Asymmetric Synthesis and Coordination Chemistry of Bidentate P-Stereogenic Phosphines Containing Ester and Thionoester Functionalities

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The asymmetric syntheses of ester- and thionoester-substituted P-stereogenic phosphines have been achieved between 3,4-dimethyl-1-phenylphosphole (DMPP) and dieneophiles, methyl acrylate and *o*-ethyl-(*E*)-2-butenethioate, respectively, in the presence of the enantiomerically pure *ortho*-palladated (1-(dimethylamino)ethyl)naphthalene as the chiral template. The *exo* and *endo* reaction pathways could be controlled stereoselectively by manipulating the number of accessible coordination sites on the chiral palladium template. Both methyl acrylate and *o*-ethyl-(*E*)-2-butenethioate underwent intramolecular *exo*-cycloaddition on the palladium template to form the corresponding P-stereogenic *exo*-phosphanorbornenes as P−O and P−S bidentate chelates, respectively. When the ester-substituted P−O bidentate template complex was treated with an aqueous solution of sodium chloride under mild reaction conditions, the Pd−O bond was displaced chemoselectively by the chloride ion, but the phosphanorbornene remained coordinated on palladium as a monodentate ligand via its phosphorus donor atom. A similar aqueous treatment of the thionoester-substituted P−S bidentate did not cleave the Pd−S bond but resulted in the rapid hydrolysis of the C(S)−OEt bond to give a new thioester P−S metal chelate. In the intermolecular *endo*-cycloaddition pathway, only methyl acrylate coupled with DMPP to give a pair of separable ester-substituted *endo*-cycloadducts. The thionoester-substituted dienophile *o*-ethyl-(*E*)-2-butenethioate was not reactive toward the *endo*-cycloaddition reaction.

Introduction

Functionalities play a major role in classical organic chemistry. It has long been demonstrated that a particular functional group may determine the fundamental physical and chemical properties of the organic molecules that it is attached to. On the other hand, both the inorganic and organometallic chemists have frequently utilized metal ions to modify the reactivity of these functional groups and thus control the chemistry of the corresponding organic molecules.[2] Such studies have contributed significantly to the development of modern synthetic methodologies, such as metal-based catalysis. Several well-established concepts, such as the Hard and Soft Acid and Base (HSAB) approach, have been frequently applied to understand the interactions of a particular functional group with various types of metal ions. These fundamental chemical concepts contribute critically, not only to the advancement of chemistry itself but also to the evolution of biology and biochemistry. Recently we utilized several chiral organometallic palladium(II) and platinum(II) complexes to promote the intramolecular asymmetric *exo*-cycloaddition reaction between a series of functionalized organic dienophiles and the heterocyclic diene 2,3-dimethylphenylphosphole (DMPP).[3] In these earlier investigations, we observed some previously unknown

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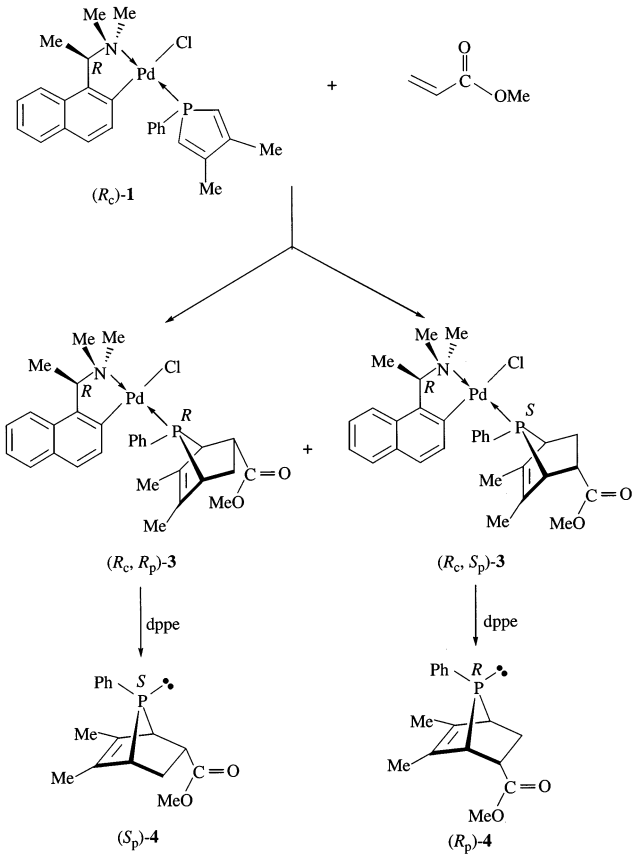
Scheme 1



and interesting interactions between several organic functional groups in the dienophilic components and the two heavy d^8 metal ions. For instance, we found that amides are able to form highly stable oxygen→metal coordination bonds with these typically soft metal ions, provided π-acid ligands are present in the *trans* coordination positions.[4]

In conjunction with our interest in the systematic development of functionalized P-stereogenic phosphines, we herein report the asymmetric Diels−Alder reaction between the coordinated DMPP in the chiral template complex **1** and two structurally analogous dienophiles, methyl acrylate and ethyl-*trans*-crotonthioate. The stable and inert *ortho*-palladated naphthylamine chelate serves as the reaction promoter for DMPP, since the free phosphole shows no reactivity toward any dienophile.[5] Furthermore, the fourth coordination site in complex **1** serves as a controlling site for the possible *endo*- and *exo*-cycloaddition reactions. The Pd−Cl bond in **1** is thermodynamically stable and kinetically inert.[6] Thus the coordinated DMPP in **1** can only undergo intermolecular *endo*-cycloaddition reaction with the incoming dienophiles. On the other hand, when the chloro ligand in this metal template is replaced by a labile counterpart, such as the perchlorato ligand in complex **2**, the subsequent interactions between the palladium center and the incoming dienophiles should favor the intramolecular *exo*-cycloaddition mechanism. Indeed, the metal ion functional group interactions in the current asymmetric syntheses form the essential intermediates for the chemoselective formation of the optically active *exo*-cycloadducts.

