. The reaction of bisfluoride **9** with potassium diphenylphosphide in THF solvent afforded the required bisphosphinobioxazoline **4** in 46% yield after

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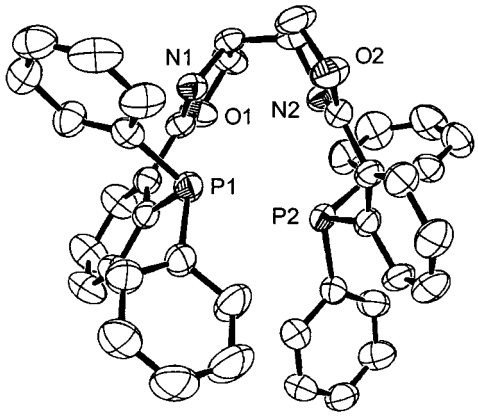
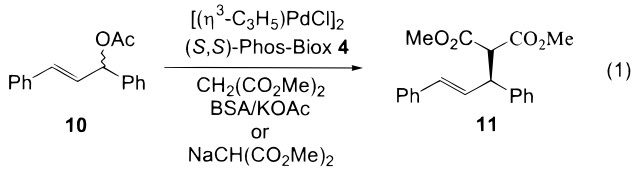


Figure 1. X-ray structure of Phos-Biox **4**.

chromatographic purification on silica gel (*n*-hexane:ethyl acetate = 2:1).[6c] Recrystallization of **4** from methanol-diethyl ether afforded a single-crystal suitable for X-ray crystallography. In solid state, the two oxazoline rings formed U-shaped concave conformation, and two phosphine atoms were placed at the side opposite each other (Figure 1).

Palladium-Catalyzed Allylic Substitution Reactions Using (*S*,*S*)-Phos-Biox 4. To test the effectiveness of (*S*,*S*)-Phos-Biox **4** as a chiral ligand in Pd-catalyzed allylic substitutions, the benchmark reaction between *rac*-1,3-diphenyl-2-propenyl acetate (**10**) and dimethyl malonate has been examined (eq 1).[1,3,4] In a typical run,



(1)

the allylic substrate **10** was treated with a dimethyl malonate derived nucleophile in the presence of [(η^3-C_3H_5)PdCl]$_2$ (1 mol %) and (*S*,*S*)-Phos-Biox **4** (2.5 mol %). The effects of the base, solvent, and temperature were investigated, and the results are summarized in Table 1.

As shown in Table 1, the Phos-Biox **4** exhibited very high efficiency for the Pd-catalyzed allylic substitution reactions. All reactions examined gave very high enantioselectivities (94−97% ee) with almost quantitative chemical yields. The enantiomeric purity was determined by ^{1}H NMR analysis with chiral shift reagent Eu(hfc)$_3$ in which one of the methyl ester groups that appears at δ 3.70 was splitted into two peaks: (*R*)-enantiomer at δ 3.99 and (*S*)-enantiomer at δ 3.93 when 0.8 equiv of the shift reagent was added.[4b,9] The assignment of (*S*)-configuration has been made based on the sign of optical rotation of **11**.[3b,9] The enantioselectivities were not dependent on the methods for the generation of the malonate anion nuclephiles. Instead, although the dependencies were not large, the reactivities at 20 °C were slightly dependent on reaction conditions. The reaction of *rac*-**10** with dimethyl sodiomalonate, generated in situ from $CH_2(CO_2Me)_2$ and NaH, as a nucleophile in CH_2Cl_2 solvent was completed in 1 h, and afforded (*S*)-(−)-**11** in 95% ee and >99% yield (Table 1, entry 1). The reactivity and enantioselectivity were slightly increased in polar THF solvent, and the reaction was completed within 40 min with 97% ee and >99% chemical yield (Table 1, entry 2). At the same reaction temperature, the silyl enol ether generated in situ from dimethyl malonate by the reaction with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in the presence of AcOK in CH_2Cl_2 and THF solvents afforded (*S*)-(−)-**11** in 96% ee and 94% ee, respectively (entries 3 and 4). However, in both CH_2Cl_2 and THF solvents, the reactions proceeded slowly compared with sodium malonate nucleophile and were completed within 3−4 h. By increasing the reaction temperature to 40 °C, the reaction rates were increased in both sodium malonate and *N*,*O*-bis(trimethylsilyl)acetamide reaction conditions without any significant loss of enantioselectivities and chemical yields (Table 1, entries 5−8). The observed reactivity and enantioselectivity using Phos-Biox **4** as a chiral ligand are very comparable with other chiral ligands which exhibited high chiral induction abilities. For examples, the observed reactivities and enantioselectivities in Pd(0)-catalyzed allylic substitution of **10** with malonate nucleophile are similar with those obtained using phosphinooxazolines **2** (where R = *i*-Pr, 98% yield, 98% ee; R = Ph, 99% yield, 99% ee, R = CH_3, 88−98% yield, 89−90% ee, R = *t*-Bu, 94% yield, 95% ee)[3a,c,d] and C_2-symmetric ligand **3** (where R = *t*-Bu, 99% yield, 94% ee).[4]

