Organopalladium Complex Promoted Asymmetric Hetero Diels−Alder Reactions between a Thiocarbonyl Dienophile and a Phospha-Substituted Cyclic Diene

Ying Qin,[1a] Andrew J. P. White,[1b] David J. Williams,[1b] and Pak-Hing Leung*,[1a]

Departments of Chemistry, National University of Singapore, Kent Ridge, Singapore 119260, and Imperial College, London, U.K. SW7 2AY

Received August 27, 2001

The asymmetric [4 + 2] hetero cycloaddition reaction between methyl cyanodithioformate and 1-phenyl-3,4-dimethylphosphole has been achieved stereoselectively by use of the organopalladium(II) complex derived from (*S*)-*N*,*N*-dimethyl-1-(1-naphthylamine) as the chiral reaction template to produce the corresponding (+)-*exo*-*syn*-methylthio-substituted phosphanorbornene P−S bidentate chelate. The generation of the chelating cycloadduct involved an intramolecular cycloaddition mechanism in which both the cyclic diene and the hetero dienophile were coordinated simultaneously to the chiral palladium template during the course of the cycloaddition reaction.

Introduction

The utilization of hetero dienes and hetero dienophiles in Diels−Alder reactions has received a great deal of attention because of the hetero substituents, which play important roles in the course of cycloaddition reactions and facilitate further transformations of the cycloadducts.[2] Recently, metal ions and metal complexes have been used very successfully as reaction activators in these hetero-cycloaddition reactions. In many cases, these classic inorganic reaction promoters exert significant control over the stereochemistry of the resulting hetero-substituted cycloadducts.[3] We are interested in asymmetric versions of such cycloaddition reactions and have recently reported a series of chiral palladium and platinum complex promoted asymmetric Diels−Alder reactions involving oxygen- and phosphorus-substituted cyclic dienes.[4] Here we report the novel asymmetric hetero Diels−Alder reaction between the cyclic diene 1-phenyl-3,4-dimethylphosphole (DMPP) and the C=S dienophile methyl cyanodithioformate in the presence of the chiral palladium(II) complex derived from (*S*)-*N*,*N*-dimethyl-1-(1-naphthylamine).

Results and Discussion

We have reported previously that the coordinated DMPP in both complexes (S_C)-**1** and (S_C)-**2** behaves as a typical cyclic diene toward reactive dienophiles.[4] For the intermolecular cycloaddition reactions, the cyclic diene in the neutral complex (S_C)-**1** frequently exhibits a higher reactivity than its counterpart in the complex (S_C)-**2**. However, no reaction was observed when (S_C)-**1** was treated with cyanodithioformate. In contrast, when the perchlorato complex (S_C)-**2** was treated with the C=S dienophile in dichloromethane at room temperature for 1 day, the chelating P−S cycloadduct (S_C,S_P)-**3** was generated as the sole product in the hetero Diels−Alder reaction (Scheme 1). Prior to isolation, the ^{31}P NMR spectrum ($CDCl_3$) of the crude reaction product exhibited a singlet at δ 115.0. No other ^{31}P NMR signals could be detected in this 202 MHz NMR spectrum, thus indicating that the cycloaddition reaction had proceeded in a stereospecific manner. The complex (S_C,S_P)-**3** was subsequently isolated as pale yellow prisms via silica gel chromatography and recrystallization from dichloromethane−hexane (42%): mp 187−190 °C, $[\alpha]_D$ +129.0 (*c* 1.0, CH_2Cl_2). The molecular structure and absolute configuration of (S_C,S_P)-**3** was established by a single-crystal X-ray structure determination, which revealed that the configurations at P(1), C(22), C(25), and C(27) are *S*, *R*, ***R*,** and *R*, respectively (Figure 1). Selected bond distances and angles of the cycloadduct complex are given in Table 1. The geometry at palladium is slightly distorted square planar, the coordination plane being planar to within only 0.11 Å, there being a ca. 7° twist

(1) (a) National University of Singapore. (b) Imperial College.