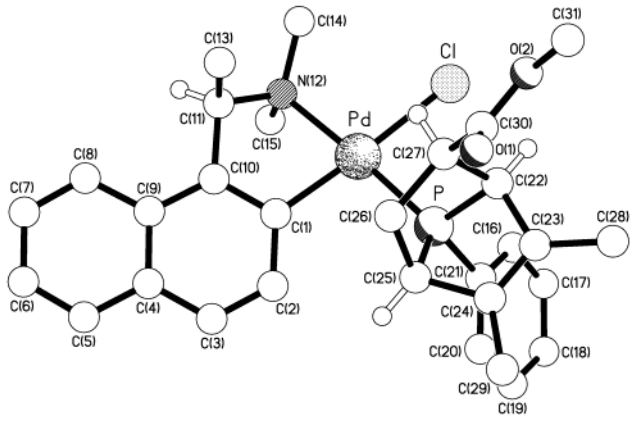


Figure 1. Molecular structure and absolute stereochemistry of (R_C,R_P)-**3** (the cocrystallized solvent molecule has been omitted for clarity).

Results and Discussion

Palladium Template Promoted Cycloaddition Reaction of DMPP with Methyl Acrylate. As intimated earlier, uncoordinated DMPP shows no reaction with methyl acrylate despite the forcing reaction conditions employed. The coordination of the phosphole ligand to the chiral palladium template (*R*)-**1** activates the cyclic diene toward [4+2] cycloaddition. Hence, the treatment of the neutral chloro complex (*R*)-**1** with methyl acrylate in refluxing 1,2-dichloroethane for 3 days gave a mixture of the two diastereomeric *endo*-cycloaddition products (R_C,R_P)-**3** and (R_C,S_P)-**3**, in quantitative yield (Scheme 1). The ^{31}P NMR spectrum of the crude product in $CDCl_3$ exhibited two sharp singlets at δ 124.6 and 125.6 with an intensity ratio of 1.5:1, respectively. The major isomer (R_C,R_P)-**3** was subsequently isolated by fractional crystallization from dichloromethane−diethyl ether as colorless prisms in 35% yield, $[\alpha]_D$ −18.0° (CH_2Cl_2). The IR (KBr) analysis revealed a characteristic carbonyl stretching mode at 1734 cm^{-1}, consistent with the presence of a free ester function. The minor isomer (R_C,S_P)-**3** was found to be highly soluble in most solvent systems tried and could not be induced to crystallize.

The molecular structure and the absolute stereochemistry of the major isomer (R_C,R_P)-**3** are depicted in Figure 1. Selected bond lengths and bond angles are given in Table 1. The X-ray analysis reveals that the cycloaddition reaction between the coordinated DMPP and methyl acrylate has resulted in the formation of the *syn-endo* phosphinoester. The chiral ligand coordinates as a monodentate ligand via the bridgehead phosphorus to the palladium template, with the free ester moiety occupying the *endo* position at C(27). The absolute configurations of the four new stereogenic centers are *R*, *S*, *R*, and *S* for P, C(22), C(25), and C(27), respectively. The geometry at the palladium center is distorted square-planar, and the bond angles are in the ranges 80.6(2)−95.8(1)° and 175.1(1)−176.0(1)°. The

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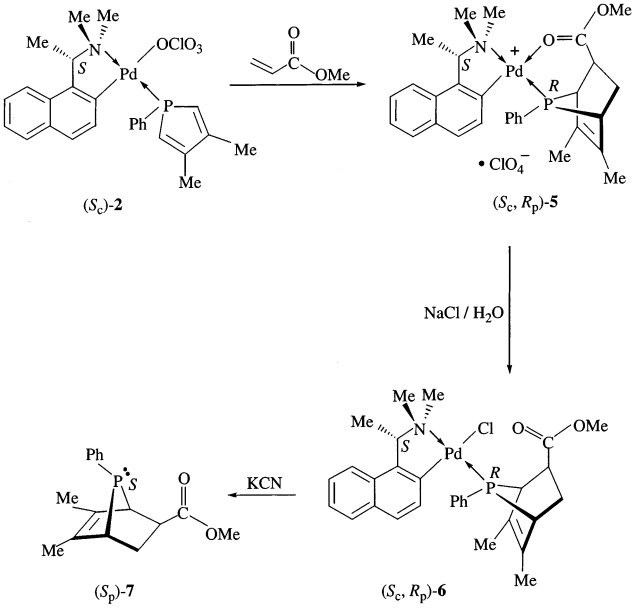
Table 1. Selected Bond Lengths (Å) and Angles (deg) for Compounds (R_C,R_P)-3, (S_C,R_P)-6, and (S_C,R_P)-9

