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A Rational Approach to the Design and Synthesis of Chiral Organopalladium-Amine Complexes

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A new chiral auxiliary, (±)-*N*,*N*-dimethyl-1-(2,5-dimethylphenyl)ethylamine, was designed and synthesized in two steps from 1-acetyl-2,5-dimethylbenzene. Its cyclopalladated dimeric complex could be efficiently resolved via the formation of (*S*)-prolinate derivatives. Both hand forms of the complex could be obtained in similar yields. Despite the enormous inter-chelate steric constraints, the bulky monodentate ligand 3,4-dimethyl-1-phenylphosphole (DMPP) is able to coordinate regiospecifically to the orthopalladated 2,5-dimethylbenzylamine unit trans to the NMe_2 group. Compared to its naphthylamine analogue, the orthopalladated 2,5-dimethylbenzylamine complex exhibits a significantly higher stereoselectivity in the chiral template promoted asymmetric cycloaddition reaction between DMPP and ethyl vinyl ketone.

Introduction

In the past decade, chiral organopalladium complexes have been developed as useful reagents in many aspects of synthetic stereochemistry. For examples, they have been used as efficient resolving agents for the optical resolution of chiral ligands,[1] highly sensitive diamagnetic shift reagents for the determination of enantiomeric purities by NMR spectroscopy,[2] clear and reliable stereochemical references for the NMR assignments of absolute configurations of new compounds in solution,[3] highly versatile catalysts in several stereochemically demanding asymmetric transformation,[4] and chiral templates for asymmetric Diels−Alder reactions.[5]

Among these complexes, (*S*)-**1** and (*S*)-**2**, as well as their derivatives, are the most commonly used. It has been proven that (*S*)-**2** is superior to (*S*)-**1** in many applications, because the five-membered cyclopalladated ring in (*S*)-**2** is conformationally rigid in both solid state and solution form.[1,6] The steric interaction between H(8) and the methyl group at the stereogenic carbon center confines the methyl group in the

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(1) For recent examples, see: Hockless, D. C.; Gugger, P. A.; Leung, P. H.; Mayadunne, R. C.; Pabel, M.; Wild, S. B. *Tetrahedron* **1997**, *53*, 4083 and references therein. Doucet, H.; Brown, J. M. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3775. Albert, J.; Cadena, J. M.; Granell, J.; Muller, G.; Ordinas, J. I.; Panyella, D.; Puerta, C.; Sanudo, C.; Valerga, P. *Organometallics* **1999**, *18*, 3623. Bienewald, F.; Ricard, L.; Mercier, F.; Mathey, F. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4701. He, G. S.; Mok, K. F.; Leung, P. H. *Organometallics* **1999**, *18*, 4027.

(2) Chooi, S. Y. M.; Leung, P. H.; Lim, C. C.; Mok, K. F.; Quek, G. H.; Sim, K. Y.; Tan, M. K. *Tetrahedron*: *Asymmetry* **1992**, *3*, 529. Kyba, E. P.; Rines, S. P. *J. Org. Chem.* **1982**, *47*, 4800. Böhm, A.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3262.

(3) Bookham, J. L.; McFarlane, W. *Chem. Commun.* **1993**, 1352. Aw, B.-H.; Selvaratnam, S.; Leung, P. H.; Rees, N. H.; McFarlane, W. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1753. 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. Leung, P. H.; Selvaratnam, S.; Cheng, C. R.; Mok, K. F.; Rees, N. H.; McFarlane, W. *Chem. Commun.* **1997**, 751. Leung, P. H.; Quek, G. H.; Lang, H. F.; 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. Lang, H. F.; Leung, P. H.; Rees, N. H.; McFarlane, W. *Inorg. Chim. Acta* **1999**, *284*, 99.

(4) Leung, P. H.; Ng, K. H.; Li, Y.; White A. J. P.; Williams, D. J. *Chem. Commun.* **1999**, 2435. Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933. Cohen, F.; Overman, L. E. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3213.