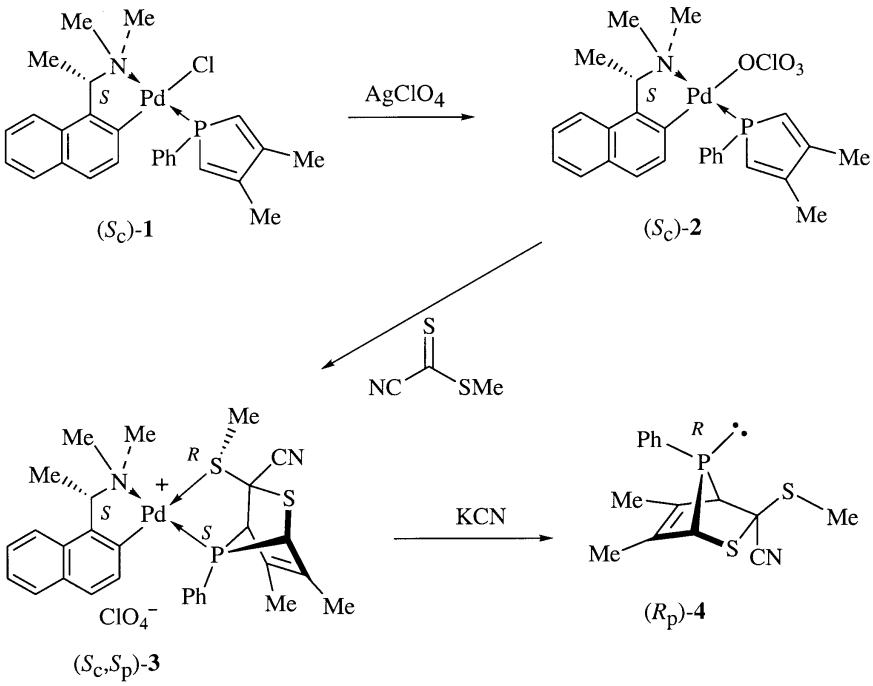
(2) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. Takahashi, T.; Noriyuki, K.; Koizumi, T. *Heterocycles* **1993**, *36*, 1601. Sera, A.; Ueda, N.; Itoh, K.; Yamada, H. *Heterocycles* **1996**, *43*, 2205. Babu, G.; Perumal, P. *Tetrahedron Lett.* **1997**, *38*, 5025. Babu, G.; Perumal, P. *Tetrahedron* **1998**, *54*, 1627. Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001. Nair, V.; Mathew, B.; Radhakrishnan, K. V.; Rath, N. P. *Tetrahedron* **1999**, *55*, 11017. Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660. Simonsen, K. B.; Sevenstrup, N.; Roberson, M.; Jorgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123. Yamada, T.; Kezuka, S.; Mita, T.; Ikeno, T. *Heterocycles* **2000**, *52*, 1041. Saito, T.; Furuie, H.; Ishigo-oka, Y.; Watanabe, I.; Kobayashi, K. *Heterocycles* **2000**, *53*, 1685. Shimizu, T.; Kamigata, N. *J. Organomet. Chem.* **2000**, *611*, 106. Nakash, M.; Sanders, J. K. M. *J. Org. Chem.* **2000**, *65*, 7266. Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. *Heterocycles* **2000**, *53*, 2667. Roberson, M.; Jepsen, A. S.; Jorgensen, K. A. *Tetrahedron* **2001**, *57*, 907. Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845. Mihara, J.; Aikawa, K.; Uchida, T.; Frie, R.; Katsuki, T. *Heterocycles* **2001**, *54*, 395. Pautet, F.; Nebois, P.; Bouaziz, Z.; Fillion, H. *Heterocycles* **2001**, *54*, 1095.

(3) Noels, A. F.; Graziani, M.; Hubert, A. J. *Metal Promoted Selectivity in Organic Synthesis*; Kluwer: Dordrecht, The Netherlands, 1991. Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff: Boston, MA, 1986. Fruhauf, H. W. *Chem. Rev.* **1997**, *97*, 523. Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997.