Having the results that the (*S*,*S*)-Phos-Biox **4** exhibits high asymmetric induction in allylic substitution of acyclic acetate **10**, we next examined the enantiodiscrimination ability of **4** with *meso*-dibenzoate (**12**) of *cis*-2-cyclopenten-1,4-diol for which the methods for the determination of the products configurations and ees were well established by Trost (eq 2).[2b] First, the desymmetrization reactions were carried out with dimethyl malonate anion nucleophile. The effects of Pd/ligand ratio, reaction temperature and base were investigated, and the results are summarized in Table 2 (entries 1−5). Initially, the reaction was performed using 2.5 mol % [(η^3-

Table 1. Pd-Catalyzed Enantioselective Allylic Alkylation of *Rac*-1,3-diphenyl-2-propenyl Acetate with Dimethyl Malonate Using (*S*,*S*)-Phos-Biox 4 as a Chiral Ligand

entry[a]	method[b]	temp (°C)	solvent	time[c]	yield (%)[d]	% ee[e] (config)[f]
1	A	20	CH_2Cl_2	1 h	>99	95 (*S*)
2	A	20	THF	40 min	>99	97 (*S*)
3	B	20	CH_2Cl_2	3 h	>99	96 (*S*)
4	B	20	THF	4 h	96	94 (*S*)
5	A	40	CH_2Cl_2	<30 min	>99	94 (*S*)
6	A	40	THF	<30 min	>99	96 (*S*)
7	B	40	CH_2Cl_2	40 min	>99	95 (*S*)
8	B	40	THF	40 min	>99	94 (*S*)

[a] The ratio of [(η^3-C_3H_5)PdCl]$_2$:ligand:substrate was 1:2.5:100. [b] Method A: reaction of 0.4 mmol of allylic acetate with the sodium salt prepared from 0.8 mmol of dimethyl malonate and 0.87 mmol of NaH in 1 mL of solvent. Method B: reaction of 0.4 mmol of allylic acetate with 0.8 mmol of dimethyl malonate, 1.2 mmol of *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and 4 μmol of KOAc in 1 mL of solvent. [c] The reaction time in which all of the substrate was consumed. [d] Isolated yield. [e] Determined by ^{1}H NMR ($CDCl_3$) analysis with chiral shift reagent Eu(hfc)$_3$ (one of the two methyl ester groups that appears at 3.70 ppm was splitted into two peaks: (*R*)-enantiomer at 3.99 ppm and (*S*)-enantiomer at 3.93 ppm when 0.8 equiv of the shift reagent was added. [f] Determined by comparing the sign of the optical rotation.

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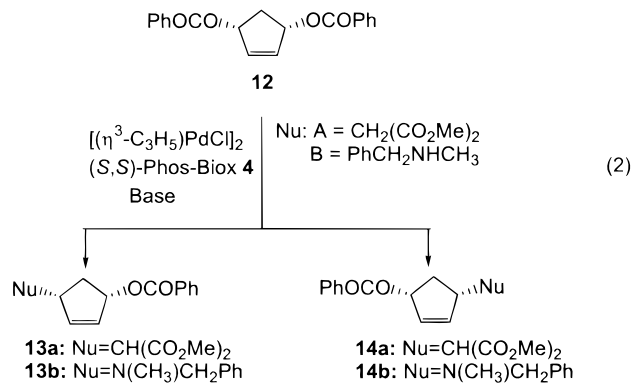
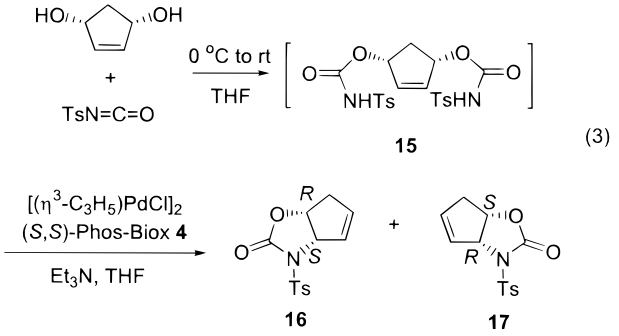
Table 2. Pd-Catalyzed Desymmetrizations of 12 with Dimethyl Malonate (A) and *N*-Benzylmethyl Amine (B) Nucleophiles Using (*S*,*S*)-Phos-Biox 4 as a Chiral Ligand

entry[a]	base (solvent)	*ν*	temp (°C)	yield (%)[c]	**13**:**14** (% ee)[d]	(config)[e]
1[b]	NaH (THF)	A	20	51	69:31 (38)	(1*S*,4*R*)
2	NaH (THF)	A	20	78	77:23 (54)	(1*S*,4*R*)
3	NaH (THF)	A	0	66	79:21 (58)	(1*S*,4*R*)
4	NaH (THF)	A	−78	62	79:21 (58)	(1*S*,4*R*)
5	BSA (CH_2Cl_2)	A	0	68	74:26 (48)	(1*S*,4*R*)
6	Et_3N (THF)	B	0	87	2:1 (33)	(1*S*,4*R*)

[a] The ratio of [(η^3-C_3H_5)PdCl]$_2$:ligand:substrate was 2.5:10:100. [b] The ratio of [(η^3-C_3H_5)PdCl]$_2$:ligand:substrate was 2.5:5:100. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the corresponding mandelic ester,[2b] and confirmed by HPLC using a CHIRALCEL OJ chiral column for entries 1−5. [e] Determined by ^{1}H NMR analysis according to the reported chemical shifts of the vinyl protons.[2b]