	(R_C,R_P)-**3** [X = Cl]	(S_C,R_P)-**6** [X = Cl]	(S_C,R_P)-**9** [X = S]
Pd−C(1)	1.998(4)	2.009(2)	2.025(4)
Pd−N(12)	2.141(3)	2.147(2)	2.161(5)
Pd−P	2.2303(9)	2.2363(6)	2.2054(13)
Pd−X	2.4039(10)	2.3892(6)	2.3684(14)
P−C(21)	1.822(4)	1.818(2)	1.815(3)
P−C(22)	1.857(4)	1.858(2)	1.850(5)
P−C(25)	1.857(4)	1.849(3)	1.845(6)
C(1)−Pd−N(12)	80.60(15)	80.24(9)	81.0(2)
C(1)−Pd−P	95.78(12)	97.65(7)	93.6(2)
C(1)−Pd−X	175.11(12)	174.19(8)	169.94(14)
N(12)−Pd−P	175.98(9)	175.14(7)	172.66(14)
N(12)−Pd−X	94.88(9)	94.02(6)	92.22(12)
P−Pd−X	88.79(4)	88.00(2)	93.79(6)
C(21)−P−Pd	114.22(12)	109.95(8)	116.3(2)
C(22)−P−Pd	114.93(12)	124.76(8)	118.2(2)
C(25)−P−Pd	122.94(13)	118.96(9)	119.1(2)
C(21)−P−C(22)	108.9(2)	109.96(11)	105.6(2)
C(21)−P−C(25)	110.2(2)	109.11(12)	111.5(2)
C(22)−P−C(25)	80.7(2)	80.75(12)	80.5(3)

Scheme 2



Pd−C(1), Pd−N(12), Pd−P, and Pd−Cl bond lengths are 1.998(4), 2.141(3), 2.230(1), and 2.404(1) Å, respectively. The bond lengths of C(30)−O(1) and C(30)−O(2) [1.174(5) and 1.339(5) Å, respectively] are within the normal range for noncoordinated ester functional groups.[7]

The treatment of (R_C,R_P)-**3** with 1,2-bis(diphenylphosphino)ethane (dppe) in dichloromethane (Scheme 1) liberated the optically pure phosphinoester (S_P)-**4** from the chiral metal template as an air-sensitive colorless oil in 80% yield, $[\alpha]_D$ +34.6° (CH_2Cl_2). The ^{31}P NMR spectrum of (S_P)-**4** in $CDCl_3$ recorded a singlet at δ 107.9. The apparent inversion of the configuration that takes place at the phosphorus stereogenic center when it is liberated is merely a consequence of the Cahn−Ingold−Prelog (CIP) sequence rule.[8] It is noteworthy that, due to the difficulties involved in the storage of the reactive phosphine ligand, (S_P)-**4** should be liberated freshly when it is required for further reactions.

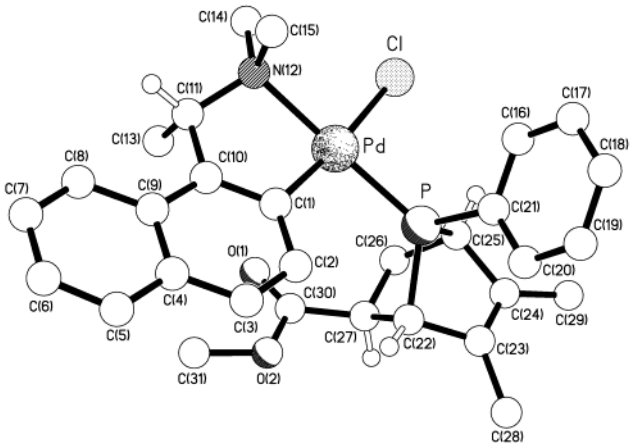


Figure 2. Molecular structure and absolute stereochemistry of (S_C,R_P)-**6**.

In the corresponding intramolecular *exo*-cycloaddition reaction, the highly reactive perchlorato complex (S_C)-**2** was reacted with excess methyl acrylate under reflux conditions in 1,2-dichloroethane and was found to be complete in two weeks to give the *exo*-cycloadduct (S_C,R_P)-**5** (Scheme 2). Prior to purification, the $^{31}P\{^1H\}$ NMR spectrum exhibited a sharp singlet at δ 108.8. Attempts to crystallize the product were unsuccessful, as the compound decomposed rapidly in solution. Similarly, the complex decomposed while it was being purified by column chromatography. However, when this unstable complex was treated with an aqueous solution of sodium chloride for ca. 30 min, a stable chloro complex (S_C,R_P)-**6** was obtained. Prior to isolation, the ^{31}P NMR spectrum of (S_C,R_P)-**6** exhibited a sharp singlet at δ 113.8, which indicated that the *exo-syn* stereochemistry of the cycloadduct had been retained. After purification by column chromatography, the product (S_C,R_P)-**6** was subsequently crystallized as colorless prisms from dichloromethane−hexane, $[\alpha]_D$ +109.6° (CH_2Cl_2). The IR spectrum of (S_C,R_P)-**6** exhibited a C=O stretching mode at 1728 cm^{-1}, confirming the presence of an uncoordinated ester carbonyl functional group.