(5) For some recent examples, see: Leung, P. H.; Siah, S. Y.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1998**, 893. Lang, H. F.; Vittal, J. J.; Leung, P. H. *J. Chem. Soc., Dalton Trans.* **1998**, 2109. Song, Y. C.; Mok, K. F.; Leung, P. H.; Chan, S. H. *Inorg. Chem.* **1998**, *37*, 6339. Leung, P. H.; Liu, A.; Mok, K. F. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1309. Song, Y.; Vittal, J. J.; Chan, S. H.; Leung, P. H. *Organometallics* **1999**, *18*, 650. He, G.; Qin, Y.; Mok, K. F.; Leung, P. H. *Chem. Commun.* **2000**, 167. Leung, P. H.; Qin, Y.; He, G.; Mok, K. F.; Vittal, J. J. *J. Chem. Soc., Dalton Trans.* **2001**, 309. Yeo, W. C.; Vittal, J. J.; White, A. J. P.; Williams, D. J.; Leung, P. H. *Organometallics* **2001**, *20*, 2167. 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. Liu, X.; Mok, K. F.; Vittal, J. J.; Leung, P. H. *Organometallics* **2000**, *19*, 3722. Liu, X.; Mok, K. F.; Leung, P. H. *Organometallics* **2001**, *20*, 3918.

(6) Alcock, N. W.; Hulmes, D. I.; Brown J. M. *Chem. Commun.* **1995**, 395. Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron*: *Asymmetry* **1993**, *4*, 743.

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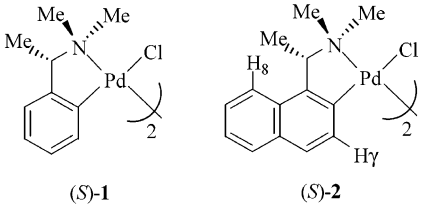
axial position and, hence, locks the cyclopalladated ring in the λ conformation. On the other hand, the organometallic ring conformation of (*S*)-**1** is not locked and the puckered ring undergoes rapid interconversion between δ and λ conformations in solution. In the solid state, both δ and λ conformations are also frequently found in (*S*)-**1** derivatives.



(*S*)-**1** (*S*)-**2**

Complex **3** is derived from **2** by the cleavage reaction with 3,4-dimethyl-1-phenylphosphole (DMPP) (Scheme 1). We have studied the Diels−Alder cycloaddition reactions of this complex with a series of dienophiles.[5,7] These endo-cycloadditions exclusively produce two stereoisomeric endo-cycloadducts, which are generated from the two possible orientations of the dienophiles in the transition states. For example, when (*S*)-**3** was treated with ethyl vinyl ketone at 70 °C, two endo-cycloaddition products—(S_C,S_P)-**4** and (S_C,R_P)-**4**—were obtained as a ca. 1:1 diastereomeric mixture (Scheme 1).[7] It appears that the chiral naphthylamine auxiliary exerts a weak influence on the reaction site. Evidently, the DMPP moiety enjoys a certain degree of rotation about the P−Pd coordination bond and, thus, the observed poor stereoselectivity..

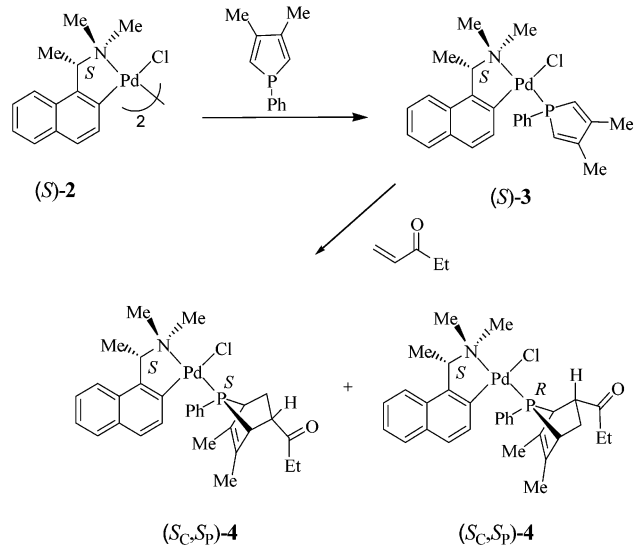
It has been established that the coordination site cis to the N atom is controlled stereochemically by the two prochiral NMe groups.[8] We believe that if a spacer group is introduced in the γ-position of the aromatic ring, the stereochemistry of the coordination site trans to the N donor atom would also be controlled more efficiently by the chiral auxiliary. To test this idea, we synthesized the chiral 2,5-dimethylphenylamine complex, **5**. In this new complex, the methyl group in position 2 is designed to lock the five-membered organopalladium ring in a fixed conformation, and the other methyl substituent, in position 5, protrudes into the space close to the coordination site trans to the N atom and is expected to exert stereochemical influence on the reaction site. In this paper, we report the synthesis and efficient resolution of complex **5**. Application of this new chiral template in the asymmetric Diels−Alder reaction is also presented.