C_3H_5)PdCl]$_2$ and 5 mol % **4** at 20 °C during 12 h and afforded a mixture of **13a** and **14a** in 51% yield (Table 2, entry 1). Analysis of the enantioselectivity and the assignment of absolute configuration were performed with differential NMR shifts of the vinyl protons after conversion of the mixture of **13a** and **14a** to its diastereomeric mixture of (*S*)-*O*-methylmandelate according to the reported procedure,[2b] and it turned out that 1*S*,4*R*-isomer **13a** of 38% ee was formed as a major isomer. The enantiomeric excess was also confirmed by HPLC analysis of a mixture of **13a** and **14a** using CHIRALCEL OJ chiral column (2-propanol:*n*-hexane = 1:9 v/v, flow rate: 1 mL/min) in which the retention time of the major isomer **13a** was 18.4 min and the minor isomer **14a** was 13.4 min with 69:31 ratio.[10] Substantial improvements in both yields (78%) and ee (54% ee) occurred upon increasing the amount of ligand **4** to 10 mol % (Table 2, entry 2). The enantioselectivities were slightly increased to 58% ee by lowering the reaction temperature to 0 °C (Table 2, entry 3), but there was no difference between 0 and −78 °C (Table 2, entry 4). The same desymmetrization with the silyl enol ether of malonate generated in situ using BSA in methylene chloride solvent afforded product in 68% yield and 48% ee (74% **13a**, 26% **14a**) (Table 2, entry 5). Under similar reaction conditions, the bisphosphine ligand **1** afforded the same alkylated product with 80% yield and 93% ee (3.5% **13a**, 96.5% **14a**) using $(dba)_3Pd_2{\cdot}CHCl_3$ at 0 °C in THF (compare with entry 3 in Table 2).[2b] There was no sign for the formation of dialkylated product.[11] The desymmetrization of **12** using *N*-benzyl-*N*-methylamine as a nitrogen nucleophile also has been examined.[12] The reaction was performed by addition of 1 equiv of *N*-benzyl-*N*-methylamine and 5-fold excess triethylamine to a solution of 2.5 mol % of [(η^3-C_3H_5)PdCl]$_2$ and 10 mol % of (*S*,*S*)-Phos-Biox **4** in THF at 0 °C and afforded a mixture of **13b** and **14b** in 87% isolated yield (Table 2, entry 5). The absolute configuration and ee of the monoalkylation products **13b** and **14b** were determined by ^{1}H NMR analysis according to the reported method, i.e., conversion of a mixture of **13b** and **14b** to the corresponding diastereomeric *O*-methylmandelate esters by hydrolysis (LiOH, C_2H_5OH, H_2O, 60 °C) followed by acylation with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, room temperature).[2b] Analysis of the ^{1}H NMR spectra indicated that the 1*S*,4*R* isomer **13b** was formed as a major isomer (**13b**:**14b** = 2:1, 33% ee). The observed reactivity (87% yield) is quite comparable with ligand **1** (75−85% yield), however, the enantiodiscrimination ability of (*S*,*S*)-Phos-Biox **4** is inferior than that of the Trost's ligand **1** (73−78% ee of **14b**).[2b]



For the extension of Pd-catalyzed desymmetrization of *meso*-cyclic compounds using (*S*,*S*)-Phos-Biox **4** as a chiral ligand, intramolecular cyclization of biscarbamate **15** of *cis*-2-cyclopenten-1,4-diol has been examined as a standard reaction to form oxazolidin-2-ones **16** and **17** (eq 3). The *cis*-2-cyclopenten-1,4-diol was treated with *p*-toluenesulfonyl isocynate(TsNCO) in THF at 50 °C for 1 h to give the corresponding biscarbamate **15** which was used directly without isolation. A solution of 2.5 mol % [(η^3-C_3H_5)PdCl]$_2$ and 10 mol % Phos-Biox **4** in THF was added at −78 °C, and the reaction was monitored by TLC. After completion of the reaction, a mixture of **16** and **17** was isolated by chromatography on silica gel in 90% yield. The ee and absolute configuration were determined by ^{1}H NMR analysis of the (*S*)-*O*-methylmandelate esters of the hydrolyzed product according to the reported method.[2b] The *R*,*S*-isomer **16** was formed as a major isomer (**16**:**17** = 1:3, 50% ee). It has been reported that, under the similar reaction conditions, the *S*,*R*-**17** was formed as a major isomer in 97% yield and 80% ee using **1** as a chiral ligand.[2a]

Complexation Behavior of (*S*,*S*)-Phos-Biox 4 with Pd(II). In contrast to *P*,*P*- or *P*,*N*-bidentate ligands such

(10) The retention time of the major **13** and minor **14** isomers were determined by comparison of the results obtained by ^{1}H NMR analysis method established by Trost in ref 2b.

(11) Significant dialkylation (32%) was occurred using (*S*)-BINAPO (38% yield, 57% ee of **13**). See (a) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. (b) Mori, M.; Nukui, S.; Shibasaki, M. *Chem. Lett.* **1991**, 1791. (c) For desymmetrization of meso-cyclohexendiol using BINAPO−Pd complex, Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016.

(12) (a) Review for allylic amination: Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (b) Muchow, G.; Brunel, J. M.; Maffei, M.; Pardigon, O.; Buono, G. *Tetrahedron* **1998**, *54*, 10435.