(4) Leung, P. H.; He, G.; Lang, H.; Liu, A.; Loh, S. K.; Selvaratnam, S.; Mok, K. F.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2000**, *56*, 7. Yeo, W. C.; Vittal, J. J.; White, A. J. P.; Williams. D. J.; Leung, P. H. *Organometallics* **2001**, *20*, 2167.

10.1021/om0107791 CCC: $22.00
Publication on Web 12/04/2001

Scheme 1



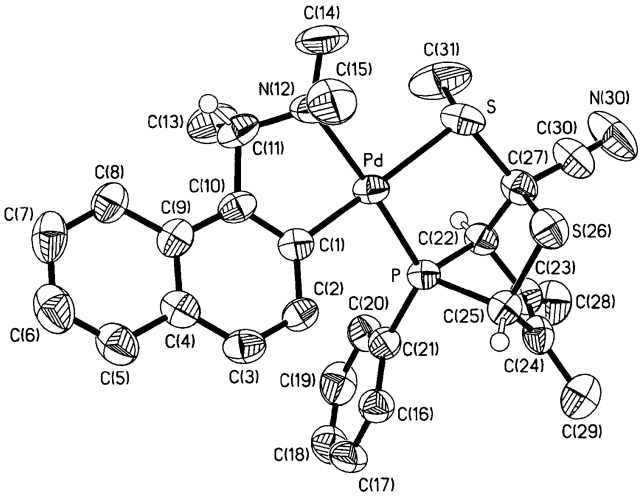


Figure 1. Molecular structure and absolute stereochemistry of the complex (S_C,S_P)-**3**.

Table 1. Selected Bond Lengths (Å) and Angles (deg) for the Complex (S_C,S_P)-3

Pd−S	2.427(2)	Pd−P	2.241(2)
Pd−C(1)	2.014(6)	Pd−N(12)	2.121(6)
S−C(27)	1.844(7)	P−C(25)	1.859(7)
C(25)−S(26)	1.840(7)	S(26)−C(27)	1.842(8)
C(27)−C(30)	1.465(10)	C(30)−N(30)	1.138(10)
C(1)−Pd−N(12)	79.8(2)	C(1)−Pd−P	97.5(2)
N(12)−Pd−P	175.2(2)	C(1)−Pd−S	173.1(2)
N(12)−Pd−S	96.9(2)	P−Pd−S	86.2(1)
Pd−S−C(27)	98.2(2)	Pd−P−C(25)	118.1(2)
S(26)−C(25)−P	101.4(3)	C(25)−S(26)−C(27)	92.2(3)
S(26)−C(27)−S	104.0(3)	C(27)−C(30)−N(30)	176.3(11)

between the N−Pd−C and S−Pd−P planes. The cis angles at palladium within the two chelate rings are 79.8(2)° within the naphthylamine and 86.2(1)° within the P−S heterocycle, respectively. The Pd−P distance is typical at 2.241(2) Å, but the Pd−S bond is longer than normal at 2.427(2) Å, a value very similar to that observed in a related compound containing the same naphthylamine auxiliary and the P−S bidentate species $Ph_2PCH_2CH_2SMe$ (average 2.40 Å).[5] The angles at phosphorus range between 82.1(3) and 126.8(2)°, the latter being associated with Pd−P−C(21). The angles at S, S(26), and C(25) within the six-membered chelate ring are all contracted significantly from normal values. The six-membered (P−S)−Pd chelate ring has a twist conformation, Pd−P−S−C(27) being planar to within 0.11 Å with S(26) and C(25) lying 1.85 and 1.36 Å, respectively, above this plane. It should be noted that the coordinated sulfur atom in (S_C,S_P)-**3** is a stereogenic center with an *R* absolute configuration. The *R* rather than *S* stereochemistry for this sulfur center can be attributed to the unfavorable steric congestion that would otherwise arise between the S−Me and the neighboring N−Me_2 groups.