Results and Discussion

Synthesis of the Racemic Ligand and Its Palladium Complexes. The primary amine **6** was obtained readily in the racemic form by acid hydrolysis of the reaction product between 1-acetyl-2,5-dimethylbenzene and ammonium formate at 180 °C (Scheme 2). Methylation of this amine with a mixture of formic acid and formaldehyde afforded the *N*,*N*-dimethyl-substituted amine (±)-**7**, in 78% yield. Neither (±)-**6** nor (±)-**7** could be resolved by various enantiopure acids, such as mandelic acid, tartaric acid and its derivatives, malic acid, and (−)-DAG.[9] The racemic (±)-**7** was therefore used directly for the cyclopalladation reaction.

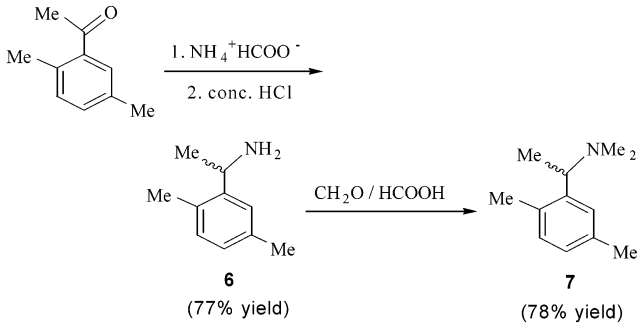
In contrast to **1** and **2**, the dimeric complex **5** could not be prepared directly from $Li_2[PdCl_4]$. The orthopalladation of (±)-**7**, however, could be achieved in acetonitrile, using $[Pd(MeCN)_4](ClO_4)_2$ as the palladium source in the presence of an equimolar amount of triethylamine (Scheme 3). Treatment of the reaction mixture with dilute HCl gave (±)-**5**

Scheme 1



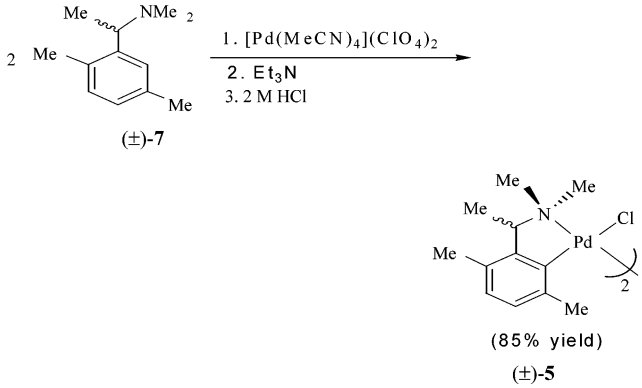
(S_C,S_P)-**4** (S_C,S_P)-**4**

Scheme 2



6 (77% yield) **7** (78% yield)

Scheme 3



(±)-**7** (85% yield) (±)-**5**

(7) Leung, P. H.; Loh, S. K.; Mok, K. F.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1997**, 1987.
(8) Chooi, S. Y. M.; Tan, M. K.; Leung, P. H.; Mok, K. F. *Inorg. Chem.* **1994**, *33*, 3096.
(9) Mohacsi, E.; Leimgruber, W. *Org. Synth.* **1976**, *55*, 80.

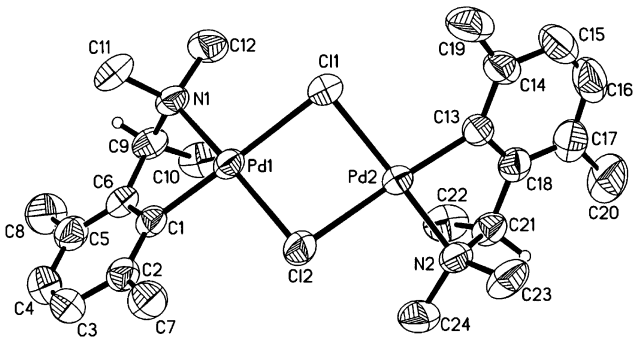


Figure 1. Molecular structure and absolute stereochemistry of the *S*-enantiomer in the μ-dichloro complex (±)-**5**.