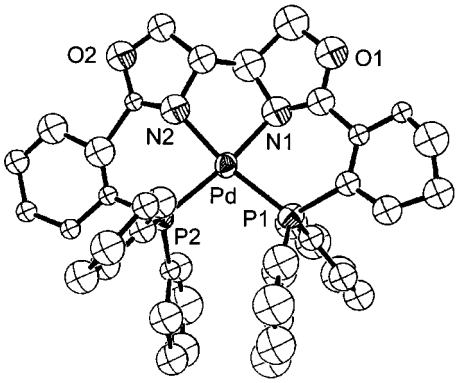
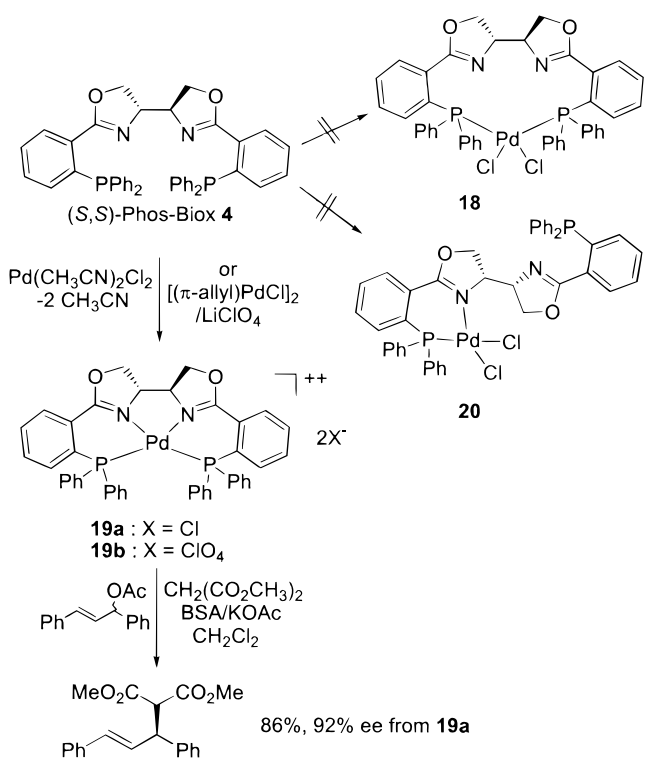


Figure 2. X-ray structure of **19a**. Selected bond lengths (Å) and angles (°): Pd−N(1), 2.03(5); Pd−N(2), 2.05(5); Pd−P(1), 2.23(1); Pd−P2, 2.26(2); N(1)−Pd−N(2), 86(2); N(1)−Pd−P(1), 86(2); P(1)−Pd−P(2), 101.6(5); N(2)−Pd−P(2), 87(1).

as **1** and **2**, the complexation behavior of C_2-symmetric phosphine-oxazoline hybrid ligand **3** with Pd(II) could be complicated since several chelation modes such as *P,P*-, *P,N*-, *P,P,N*-, *P,N,N*-, or *P,N,N,P*-chelates are possible. As mentioned above, the complexation behavior of ligand **3** with Pd(II) depends on the source of palladium. The ligand **3** gave a C_2-symmetric 1:2 *P,N*-chelate upon treatment of dichlorobis(acetonitrile)palladium (II).[4a] However, a 1:1 *P,P*-chelate was formed with $[(\eta^3\text{-}C_3H_5)\text{-}PdCl]_2$.[4b,5] Therefore, it is of interest to investigate the complexation behavior of (*S,S*)-Phos-Biox **4** with different kinds of Pd(II) sources. First, the (*S,S*)-Phos-Biox **4** was treated with 1 equiv of dichlorobis(acetonitrile)palladium (II) in CD_2Cl_2. The diagnostic downfield chemical shift in ^{31}P NMR spectra relative to the free ligand **4** was observed.[13] Thus, only one singlet resonance signal was appeared at δ 31.4, while free ligand **4** exhibited a resonance at δ −1.95 (triphenylphosphine as an external reference). The observed singlet resonance in ^{31}P NMR spectrum suggests that the two phosphorus atoms are magnetically equivalent. In the ^{1}H NMR spectrum, both of the methine (δ 4.38, m, 2H) and methylene (δ 3.87, pseudo d, J = 8.2 Hz, 4H) resonance signals of the bioxazoline ring of the free ligand **4** were shifted to downfield (δ 5.62 and δ 5.33, respectively), and the C_2-symmetry of these proton signals was maintained. Moreover, 2 equiv of free CH_3CN singlet resonance signal at δ 1.97 clearly indicates that the coordinated acetonitrile molecules were completely substituted with 1 equiv of (*S,S*)-Phos-Biox **4**. When the (*S,S*)-Phos-Biox **4** was treated with 2 equiv of dichlorobis(acetonitrile)palladium (II) in CD_2Cl_2, the resonance signals mentioned above were not changed in ^{1}H and ^{31}P NMR spectra. Therefore, based on the signal pattern resulted from C_2-symmetry of the complex, the possibility for the formation of *P,N*-(**20**), *N,N*-, and *P,N,N*-chelates could be excluded. If a 1:1 *P,N*-chelate or *P,N,N*-chelate was formed, there should be two different P-resonance signals due to coordinated and free phosphorus atoms. However, from the NMR data, it is hard to determine which of the *P,P*-chelated complex **18** or *P,N,N,P*-chelated complex **19a** was formed since both of the complexes will give very similar spectral