The molecular structure and absolute stereochemistry of the chloro complex (S_C,R_P)-**6** is shown in Figure 2. Selected bond lengths and bond angles are given in Table 1. The X-ray structural analysis shows that the chloro ligand coordinates to Pd(II) in the position *trans* to the *ortho*-metalated carbon atom. Most importantly, the carboxylate functional group attached to C(27) is in the *exo*-position of the phosphanorbonene skeleton. The configurations at the four new stereogenic centers are *R*, *S*, *R*, and *R* at P, C(22), C(25), and C(27), respectively. The geometry at the palladium center is slightly distorted square-planar, with the bond angles in the ranges 80.24(9)−88.00(2)° and 174.19(8)−175.14(3)°. In light of the observed *exo* structure in the chloro complex (S_C,R_P)-**6**, the same *syn-exo* cycloadduct was assigned for the preceding complex (S_C,R_P)-**5**. Clearly, the carbonyl oxygen of methyl acrylate had displaced the Pd−$OClO_3$ bond in (S_C)-**2** during the course of the intramolecular *exo*-cycloaddition reaction to generate the chiral phosphanorbornene as a P−O bidentate chelate on the chiral palladium(II) template, as illustrated in (S_C,R_P)-**5** (Scheme 2).

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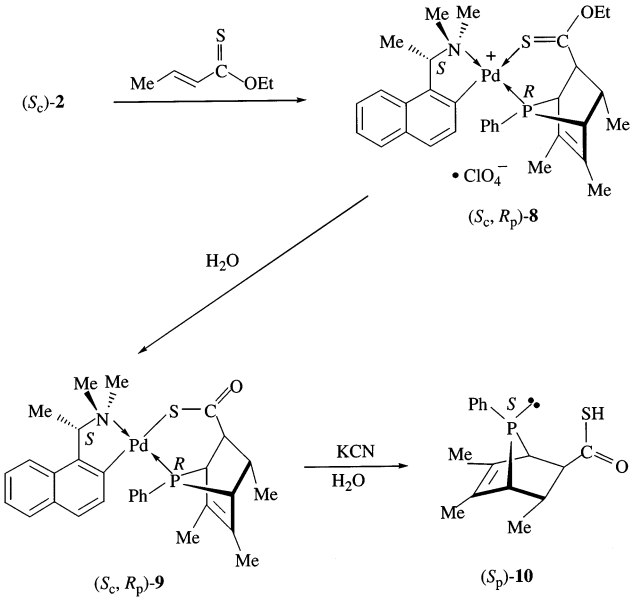
Scheme 3



Treatment of (S_C,R_P)-**6** with aqueous potassium cyanide liberated the optically pure phosphine ligand (S_P)-**7** as a colorless oil in 80% yield, $[\alpha]_D$ +38.8° (CH_2Cl_2). The ^{31}P NMR spectrum of the liberated ligand in $CDCl_3$ exhibited a singlet at δ 95.3. The low-field ^{31}P resonance confirms that the *syn-exo* stereochemistry is retained in (S_P)-**7**.[9]

Palladium Template Promoted Cycloaddition Reaction of DMPP with *O*-Ethyl-(*E*)-2-butenethioate. The thionoester functional group in *o*-ethyl-(*E*)-2-butenethioate was prepared from the corresponding ethyl-*trans*-crotonate using the standard Lawesson's reagent as the sulfurization reagent.[10] From a structural chemistry standpoint, *o*-ethyl-(*E*)-2-butenethioate may be considered as a mercapto-substituted analogue of the ester family. In contrast to methyl acrylate, however, ethyl-*trans*-crotonthioate did not undergo the intermolecular *endo*-cycloaddition with DMPP in complex (S_C)-**1**, despite the forcing reaction conditions employed. However, with the perchlorato complex (S_C)-**2**, intramolecular *exo*-cycloaddition could be induced (Scheme 3). The reaction was conducted in refluxing 1,2-dichloroethane and was found to complete in 15 h. Prior to purification, the ^{31}P NMR spectrum of the reaction mixture in $CDCl_3$ exhibited a sharp singlet at δ 115.1. No other NMR signal was observed in this low-field region. The low-field signal is consistent with the formation of the *syn-exo* phosphanorbornene. The cycloadduct decomposed during attempted purification via column chromatography. Following the same protocol as for (S_C,R_P)-**5**, the crude cycloadduct product (S_C,R_P)-**8** was treated with an aqueous solution of sodium chloride at room temperature (Scheme 3). Interestingly, the hydrolyzed P−S coordination product (S_C,R_P)-**9** was isolated from this mild aqueous treatment. The expected chloro complex, containing a monodentate P-coordinated *exo*-thionoester-substituted phosphanorbornene, was not

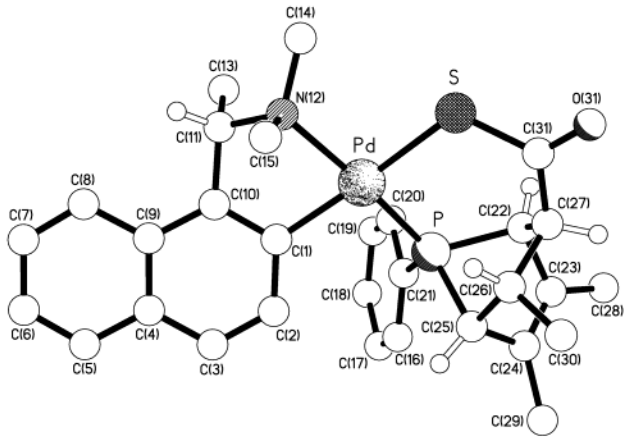


Figure 3. Molecular structure and absolute stereochemistry of (S_C,R_P)-**9**.