Table 1. Selected Bond Lengths and Bond Angles of (±)-**5**

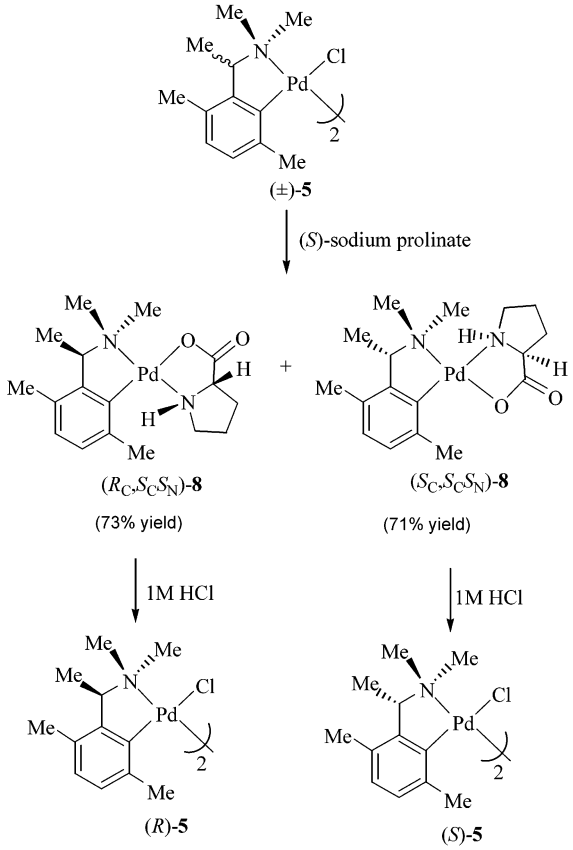
Bond Lengths (Å)			
Pd(1)−C(1)	1.987(3)	Pd(2)−C(13)	1.988(3)
Pd(1)−N(1)	2.088(3)	Pd(2)−N(2)	2.076(3)
Pd(1)−Cl(1)	2.468(1)	Pd(2)−Cl(1)	2.338(1)
Pd(1)−Cl(2)	2.343(1)	Pd(2)−Cl(2)	2.470(1)

Bond Angles (deg)			
C(1)−Pd(1)−N(1)	80.47(12)	C(13)−Pd(2)−N(2)	81.03(12)
N(1)−Pd(1)−Cl(1)	97.82(8)	N(2)−Pd(2)−Cl(1)	168.43(8)
N(1)−Pd(1)−Cl(2)	169.96(8)	N(2)−Pd(2)−Cl(2)	97.42(8)
C(1)−Pd(1)−Cl(1)	178.01(10)	C(13)−Pd(2)−Cl(1)	98.01(10)
C(1)−Pd(1)−Cl(2)	97.13(9)	C(13)−Pd(2)−Cl(2)	175.00(9)
Cl(1)−Pd(1)−Cl(2)	84.38(3)	Cl(1)−Pd(2)−Cl(2)	84.46(3)
Pd(1)−Cl(1)-−Pd(2)	91.50(3)	Pd(1)−Cl(2)−Pd(2)	91.33(3)

in the form of yellow prisms, in 85% isolated yield. Alternatively, $Pd(NO_3)_2$ in CH_3CN could be utilized to replace $[Pd(MeCN)_4](ClO_4)_2$, giving (±)-**5** in a similar high yield.

The solid-state structure of the dimeric complex (±)-**5** was determined by X-ray crystallography (Figure 1). Selected bond lengths and bond angles are listed in Table 1. The two N and C donor atoms in the molecule are trans to each other. The two halves of the asymmetric molecule have the same relative configurations but are slightly different in regard to the bond lengths and bond angles. Each Pd atom adopts the expected distorted square planar coordination geometry, with tetrahedral distortions of 6.8° for the Pd(1) atom and 12.4° for the Pd(2) atom. The central four-membered ring {Pd(1)−Cl(1)−Pd(2)−Cl(2)} is bent along the Cl(1)−Cl(2) axis by 29.8°. This angle appears to be the largest among those reported for similar dimeric cyclopalladated arylamines.[10] Both five-membered palladacycles of the molecule adopt the λ conformation. The methyl substituents {C(10) and C(22)} borne on the stereocenters adopt axial positions, as expected. The torsion angles are Cl(2)−Pd(1)−C(1)−C(2) = 41.2° and Cl(1)−Pd(2)−C(13)−C(14) = 39.8°. Such a twisting can be partially attributed to the repulsive interactions between the methyl "spacers" (C(7), C(19)) and the two bridged Cl atoms. The distances of C(7)−Cl(2) and C(19)−Cl(1) were found to be 3.220 and 3.236 Å, respectively, which are significantly less than the sum of the van der Waals radii of the two atoms, 3.8 Å. Hence, these two methyl groups, as well as the aromatic rings, are projected away from the chloro bridges.