Scheme 2



data. To determine the chelation mode of the (*S,S*)-Phos-Biox **4** with $Pd(II)Cl_2$, we carried out an X-ray cryatal structure analysis. Thus, a 1:1 mixture of (*S,S*)-Phos-Biox **4** and $Pd(CH_3CN)_2Cl_2$ in methylene chloride afforded complex **19a**, which was recrystallized from acetone/ethyl acetate. In X-ray analysis, it has been found that the Phos-Biox **4** acts as a *P,N,N,P*-chelation ligand, and the complex **19a** has square planar ligand arrangement around Pd (Figure 2). Having this result, to obtain an insight into the mechanism of the stereocontrol in Pd-catalyzed allylic substitution reactions, we tried to get a crystal of a palladium complex which has both (*S,S*)-Phos-Biox **4** ligand and π-allyl group, and would generate a complex close to a real intermediate. Surprisingly, it has the same *P,N,N,P*-chelated structure with **19a** in X-ray analysis of **19b**, which was prepared by reaction of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with Phos-Biox **4**, followed by treatment with lithium perchlorate.[14] Moreover, the ^{31}P NMR of a 1:2 mixture of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and (*S,S*)-Phos-Biox **4** in CD_2Cl_2 exhibited a major resonance signal at δ 31.4 (PPh_3 as an external reference) along with several minor resonance signals. This result also suggests that the *P,N,N,P*-tetradentated complex **19a** may be formed as a major complex. Unfortunately, all other attempts failed to get the π-allyl coordinated Pd complex. Nevertheless,

(13) (a) Garrou, P. E. *Chem. Rev.* **1981**, *81*, 229. (b) Lindner, E.; Wang, Q.; Mayer, H. A.; Fawzi, R.; Steimann, M. *J. Organomet. Chem.* **1993**, *453*, 289. (C) Lindner, E.; Andres, B. *Chem. Ber.* **1987**, *120*, 761. (d) Brown, J. M.; Cook, S. J.; Kent, A. G. *Tetrahedron* **1986**, *42*, 5097. (e) Lindner, E.; Wang, Q.; Mayer, H. A.; Fawzi, R.; Steimann, M. *Organometallics* **1993**, *12*, 1865.

(14) A 1:2 molar mixture of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and (*S,S*)-Phos-Biox **4** in methanol was stirred until the solution became clear, then treated with $LiClO_4$ at room temperature. The white precipitate was filtered off, and the filtrate was concentrated in vacuo to give dark yellow solid. However, very small amounts of **19b** suitable for X-ray analysis could be isolated from ethyl acetate/acetone solvent system. All other attempts in other solvent systems were failed to get a single crystal. Crystal data for **19b**: $C_{42}H_{34}N_2O_2P_2Pd\cdot 2ClO_4\cdot EtOAc$, monclinic, $P2_1/n$ (No.14), a = 1.0772(18), b = 30.014(9), c = 12.597(3) Å, V = 4512.2-(17) Å^3, Z = 4, D_c = 1.552 g/cm^3, $F(000)$ = 2152, 4998 Independent reflections with $I/\sigma(I)$ 2.0 were used on the analysis. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractormeter using graphite-monochromate MoKα (λ = 0.710 73 Å) and ω-2 scans in the range of θ; 1.36 < θ < 25.35. Structure was solved by direct methods and refined by least squares using the SHEL-X.

to our best knowledge, the Phos-Biox **4** is the first C_2-symmetric phosphine-oxazoline hybrid ligand which forms *P,N,N,P*-tetradentate Pd(II) complex.[15] Finally, we examined whether the *P,N,N,P*-chelated complex **19** is a catalyst precursor or not in allylic substitution reactions. For this purpose, the allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate (**10**) with dimethyl malonate using complex **19a** was carried out under the same reaction condition with entry 3 in Table 1, and the product **11** of 92% ee was isolated in 86% yield. Although we do not have any direct evidence supporting the structure of real catalyst at the present stage, this result indicates that two of the *P,N,N,P* dissociated to form catalytically active species.

Conclusions

The C_2-symmetric bisphosphinobioxoline ligand [(*S,S*)-Phos-Biox, **4]** has been efficiently prepared in four steps (overall 21.3% yield) starting from readily available chiral dimine **5**. The (*S,S*)-Phos-Biox **4** was found to be an efficient chiral ligand for Pd-catalyzed enantioselective allylic substitution reactions. It has been also found that (*S,S*)-Phos-Biox **4** acts as a *P,N,N,P*-tetradentate chelating ligand, i.e., a 1:1 molar mixture of **4** with $Pd(CH_3CN)_2Cl_2$ and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ afforded the same *P,N,N,P*-chelated complexes **19a** and **19b**, respectively. The structures of the complexes **19a**,**b** were determined by X-ray analysis. The tetradentate complex **19a** also exhibited high catalytic efficiency in enantioselective allylic substitutions of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

Experimental Section

General Methods. All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. The reaction solvents (THF from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2) were distilled prior to use. Anhydrous solvents were transferred by oven-dried syringe. Flasks were flame dried under a stream of nitrogen. The NMR spectra were recorded at 300 MHz (^{1}H), 75.5 MHz (^{13}C), and 121 MHz (^{31}P). The chemical shifts were relative to TMS (as an internal reference) for ^{1}H NMR and PPh_3 or H_3PO_4 (as an external reference) for ^{31}P NMR. Chemical analyses were carried out by the Advanced Analysis Center at Korea Institute of Science and Technology. HRMS (FAB) analysis was carried out by the Mass Spectrometry Analysis Group at Korea Basic Science Institute.