generated in this process. The ^{31}P NMR spectrum of the crude hydrolyzed product in $CDCl_3$ exhibited a single prominent peak at δ 119.3. The neutral product (S_C,R_P)-**9** could be purified by silica gel column chromatography and subsequently crystallized from dichloromethane diethyl ether as orange prisms in 15% yield, $[\alpha]_D$ +267.6° (CH_2Cl_2). The absolute stereochemistry and the molecular structure of complex (S_C,R_P)-**9** is depicted in Figure 3. Selected bond lengths and bond angles are given in Table 1. The X-ray structural analysis confirms that the chiral phosphanorbornene coordinates to the palladium template as a bidentate chelate via the bridgehead phosphorus and the thioester-sulfur atoms. The geometry at palladium is slightly distorted square-planar with *cis* angles in the range 81.9(2)−93.8(1)° and *trans* angles of 169.9(1)° and 172.7(1)°. The absolute configurations of the five new chiral centers at P, C(22), C(25), C(26), and C(27) are *R*, *S*, *R*, *S*, and *S*, respectively, with the thioester functional group being orientated in the *exo* position at C(27). It is noteworthy that the same hydrolyzed product product (S_C,R_P)-**9** was obtained when (S_C,R_P)-**8** was treated with water, in the absence of sodium chloride.

The optically active phosphanorbornene *exo*-(S_P)-**10** could be liberated by treatment of (S_C,R_P)-**9** with aqueous potassium cyanide (Scheme 3). The thioester-substituted ligand was obtained as a viscous oil in 50% yield, $[\alpha]_D$ +21.7° (CH_2Cl_2). The ^{31}P NMR spectrum of the liberated ligand in $CDCl_3$ exhibited a singlet at the typical low-field position (δ 103.1) for phosphanorbornenes.

Compared with methyl acrylate, ethyl-*trans*-crotonthioate itself is not a reactive dienophile toward DMPP. The vinylic double bond in this thionoester-substituted compound does not undergo the intermolecular *endo*-cycloaddition reaction with the activated DMPP in the chloro complex (S_C)-**1**. However, when the perchlorato complex (S_C)-**2** was used as the template, ethyl-*trans*-crotonthioate was activated via coordination to the metal template and underwent the intramolecular *exo*-cycloaddition reaction. Interestingly, the rate of the *exo*-cycloaddition reaction involving ethyl-*trans*-crotonthioate is even faster (15 h) than that observed with methyl acrylate (2 weeks). Clearly the sulfur−palladium coordination polarizes the thionoester moiety, which, in turn, polarizes the double bond of ethyl-*trans*-

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crotonthioate toward the intramolecular cycloaddition reaction with the coordinated DMPP.

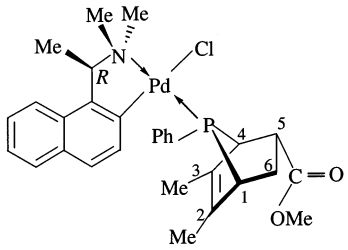
Apart from the activation of the C=C bond, the thionoester-S coordination also affects the reactivity of the thionoester function itself. The P−S coordination of the cycloadduct in (S_C,R_P)-**8** polarizes the C−O−C bond and renders the attached thionoester functional group highly susceptible to hydrolysis. The reactivity of the thionoester functional group in (S_C,R_P)-**8** is expected to diminish when the S→Pd coordination bond is displaced by a chloro ligand. The isolation of the dealkylation complex (S_C,R_P)-**9** from this aqueous treatment, however, indicates that the P−S bidentate metal chelate in (S_C,R_P)-**8** is kinetically inert, and hence, the hydrolysis process occurs faster than the ligand displacement reaction. We have previously observed a similar functional group transformation in which a palladium(II) complex containing a sulfinyl-substituted phosphine P−O bidentate ligand was converted to the corresponding thiolato-substituted P−S chelate by treatment with aqueous hydrochloric acid. This earlier study involved another unexpected reductive cleavage of the S=O and the S−alkyl bonds from the oxygen-coordinated sulfinyl group.[11] In general, sulfinyl and thionoester functional groups are stable toward hydrolysis under ambient conditions. The functional group transformations observed are clearly due to their interaction with the palladium ion. On the other hand, in the current study of the oxygen-coordinated ester complex (S_C,R_P)-**5**, the O→Pd coordination bond could be displaced rapidly by the chloro ligand with the ester group remaining unchanged by the aqueous treatment. Clearly, the O→Pd interaction in the ester complex is not sufficiently strong to weaken other C−O bonds within the ester function. We are currently investigating the cytotoxicity of a series of gold-based anticancer drugs containing functionalized phosphanorbornenes.[12] Preliminary studies shown that the metal functional group interactions play an important role in the biological activities of these chiral gold(I) complexes. Further exploration of this aspect in functionalized P-stereogenic phosphines containing ester and thionoester moieties will be investigated.

Experimental Section

Reactions involving air-sensitive compounds were performed under a positive pressure of purified nitrogen. Routine ^{1}H and ^{31}P NMR spectra were recorded at 300 and 120 MHz, respectively, on a Bruker ACF 300 spectrometer. Optical rotations were measured in the specified solution in a 1 cm cell at 25 °C with a Perkin-Elmer model 341 polarimeter. Melting points were determined using an Electrothermal IA 9200 apparatus. All FT-IR spectra were measured using a FTs-165 spectrometer. Elemental analyses were performed by the Elemental Analysis Laboratory of the Department of Chemistry at the National University of Singapore.