Treatment of (S_C,S_P)-**3** with excess aqueous potassium cyanide liberated the optically pure hetero cycloadduct (R_P)-**4** as an air-sensitive colorless oil in 70% yield: $[\alpha]_D$ +10.0 (*c* 0.5, CH_2Cl_2). The ^{31}P NMR spectrum of the free ligand in $CDCl_3$ exhibits a singlet at δ 91.1. This low field signal confirms that the exo-syn stereochemical relationship is retained. It is noteworthy that the apparent inversion of configuration that takes place at the phosphorus stereogenic center when the cycloadduct is liberated from the metal is merely the consequence of the Cahn−Ingold−Prelog (CIP) sequence rules.[6] Owing to the air sensitivity and the configurational instability of the noncoordinated bridgehead phosphorus atom, the liberated (R_P)-**4** cannot be stored in its pure form. For storage purposes, it was necessary to recoordinate the optically active ligand immediately to selected metal ions to form stable metal complexes.

From a mechanistic standpoint, the formation of complex (S_C,S_P)-**3** requires both DMPP and cyanodithio-

(5) Chooi, S. Y. M.; Hor, T. S. A.; Leung, P. H.; Mok, K. F. *Inorg. Chem.* **1992**, *31*, 1494.
(6) Cahn, R. S.; Ingold, C. K. Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

formate to coordinate simultaneously to the cationic palladium template during the course of the intramolecular hetero cycloaddition reaction. It should be noted that there are two potential sulfur donors within the reacting dienophile but that the cycloaddition reaction proceeds only when the thioether sulfur is coordinated to the palladium. Sterically, however, the coordination of the C═S sulfur to Pd would be preferred. Thus, it is clear that the C═S→Pd bond must be kinetically unstable to allow the competing thioether-S→Pd coordination. Being a more bulky monodentate donor, however, it has been established that such a thioether-S→Pd bond is also kinetically unstable. Nevertheless, this labile thioether-S→Pd bond is crucial for the activation of the hetero cycloaddition reaction. Thus, in complex (S_C)-**1** where one of the coordination sites is blocked by a relatively stable and inert chloro ligand,[7] DMPP failed to undergo the cycloaddition reaction.

It is interesting to note that the thioether-S→Pd bond in cycloadduct complex (S_C,S_P)-**3** remains kinetically labile in solution. Such dynamic properties of the S→Pd bonding can be clearly revealed by the two-dimensional ^{1}H ROESY NMR studies.[8] In this NMR investigation, the characteristic orientation of the chiral organopalladium−naphthylamine unit is used as the spectroscopic reference. It is well established that, both in the solid state and in solution, the chiral (*S*)-metalated naphthylamine ring invariably adapts the static λ ring conformation in solution.[9] Thus, the NMe groups and the protruding naphthylamine proton at C(2) are particularly sensitive to the stereochemical features of their neighboring donor atoms. Figure 2 shows the ROESY NMR spectrum of (S_C,S_P)-**3** in $CDCl_3$. The naphthylamine auxiliary shows all the expected inter-chelate NOE interactions with the P−S bidentate cycloadduct.[8] For example, the protruding naphthylamine proton at C(2) contacts clearly with the proton at C(25) of the rigid phosphanorbornene unit (signal O). This NOE contact between the two chelating ligands is indeed expected, as the two protons involved are located on the same side of the square-planar complex. Interestingly, the C(2) proton shows a similar closeness with the proton at C(22), which is located on the opposite side of the phosphanorbornene skeleton (signal J). Due to the absolute stereochemical orientation of the two chiral ligands, the C(2) and C(22) protons are located on the opposite sides of the square-planar complex and they are sterically separated by the PPh moiety. Thus, the strong NOE contact between these two protons could only be possible when the Pd−P bond is indeed free to rotate. Evidently, the S→Pd bond in complex (S_C,S_P)-**3** is kinetically labile in solution. It is noteworthy that the SMe group also shows strong NOE contacts with both protons at C(22) and C(25) (signals I and N). These NOE contacts, however, could be due to the same kinetic instability of the S→Pd bond or the low inversion barrier of the coordinated chiral sulfur donor,[5,10] or both.