(2*S*,3*S*)-1,4-Bis(benzyloxy)-2,3-[*N,N*′-bis(2-fluorobenzoyl)]diaminobutane (7). To a stirred solution of diamine **5** (10 g, 33.3 mmol) and triethylamine (30 mL, 0.2 mol) in anhydrous CH_2Cl_2 (150 mL) was added 2-fluorobenzoyl chloride (16 mL, 0.13 mmol) at 0 °C. After the solution was further stirred for 18 h at room temperature, the reaction was quenched by addition of water. The organic phase was washed successively with 2% aqueous HCl solution, saturated sodium bicarbonate, and saturated NaCl solution and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the yellowish solid residue was purified by recrystallization from diethyl ether to give **7 (**14.5 g, 80%) as a white solid. R_f 0.32 (ethyl acetate:*n*-hexane = 2:1); $[\alpha]_D^{24}$ −67.0 (*c* 1, $CHCl_3$); mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.03 (m, 20H), 4.74 (bs, 2H), 4.51 (m, 4H), 3.72−3.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.70, 162.31, 159.01, 137.76, 133.29, 133.16, 131.81, 128.54, 128.05, 127.96, 124.62, 116.38, 116.05, 73.61, 69.08, 50.87; IR (KBr) 3300 (N−H), 1640 (C=O) cm^{-1}. Anal. Calcd for $C_{32}H_{30}N_2O_4F_2$: C, 70.57; H, 5.55; N, 5.44. Found: C, 70.0; H, 5.53; N, 5.15.

(2*S*,3*S*)-2,3-[*N,N*′-Bis(2-fluorobenzoyl)]diamino-1,4-butanediol (8). To a solution of dibenzyl ether **7** (14 g, 25.7 mmol) in methanol (50 mL) and ethyl acetate (50 mL) were added 10% $Pd(OH)_2$/C (0.2 g) and cyclohexene (30 mL). The reaction mixture was refluxed for 18 h. The catalyst was removed by filtration over Celite 545, and the filtrate was concentrated under reduced pressure to remove all volatile materials. The white solid residue was purified by recrystallization from methylene chloride/diethyl ether to give pure diol **8** (9.2 g, 98%) as white solid. R_f 0.1 (ethyl acetate:*n*-hexane = 2:1); $[\alpha]_D^{24}$ −8.8 (*c* 1, MeOH); mp 172−173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_7.98 (d, J = 6.1 Hz, 2H), 7.65 (t, J = 7.4 Hz, 2H), 7.52 (m, 2H), 7.27 (m, 4H), 4.86 (t, J = 5.6 Hz, 2H), 4.37 (m, 2H), 3.58 (t, J = 5.3 Hz, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_164.11, 159.11 (d, $J_{C,F}$ = 248.9 Hz), 132.48, 130.11, 124.38, 123.93 (d, $J_{C,F}$ = 14.2 Hz), 116.06 (d, $J_{C,F}$ = 22.7 Hz), 60.68, 51.55; IR (KBr) 3294 (OH), 1638 (C=O) cm^{-1}. HRMS(FAB) Calcd for $C_{18}H_{19}N_2O_4F_2$ [(M+H)$^+$]: 365.1313. Found: 365.1303.

(4*S*,4′*S*)-2,2′-bis(*o*-fluorophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) (9). To a solution of diol **8** (9 g, 24.7 mmol) and triethylamine (37 mL, 0.24 mmol) in anhydrous methylene chloride (200 mL) was added methanesulfonyl chloride (8.5 g, 74.1 mmol) at 0 °C, and then the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of water at 0 °C and extracted with methylene chloride. The organic layer was successively washed with 2% HCl solution and brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was purified by crystallization from diethyl ether to give **9** (4.8 g, 59%) as a white solid: $[\alpha]_D^{24}$ −29.1 (*c* 0.9, $CHCl_3$); mp 58∼59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (t, J = 7.0 Hz, 2H), 7.47 (m, 2H), 7.17 (m, 4H), 4.93 (m, 2H), 4.47 (dd, J = 9.6, 9.0 Hz, 2H), 4.37 (dd, J = 9.6, 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.21, 161.05 (d, $J_{C,F}$ = 258.9 Hz), 132.01 (d, $J_{C,F}$ = 9.7 Hz), 131.02, 123.87, 116.55 (d, $J_{C,F}$ = 21.9 Hz), 115.76. Anal. Calcd for $C_{18}H_{14}N_2O_2F_2$: C, 65.85; H, 4.30; N, 8.53. Found: C, 65.8; H, 4.32; N, 8.58.

(4*S*,4′*S*)-2,2′-Bis(*o*-diphenylphosphinophenyl)-4,4′,5,5′-tetrahydro-4,4′-bi(1,3-oxazole) ((*S,S*)-Phos-Biox 4). Details were described in a previous paper (see ref 6c). Crystal data can be found in the Supporting Information.