The chiral template complexes (S_C)-**1** and (S_C)-**2**[13] and the thionoester-substituted dienophile *o*-ethyl-(*E*)-2-butenethioate[10] were prepared as previously described.

***endo*-Cycloaddition Reaction with Methyl Acrylate: Isolation of Chloro{(*R*)-1-[1-(dimethylamino)ethyl]-2-naphthyl-*C*^{2},*N*}{(1α,4α,5*β*,7*R*)-5-(carboxylate)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene-*P*^{7}}-palladium(II), (R_C,R_P)-3.** A solution of the neutral chloro complex (R_C)-**1** (2.00 g, 3.79 mmol) in 1,2-dichloroethane (50 mL) was treated with excess methyl acrylate (1.5 mL, 20 mmol). The reaction mixture was then refluxed for 3 days. The ^{31}P NMR spectrum of the crude product in $CDCl_3$ indicated the presence of two individual singlets at δ 124.6 and 125.6 with the intensity ratio of 1.5:1, respectively. The solvent was removed under reduced pressure, and the residue was crystallized from dichloromethane−diethyl ether solution to yield the less soluble major diastereomer (R_C,R_P)-**3** as colorless prisms: yield 0.82 g (35%); mp 188−190 °C (dec); $[\alpha]_D$ −18.0° (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{30}H_{35}ClNO_2PPd$: C, 58.6; H, 5.7; N, 2.3. Found: C, 58.4; H, 5.7; N, 2.2. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 1H, C=C*Me*), 1.76 (s, 1H, C=C*Me*), 1.90 (d, 3H, $^3J_{HH}$ = 6.4 Hz, CH*Me*), 1.99 (dddd (partially obcured), 1H, $^3J_{PH}$ = 34.8, $^2J_{HH}$ = 12.7, $^3J_{HH}$ = 4.7, $^3J_{HH}$ = 1.7 Hz, *H6*(*endo*)), 2.45 (m, 1H, *H6*(*exo*)), 2.55 (d. 3H, $^4J_{PH}$ = 1.3 Hz, N*Me*), 2.86 (d, 3H, $^4J_{PH}$ = 3.1 Hz, N*Me*), 3.05 (s, 1H, *H4*), 3.65 (s, 3H, COO*Me*), 3.90 (m, 1H, *H1*), 4.26 (dq, 1H, $^3J_{HH}$ = $^4J_{PH}$ = 6.4 Hz, C*H*Me), 4.40 (m, 1H, *H5*), 7.10−7.93 (m, 11H, *aromatics*). ^{31}P NMR ($CDCl_3$): δ 124.6 (s, 1P). IR (KBr): ν 1734 cm^{-1} (uncoordinated C=O).



The minor diastereomer (R_C,S_P)-**3** could not be induced to crystallize in all solvent systems attempted.

Liberation of (1α,4α,5*β*,7*S*)-5-(Carboxylate)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene, *endo*-(S_P)-4. A solution of (R_C,R_P)-**3** (1.5 g, 2.4 mmol) in dichloromethane (100 mL) was treated with a solution of 1,2-bis-(diphenylphosphino)ethane (1.0 g, 2.4 mmol) in the same solvent (50 mL) for 0.75 h. The resulting yellowish mixture was passed through a column of Florisil (20 g) using dichloromethane to yield a colorless solution. Removal of solvent under reduced pressure gave (S_P)-**4** as a colorless viscous oil: yield 0.05 g (75%); $[\alpha]_D$ +34.6° (*c* 1.0, CH_2Cl_2). ^{31}P NMR ($CDCl_3$): δ 107.9 (s, 1P).

***exo*-Cycloaddition Reaction with Methyl Acrylate: Formation of {(*S*)-1-[1-(Dimethylamino)ethyl]-2-naphthyl-*C*^{2},*N*}{(1α, 4α, 5α, 7*R*)-5-(carboxylate)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene-*P*^{7},*O*^{5}}-palladium(II) Perchlorate, (S_C,R_P)-5, and Isolation of Chloro{(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthyl-*C*^{2},*N*}-{(1α,4α,5α,7*R*)-5-(carboxylate)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene-*P*^{7}}palladium(II), (S_C,R_P)-6.** A mixture containing the freshly prepared perchlorato template complex (S_C)-**2** (1.23 g, 2.07 mmol) and methyl acrylate (0.37 mL, 4.14 mmol) in 1,2-dichloroethane (20 mL) was refluxed for 14 days. The resulting solution was filtered through a layer of Celite, washed with distilled water (2 × 15 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude cycloadduct as a viscous orange oil. The ^{31}P NMR spectrum of the crude product in $CDCl_3$ indicated only one intense singlet at δ 108.8. No other signal was observed at this low-field region. IR (KBr): 1654 cm^{-1} (C=O→Pd), 1090 cm^{-1} (ClO_4). Attempts to isolate the pure perchlorate salt by fractional crystallization and by column chromatography were not successful. The crude cyclo-

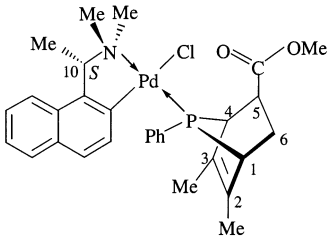
(11) Leung, P. H.; Siah, S. Y.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 893.
(12) Leung, P. H.; Chan, S. H.; Song, Y. S. Patent WO 2001077121, 2001.
(13) Siah, S. Y.; Leung, P. H.; Mok, K. F. *Chem. Commun.* **1995**, 1747. Loh, S. K.; Mok, K. F.; Leung P. H. *Tetrahedron: Asymmetry* **1996**, *7*, 45.