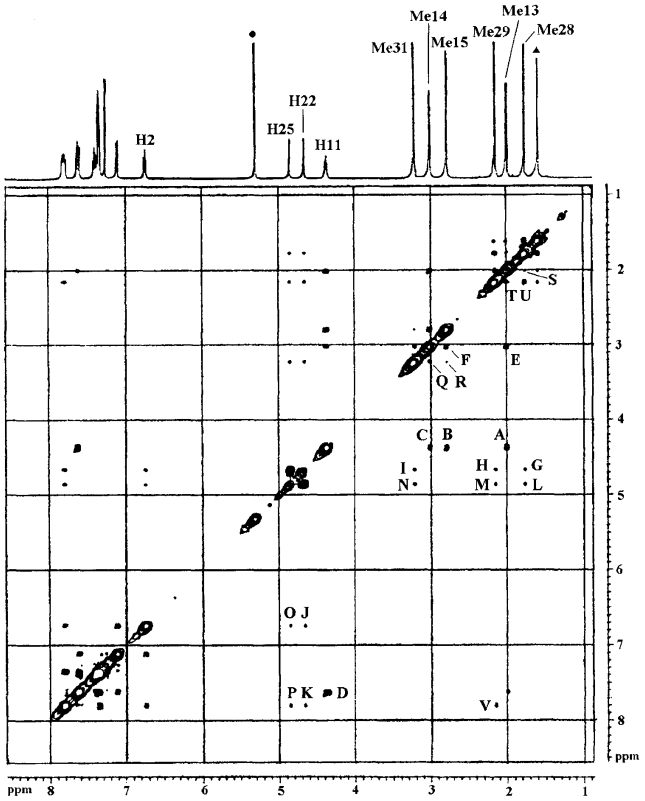


Figure 2. Two-dimensional ^{1}H ROESY NMR spectrum of the complex (S_C,S_P)-**3** in $CDCl_3$ (●, CH_2Cl_2; ▲, H_2O). All off-diagonal peaks are of negative intensity. Selected NOE contacts: A, H11−Me13; B, H11−Me15; C, H11−Me14; D, H11−H8; E, Me13−Me14; F, Me14−Me15; G, H22−Me28; H, H22−Me29; I, H22−Me31; J, H22−H2; K, H22−Ph21; L, H25−Me28; M, H25−Me29; N, H25−Me31; O, H25−H2; P, H25−Ph21; Q, Me14−Me31; R, Me15−Me31; S, Me13−Me28; T, Me13−Me29; U, Me28−Me29; V, Me29−Ph21.

The above spectroscopic investigations illustrate that the S→Pd coordination is important to the activation of cyanodithioformate toward the exo-cycloaddition reaction, although it does not contribute significantly to the kinetic stability of the resulting P−S bidentate chelate. Interestingly, when the labile cyanodithioformate dienophile was replaced with the powerful ligand *N*,*N*-dimethyl(diphenylphosphino)thioacrylamide, the analogous C═S activation did not occur under similar reaction conditions.[11] The formation of the chiral cycloadduct complex (S_C,S_P)-**3** represents what we believe to be the first example of a phospha-substituted cyclic diene being involved in the asymmetric [4 + 2] cycloaddition reaction with a hetero C═X dienophile. Investiga-

(7) Dunina, V. V.; Golovan, E. B.; Qulyukina, N. S.; Buyevich, A. V. *Tetrahedron: Asymmetry* **1995**, *6*, 2731.