General Procedure for the Pd-Catalyzed Allylic Substitutions of *rac*-1,3-Diphenyl-2-propenyl Acetate with Dimethyl Malonate Using (*S,S*)-Phos-Biox 4 as a Chiral Ligand. In a Schlenk tube, 1.6 mg (4 μmol) of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 5 mg (10 μmol) of (*S,S*)-Phos-Biox **4** were dissolved in solvent (1 mL) indicated in Table 1, degassed, and then stirred for 1 h at 25 °C under an atmosphere of argon. To this solution were successively added *rac*-1,3-diphenyl-2-propenyl acetate **10** (100 mg, 0.4 mmol) and a solution of nucleophile, generated in situ from dimethyl malonate (100 mg, 0.8 mmol) and base [NaH (35 mg, 0.87 mmol) or BSA (240 mg, 1.2 mmol)] in a solvent (1 mL) at 25 °C. After completion of the reaction, the reaction mixture was diluted with methylene chloride (20 mL) and poured into a cold saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with methylene chloride (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated. The crude product was purified by preparative TLC (ethyl acetate:*n*-hexane = 1:4, R_f 0.4) to give the pure product **11**. The enantiomeric purities were determined by the ^{1}H NMR spectra measured in the presence of Eu(hfc)$_3$. When 0.8 equiv of Eu(hfc)$_3$ was added, one of the two methyl ester signals appeared at δ 3.70 was splitted into two peaks: (*R*)-enantiomer at δ 3.99, (*S*)-enantiomer at δ 3.93. The yields and enantioselectivities are given in Table 1.

Typical Procedure for the Desymmetrization of *cis*-1,4-bis(benzoyloxy)cyclopent-2-ene (12) with Dimethyl Malonate. A mixture of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (1.6 mg, 4 μmol) and (*S,S*)-Phos-Biox **4** (11 mg, 16.2 μmol) in THF (1 mL) was stirred for 1 h at room temperature and then cooled to −78 °C using

(15) Ferrocene based *P,O,O,P*-tetradentate Pd(II) complexes, $[Pd(\eta^4\text{-}(\eta^5\text{-}C_5H_4OCH_2CH_2PR_2)_2Fe)]^{2+}$ where R = Ph and cyclohexyl, have been recently reported. See Allgeier, A.; Slone, C. S.; Mirkin, C. A.; Liable-Sands, L. M.; Yap, G. P. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 550.

dry ice-acetone bath. To this solution were successively added a solution of dimethyl sodiomalonate, prepared from dimethyl malonate (20 mg, 0.19 mmol) and sodium hydride (7 mg, 0.18 mmol in THF (1 mL), and *cis*-1,4-bis(benzoyloxy)cyclopent-2-ene (**12**) (50 mg, 0.16 mmol) at −78 °C. The reaction mixture was degassed by freeze and thaw cycles (three times) and stirred at temperature indicated in Table 2 (entries 1−4) for 12 h. For entry 5 in Table 2, the malonate anion was generated using BSA (50 mg, 0.24 mmol) and potassium acetate (0.3 mg, 3.2 μmol, 2 mol %). The reaction mixture was diluted with diethyl ether, washed with aqueous 0.1 N HCl solution, water, and brine, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel column (*n*-hexane:ethyl acetate = 5:1 eluent) to give a mixture of **13a** and **14a**. The yields are given in Table 2 (entries 1−5). The ^{1}H NMR spectral data agree to those reported by Trost.[2b]

Determination of Enantioselectivity. (A) ^{1}H NMR method: to determine the enantioselectivity, the benzoate (**13a** and **14a**) was converted to the corresponding (*S*)-*O*-methylmandelate ester according to the reported procedure.[2b] The enantiomeric excess was determined by the integration ratio of the vinyl proton signals appeared at δ 6.02 (major isomer, **13a**) and 5.80 (minor isomer, **14a**). (B) HPLC method: a racemic mixture of **13a** and **14a** was prepared by the reaction of **12** with dimethyl sodiomalonate in the presence of 1 mol % of tetrakis(triphenylphosphine)Pd(0) in THF. In HPLC analysis using CHIRLACEL OJ chiral column (2-propanol:*n*-hexane = 1:9, flow rate = 1 mL/min), the two enantiomers were separated. The retention times of **13a** and **14a** are 17.84 and 13.37 min, respectively. The retention times of the major (**13a**) and minor (**14a**) enantiomers were determined based on the ^{1}H NMR results obtained above. The enantioselectivities are given in Table 2 (entries 1−5).

Desymmetrization of *cis*-1,4-bis(benzoyloxy)cyclopent-2-ene (12) with *N*-Benzyl-*N*-methylamine nucleophile (Table 2, Entry 6). A solution of 1.6 mg (4 μmol) of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 11 mg of (*S*,*S*)-Phos-Biox **4** (16.2 μmol) in THF (1 mL) was stirred for 1 h at room temperature. After being cooled to −78 °C, to this catalyst solution were added successively 50 mg (0.162 mmol) of dibenzoate **12**, 20 mg (0.16 mmol) of *N*-benzyl-*N*-methylamine, and 90 mg (0.8 mmol) of triethylamine at −78 °C. The reaction mixture was degassed three times by freeze and thaw cycles, then stirred at 0 °C for 12 h. The reaction mixture was diluted with ether and washed with aqueous 1 N NaOH solution, water, and brine. After evaporation of the solvent, the crude product was purified by silica column chromatography (*n*-hexane:ethyl acetate = 4:1) to give 43 mg (87%) of a mixture of **13b** and **14b**. The ^{1}H NMR spectral data agree to those reported.[2b] For measuring enantiomeric excess, the purified product was converted to the (*S*)-*O*-methylmandelate ester according to the reported procedure [hydrolysis (LiOH, C_2H_5OH, H_2O, 60 °C) followed by acylation with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, rt)] to give vinyl proton signals at δ 6.04 and 5.82 for **13b** derivative (major) and δ 6.08 and 5.92 for **14b** derivative (minor) (**13b**/**14b** = 2/1, 33% ee).[2b]