Table 2. Crystal Data, Data Collection, and Refinement Parameters for Compounds (R_C,R_P)-3, (S_C,R_P)-6, and (S_C,R_P)-9[a]

	(R_C,R_P)-**3**	(S_C,R_P)-**6**	(S_C,R_P)-**9**
formula	$C_{30}H_{35}ClNO_2PPd$	$C_{30}H_{35}ClNO_2PPd$	$C_{30}H_{34}NOPSPd$
solvent	Et_2O		
fw	688.53	614.41	594.01
color, habit	colorless platy needles	colorless spearheads	pale orange prisms
cryst size/mm	0.50 × 0.33 × 0.20	0.28 × 0.12 × 0.08	0.87 × 0.73 × 0.67
temperature/K	296	293	293
cryst syst	orthorhombic	monoclinic	monoclinic
space group	$P2_12_12_1$ (no. 19)	$P2_1$ (no. 4)	$P2_1$ (no. 4)
a/Å	11.9415(3)	9.0291(5)	11.0191(13)
b/Å	13.9515(3)	13.5531(7)	11.0489(11)
c/Å	20.4701(4)	12.5753(7)	11.7751(15)
β/deg		105.072(1)	90.71(2)
V/Å^3	3410.36(13)	1485.93(14)	1433.5(3)
Z	4	2	2
D_c/g cm^{-3}	1.341	1.373	1.376
radiation used	Mo Kα	Mo Kα	Mo Kα
μ/mm^{-1}	0.702	0.794	0.798
θ max/deg	56	53	50
no. of unique reflns measured	7303	5634	2663
obs, $\|F_o\| > 4\sigma(\|F_o\|)$	6572	5518	2522
no. of variables	371	325	305
R_1, wR_2[b]	0.042, 0.098	0.021, 0.055	0.028, 0.067

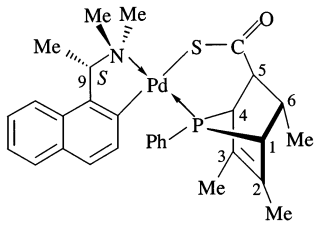
[a] Details in common: graphite-monochromated radiation, refinement based on F^2. [b] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$.

adduct was therefore dissolved in dichloromethane (100 mL) and treated with an aqueous solution of sodium chloride (5 g) in water (5 mL) for 0.5 h. The organic layer was separated, washed with water (2 × 20 mL), and dried ($MgSO_4$). The yellow crude product obtained was chromatographed through a silica gel column using ethyl acetate−hexane (1:1 v/v) as the eluent. The neutral cycloadduct complex (S_C,R_P)-**6** was subsequently crystallized from dichloromethane−hexane−diethyl ether as pale yellow prisms, 0.61 g (48%), mp 158−160 °C (dec), $[\alpha]_D$ +109.6° (*c* 0.52, CH_2Cl_2). Anal. Calcd for $C_{30}H_{35}ClNO_2PPd$: C, 58.6; H, 5.7; Cl, 5.8; N, 2.3. Found: C, 58.4; H, 5.7; Cl, 5.7; N, 2.6. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 3H, C=C*Me*), 1.56 (s, 3H, COO*Me*), 1.84 (s, 3H, C=C*Me*), 1.89 (d, 3H, $^3J_{HH}$ = 6.4 Hz, CH*Me*), 2.05 (m, 1H, *H6*(*endo*)), 2.38 (s, 1H, *H4*), 2.61 (s, 3H, N*Me*(*ax*)), 2.69 (m, 1H, *H6*(*exo*)), 2.83 (d, 3H, $^4J_{PH}$ = 3.0 Hz, N*Me*(*eq*)), 3.50 (m, 1H, *H5*), 3.70 (m, 1H, *H1*), 4.27 (m, 1H, *H10*), 7.13−7.96 (m, 11H, *aromatics*). ^{31}P NMR ($CDCl_3$): δ 113.8 (s, 1P). IR (KBr): ν 1728 cm^{-1} (C=O).



Liberation of (1α,4α,5*β*,7*S*)-5-(Carboxylate)-2,3-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene, *exo*-(S_P)-7. A solution of (S_C,R_P)-**6** (0.04 g, 0.07 mmol) in degassed dichloromethane (10 mL) was treated with excess potassium cyanide (0.34 g, 5.25 mmol) in water (3 mL) and stirred vigorously at room temperature for 5 h. The organic layer was separated and washed with water (5 × 10 mL). The organic layer was then extracted with dilute H_2SO_4 (0.5 M), washed thoroughly with water, and dried ($MgSO_4$). Removal of solvent under partial pressure gave the product as an air-sensitive and low-melting white solid, 0.02 g (80%), $[\alpha]_D$ +38.8° (*c* 0.2, CH_2Cl_2). ^{31}P NMR ($CDCl_3$): δ 95.3 (s, 1P).