(8) Aw, B. H.; Selvaratnam, S.; Leung, P. H.; Rees, N. H.; McFarlane, W. *Tetrahedron: Asymmetry* **1996**, *7*, 1753. Leung, P. H.; Delvaratnam, S.; Cheng, C. R.; Mok, K. F.; Rees, N. H.; McFarlane, W. *Chem. Commun*. **1997**, 751. Leung, P. H.; Quek, G. H.; Lang, H.; Liu, A. M.; Mok, K. F.; White, A. J. P.; Williams, D. J.; Rees, N. H.; McFarlane, W. *J. Chem. Soc., Dalton Trans.* **1998**, 1639. Aw, B.-H.; Hor, A. T. S.; Selvaratnam, S.; Mok, K. F.; White, A. J. P.; Williams, D. J.; Rees, N. H.; McFarlare, W.; Leung, P.-H. *Inorg. Chem*. **1997**, *36*, 2138. Lang, H. F.; Leung, P. H.; Rees, N. H.; McFarlane, W. *Inorg. Chim. Acta* **1999**, *284*, 99. Liu, X.; Mok, K. F.; Leung, P. H. *Organometallics* **2001**, *20*, 3918.

(9) Kerr, P. G.; Leung, P. H.; Wild, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 4321. Chooi, S. Y. M.; Tan, M. K.; Leung, P. H.; Mok, K. F. *Inorg. Chem*. **1994**, *33*, 3096. Dunina, V. V.; Golovan, E. B.; Gulyukina, N. S.; Buyevich, A. V. *Tetrahedron: Asymmetry* **1995**, *6*, 2731. Hockless, D. C, R.; Gugger, P. A.; Leung, P. H.; Mayadunne, R. C.; Pabel, M.; Wild, S. B. *Tetrahedron* **1997**, *53*, 4083. He, G.; Loh, S. K.; Vittal, J. J.; Mok, K. F.; Leung, P. H. *Organometallics* **1998**, *17*, 3931.

(10) Abel, E. W.; Bhargava, S. K.; Orrell, K. G. *Prog. Inorg. Chem*. **1984**, *32*, 1. Orrell, K. G. *Coord. Chem. Rev*. **1989**, *96*, 1.

(11) Leung, P. H.; Qin, Y.; He, G.; Mok, K. F.; Vittal, J. J. *J. Chem. Soc., Dalton Trans.* **2001**, 309.

tions on Diels−Alder reactions involving other heterosubstituted dienes and dienophiles are currently in progress.

Experimental Section

Reactions involving air-sensitive compounds were performed under a positive pressure of purified nitrogen. NMR spectra were recorded at 25 °C on Bruker ACF300 and AMX500 spectrometers. The phase-sensitive ^{1}H ROESY NMR experiments were acquired into a 1024 × 512 matrix with a 250 ms spin locking time and a spin lock field strength such that $\gamma B_1/2\pi = 5000$ Hz and then transformed into 1024 × 1024 points using a sine bell weighting function in both dimensions. Optical rotations were measured on the specified solution in a 1 dm cell at 25 °C with a Perkin-Elmer 341 polarimeter. Elemental analyses were performed by the Elemental Analysis Laboratory of the Department of Chemistry at the National University of Singapore.

The chiral palladium complexes (S_C)-**1** and (S_C)-**2** were prepared as previously described.[4]