Desymmetrization of Biscarbamate 15 of *cis*-1,4-Dihydroxycyclopent-2-ene Using (*S*,*S*)-Phos-Biox 4 as a Chiral Ligand (Equation 3). A solution of *cis*-1,4-dihydroxycyclopent-2-ene (20 mg, 0.2 mmol) in 1 mL of THF was stirred at room temperature until the solution became clear. The *p*-toluenesulfonyl isocynate (87 mg, 0.4 mmol) was added dropwise to this solution at 0 °C, and the mixture was stirred at 50 °C for 1 h to give bis-carbamate **15**. A solution of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (1.6 mg, 0.4 μmol) and (*S*,*S*)-Phos-Biox **4** (11 mg, 16.2 μmol) in THF (1 mL), stirred at room temperature for 1 h, was added to the bis-carbamate **15** solution at − 78 °C. The reaction mixture was stirred at the same temperature for 1 h, and then the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate = 5:1) to give 50 mg (90%) of a mixture of oxazolidinones **16** and **17**. For measuring enantiomeric excess, the mixture of enantiomers **16** and **17** was converted to the (*S*)-*O*-methylmandelate ester according to the reported procedure [hydrolysis (K_2CO_3, CH_3OH, H_2O, 65 °C) followed by acylation with (*S*)-*O*-methylmandelic acid (DCC, DMAP, CH_2Cl_2, rt)] to give vinyl proton signals at δ 5.68 and 5.48 for **16** derivative (minor) and δ 5.78 and 5.57 for **17** derivative (major) (**16**/**17** = 1/3, 50% ee).[2b]

Preparation of [Pd((*S*,*S*)-Phos-Biox 4)]·2Cl (19a). A mixture of (*S*,*S*)-Phos-Biox **4** (30 mg, 0.45 μmol) and $Pd(CH_3CN)_2Cl_2$ (12 mg, 0.45 μmol) in CH_2Cl_2 (1 mL) and CH_3OH (1 mL) was stirred at room temperature for 1 h. Evaporation of the solvent in vacuo afforded 34 mg (94%) of **19a** as a yellow solid which was recrystallized from acetone/ethyl acetate for a single-crystal X-ray analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.82 (m, 4H), 7.58 (t, J = 7.6 Hz, 2H), 7.45 (m, 4H), 7.31 (m, 6H), 7.02 (m, 6H), 6.92 (m, 4H), 5.67 (bs, 2H), 5.28 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.77, 135.62, 135.44, 135.07, 134.18, 134.00, 133.84, 133.33, 133.02, 132.88, 132.41, 130.53, 130.05, 129.88, 129.30, 129.15, 127.75, 127.60, 127.11, 127.06, 126.36, 125.12, 124.38. HRMS(FAB)[M^+-Cl] Calcd for $C_{42}H_{34}N_2O_2P_2PdCl$: 801.0819. Found: *m*/*e* 801.0831.

Crystal Data of 19a: $C_{42}H_{34}Cl_2N_2O_2P_2Pd$, orthorhombic, $P2_1P2_1P2_1$, a = 11.228(5), b = 19.668(6), c = 40.447(12) Å, V = 8932(6) Å^3, Z = 4, D_c = 1.246 g/cm^3, F(000) = 3408, 2852 Independent reflections with $I/\sigma(I)$2.0 were used on the analysis. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractormeter using graphite-monochromate MoKα (λ = 0.710 73 Å) and ω-2 scans in the range of θ, 1.15 < θ < 22.94. Structure was solved by direct methods and refined by least squares using the SHEL-X. Additional crystallographic details can be found in the Supporting Information.

A NMR solution of **19a** was prepared as follows. A solution of 1:1 molar mixture of (*S*,*S*)-Phos-Biox **4** and $Pd(CH_3CN)_2Cl_2$ in CD_2Cl_2 was stirred for 30 min at room temperature and placed in NMR tube. The ^{1}H NMR and ^{31}P NMR spectra were recorded at room temperature to give the following data. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 8.27 (dd, J = 7.1, 3.9 Hz, 2H), 7.94 (dd, J = 7.1, 7.0 Hz, 4H), 7.68 (t, J = 7.4 Hz, 2H), 7.54 (m, 4H), 7.48 (m, 6H), 7.08 (m, 10H), 5.71 (m, 2H), 5.35 (m, 4H); ^{31}P NMR (121 MHz, CD_2Cl_2) δ 31.46 (s).

Catalytic Activity of 19a in Allylic Substitution of *rac*-1,3-Diphenyl-2-propenyl Acetate with Dimethyl Malonate. To a solution of **19a** (3 mg, 4 μmol) and allylic acetate **10** (100 mg, 0.4 mmol) in methylene chloride (1 mL) were added dimethyl malonate (100 mg, 0.8 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (240 mg, 1.2 mmol), and potassium acetate (0.8 mg, 8 μmol) at 20 °C. The mixture was degassed, and stirred for 6 h. After work up as described in the General Procedures, the pure product **11** of 110 mg (86%) with 92% ee was obtained.

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Supporting Information Available: Copies of the ^{1}H NMR and ^{31}P NMR spectra of ligand **4** and a 1:1 mixture of **4** and $Pd(CH_3CN)_2Cl_2$, HPLC chromatogram of a mixture of **13a** and **14a**, and X-ray data for **4** and **19a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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