***exo*-Cycloaddition Reaction with Ethyl-*trans*-crotonthioate: Formation of {(*S*)-1-[1-(Dimethylamino)-ethyl]-2-naphthyl-*C*^{2},*N*}{(1α,4α,5α,6*β*,7*R*)-5-(ethylthiocarboxylate)-2,3,6-trimethyl-7-phenyl-7-phosphabicyclo[2.2.1]-hept-2-ene-*P*^{7},*S*}palladium(II) Perchlorate, (S_C,R_P)-8, and Isolation of {(*S*)-1-[1-(Dimethylamino)ethyl]-2-naphthyl-*C*^{2},*N*}{(1α,4α,5α,6*β*,7*R*)-5-(thiocarboxylate)-2,3,6-trimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene-*P*^{7},*S*}-palladium(II), (S_C,R_P)-9.** A mixture of the perchlorato complex (S_C)-**2** (2.28 g, 3.85 mmol) and ethyl-*trans*-crotonthioate (1.0 g, 7.70 mmol) in 1,2-dichloroethane (50 mL) was refluxed for 15 h. The resulting solution was filtered through a layer of Celite and concentrated under reduced pressure to give a reddish-black residue. The ^{31}P NMR spectrum of the crude product in $CDCl_3$ indicated a major peak at δ 115.1. Efforts to crystallize the product from various solvent systems failed. Purification of the crude compound by silica gel column chromatography resulted in decomposition. The reddish-black crude product of (S_C,R_P)-**8** (0.72 g, 1 mmol) in dichloromethane (20 mL) was then treated with excess aqueous sodium chloride (35 mL) with vigorous stirring at room temperature for 1 day. The organic layer was separated and dried over $MgSO_4$ and subsequently chromatographed on a silica gel column with CH_2Cl_2−hexane (4:1 v/v) as the eluent. The pure product (S_C,R_P)-**9** was crystallized from CH_2Cl_2−diethyl ether as orange prisms, 0.1 g (15%), mp 202−204 °C (dec), $[\alpha]_D$ +267.6° (*c* 0.68, CH_2Cl_2). Anal. Calcd for $C_{30}H_{34}NOPPdS$: C, 60.7; H, 5.7; S, 5.4. Found: C, 60.8; H, 5.7; S, 5.9. ^{1}H NMR ($CDCl_3$): δ 1.21 (d, 3H, $^3J_{HH}$ = 6.8 Hz, *Me6*), 1.43 (s, 3H, C=C*Me3*), 1.73 (d, 3H, $^3J_{HH}$ = 6.4 Hz, *Me9*), 1.98 (s, 3H, C=C*Me2*), 2.38 (dd, 1H, $^3J_{HH}$ = 24.5, $^3J_{HH}$ = 5.2 Hz, *H5*), 2.57 (s, 3H, N*Me*), 2.80 (d, 3H, $^4J_{PH}$ = 3.2 Hz, N*Me*), 3.10 (s, 1H, *H4*), 3.29 (s, 1H, *H1*), 3.62 (q, 1H, $^3J_{HH}$ = 4.83 Hz, *H6*), 4.26 (qn, 1H, $^3J_{HH}$ = $^4J_{PH}$ = 6.0 Hz, *H9*), 7.20−7.65 (m, 11H, *aromatics*). ^{31}P NMR ($CDCl_3$): δ 119.3 (s, 1P). IR (KBr): ν 1598.5 cm^{-1} (C=O).



Liberation of (1α,4α,5α,6*β*,7S)-5-(Thiocarboxylate)-2,3,6-trimethyl-7-phenyl-7-phosphabicyclo[2.2.1]hept-2-ene, *exo*-(S_P)-10. A solution of complex (S_C,R_P)-**9** (0.068 g, 0.1

mmol) in dichloromethane (10 mL) was stirred for 1 day with excess potassium cyanide (1.28 g, 20 mmol) in water (2 mL) under nitrogen. The organic layer was separated, washed consecutively with water and dilute sulfuric acid (to remove the naphthylamine auxiliary), and finally dried over $MgSO_4$. Removal of the solvent gave a viscous oil, 0.02 g (50%), $[\alpha]_D$ +21.7° (*c* 0.6, CH_2Cl_2). ^{31}P NMR ($CDCl_3$): δ 103.1 (s, 1P).

Crystal Structure Determination of (R_C,R_P)-3, (S_C,R_P)-6, and (S_C,R_P)-9. Table 2 provides a summary of the crystallographic data for compounds (R_C,R_P)-**3**, (S_C,R_P)-**6**, and (S_C,R_P)-**9**. Data were collected on Bruker SMART [(R_C,R_P)-**3** and (S_C,R_P)-**6**] and P4 [(S_C,R_P)-**9**] diffractometers, and the structures were refined based on F^2 using the SHELXTL program system.[14] The absolute structures of (R_C,R_P)-**3**, (S_C,R_P)-**6**, and (S_C,R_P)-**9** were determined by use of the Flack parameter [x^+ = −0.02(3), 0.000(17), and −0.03(8) respectively].

(14) *SHELXTL PC* version 5.1; Bruker AXS: Madison, WI, 1997.

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Supporting Information Available: For (R_C,R_P)-**3**, (S_C,R_P)-**6**, and (S_C,R_P)-**9**, tables of crystal data, data collection, solution and refinement, final postitional parameters, bond distances and angles, thermal parameters of non-hydrogen atoms, and calculated hydrogen parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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