{(*S*)-1-[1-(Dimethylamino)ethyl]-2-naphthyl-*C*^{2},*N*}-{(1α,4α,5*R*,7*S*)-2,3-dimethyl-5-(α-methylsulfanyl-*β*-cyano)-7-phenyl-6-thia-7-phosphabicyclo[2.2.1]hept-2-ene-*S*^{5},*P*^{7}}-palladium(II) Perchlorate ((S_C,S_P)-3). A solution of the perchlorato complex (S_C)-**2** (0.17 g, 0.28 mmol) in dichloromethane (30 mL) was treated with excess methyl cyanodithioformate (0.08 g, 0.68 mmol) at room temperature for 1 day. Removal of the solvent under reduced pressure gave a reddish oil. The crude product was purified by silica gel column chromatography with dichloromethane−acetone as eluent (9/1, v/v) and then crystallized from dichloromethane-hexane (5/1, v/v) to give (S_C,S_P)-**3** as pale yellow prisms: mp 187−190 °C dec; $[\alpha]_D$ +129.0 (*c* 0.5, CH_2Cl_2); yield 0.084 g (42%). Anal. Calcd for $C_{29}H_{32}ClN_2O_4PPdS_2$: C, 49.1; H, 4.5; N, 4.0; S, 9.0. Found: C, 49.1; H, 4.6; N, 3.8; S, 9.1. ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 3H, C=C*Me*), 1.98 (d, 3H, $^3J_{HH} = 6.4$ Hz, CH*Me*), 2.13 (s, 3H, C=C*Me*), 2.76 (s, 3H, N*Me*), 2.99 (s, 3H, N*Me*), 3.20 (s, 3H, S*Me*), 4.35 (qn, 1H, $^3J_{HH} = {}^4J_{PH} = 6.0$ Hz, C*H*Me), 4.70 (s, 1H, PC*H*), 4.82 (s, 1H, PC*H*), 6.71−7.81 (m, 11H, aromatics). ^{31}P NMR ($CDCl_3$): δ 115.0 (s, 1P).

Liberation of (1α,4α,5*R*,7*R*)-2,3-Dimethyl-5-(α-methylsulfanyl-*β*-cyano)-7-phenyl-6-thia-7-phosphabicyclo[2.2.1]-hept-2-ene ((R_p)-4). A solution of complex (S_C,S_P)-**3** (0.09 g, 0.13 mmol) in dichloromethane (10 mL) was stirred vigorously with excess potassium cyanide (0.82 g, 12.6 mmol) in water (2 mL) at room temperature for 5 h. The organic layer was separated, washed consecutively with water and dilute sulfuric acid (0.5 M), and dried over $MgSO_4$. Upon the removal of solvent, the free ligand (R_p)-**4** was obtained as a highly air-sensitive colorless viscous oil: yield 0.027 g (70%); $[\alpha]_D$ +10.0 (*c* 0.5, CH_2Cl_2). ^{31}P NMR ($CDCl_3$): δ 91.1 (s, 1P).

Table 2. Crystallographic Data for the Complex (S_C,S_P)-3

formula	$C_{29}H_{32}N_2O_4ClPS_2Pd\cdot CH_2Cl_2$
fw	794.4
space group	$P2_12_12_1$
cryst syst	orthorhombic
a/Å	10.924(2)
b/Å	13.396(1)
c/Å	24.209(4)
V/Å^3	3542.7(8)
Z	4
T/K	293(2)
ρ_{calcd}/g cm^{-3}	1.489
λ/Å	0.710 73
μ/cm^{-1}	9.5
Flack params	+0.04(5)
R1 (obsd data)[a]	0.037
wR2 (obsd data)[b]	0.083

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$, $w^{-1} = \sigma^2(F_o)^2 + (aP)^2 + bP$.

Crystal Structure Determination of (S_c,S_p)-3. A clear yellow prism of dimensions 0.83 × 0.73 × 0.60 mm obtained from a dichloromethane−hexane solution of complex (S_C,S_P)-**3** was used. Crystallographic details are given in Table 2. Data were measured on a Siemens P4/PC diffractometer with Mo Kα radiation ($\lambda = 0.710\ 73$ Å; graphite monochromator) using ω scans. The structure was solved by direct methods, and all the major occupancy non-hydrogen atoms were refined anisotropically. Semiempirical absorption corrections were applied, and refinements by full-matrix least squares were based on the SHELXL PC program system.[12] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced at fixed distances from carbon and nitrogen atoms and were assigned fixed thermal parameters.

Acknowledgment. We are grateful to the National University of Singapore for financial support and a Ph.D. research scholarship for Y.Q.

Supporting Information Available: For (S_C,S_P)-**3**, tables of crystal data and data collection and solution and refinement details, final positional 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.

OM0107791

(12) SHELXTL PC, version 5.03; Siemens Analytical X-ray Instruments, Madison, WI, 1994.