Scheme 4



Optical Resolution of the Dimeric Complex (±)-5. The resolution of the racemic mixture of complex (±)-**5** was determined using (*S*)-prolinate as an auxiliary ligand, as shown in Scheme 4. Treatment of the racemic dimeric complex (±)-**5** with two molar equivalents of sodium prolinate gave a mixture of two diastereomers (R_C,S_CS_N)-**8** and (S_C,S_CS_N)-**8**. Single crystallization by dilution of a dichloromethane solution of the diastereomeric mixture with hexane afforded the less-soluble diastereomer (R_C,S_C,S_N)-**8** in the form of pale-yellow flakes in 73% yield with $[\alpha]_D$ = +36.1° (CH_2Cl_2). A subsequent protonation of the auxiliary amino acidate ligand with dilute hydrochloric acid in a two-phase solvent system led to the enantiomerically pure complex dimer (*R*)-**5** in the form of a yellow powder in 98% yield with $[\alpha]_D$ = −214° (CH_2Cl_2). The remaining diastereomer in the mother liquor was recrystallized from acetonitrile−diethyl ether to give (S_C,S_CS_N)-**8** in the form of pale-yellow prisms in 75% yield (via NMR) with $[\alpha]_D$ = +236° (CH_2Cl_2). This prolinate complex was converted to the dichloro dimer (*S*)-**5** in a similar way, using dilute hydrochloric acid (98% yield).

Molecular Structure of (R_C,S_CS_N)- and (S_C,S_CS_N)-8. The solid structures of both prolinate derivatives (R_C,S_CS_N)-**8** and (S_C,S_CS_N)-**8** were determined by single-crystal X-ray diffraction investigations. For the less-soluble diastereomer, (R_C,S_CS_N)-**8**, single crystals were obtained by slow evaporation of a dichloromethane−hexane mixture. Figure 2 depicts

(10) Dunina, V. V.; Kuz'mina, L. G.; Kazakova, M. Y.; Grishin, Y. K.; Veits, Y. A.; Kazakova, E. I. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2537. Alyea, E. C.; Dias, S. A.; Ferguson, G.; McAlees, A. J.; McGrindle, R.; Roberts, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 4985.

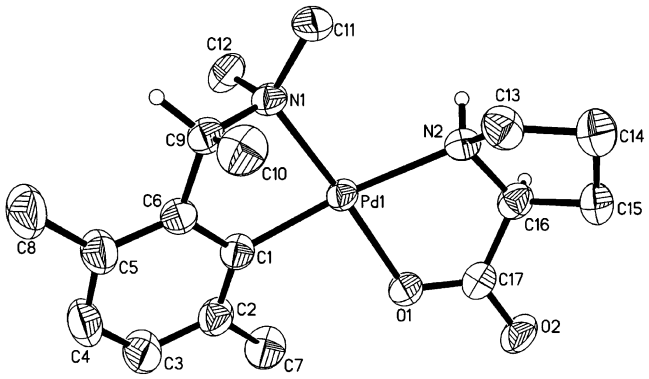


Figure 2. Molecular structure and absolute stereochemistry of (R_C,$S_C$$S_N$)-**8**.

Table 2. Selected Bond Lengths and Bond Angles of Complex (R_C,$S_C$$S_N$)-**8**

Bond Lengths (Å)			
Pd(1)−C(1)	2.005(3)	Pd(1)−O(1)	2.032(2)
Pd(1)−N(1)	2.071(2)	Pd(1)−N(2)	2.180(2)
C(8)−C(10)	3.551(5)	C(7)−O(1)	2.945(5)
C(8)−H(9)	2.677(5)	C(11)−C(13)	3.465(5)
Bond Angles (deg)			
C(1)−Pd(1)−N(1)	80.49(11)	C(1)−Pd(1)−O(1)	96.13(10)
N(1)−Pd(1)−O(1)	176.48(9)	N(2)−Pd(1)−C(1)	172.06(10)
N(2)−Pd(1)−O(1)	80.13(8)	N(1)−Pd(1)−N(2)	103.09(9)

the molecular structure, and Table 2 lists the selected bond lengths and bond angles. The (R_C) absolute configuration of the α-carbon stereocenter of the palladacycle is confirmed using (S_C,S_N)-prolinate as the internal stereochemical reference.

In contrast to the trans-(*N*,*N*) arrangement of the coordination sphere found in other (*S*)-prolinate palladium(II) complexes containing orthopalladated ligands of the C,N-type,[11] a cis-(*N*,*N*) geometry was observed for the present complex, (R_C,$S_C$$S_N$)-**10**. The coordination geometry is distorted square planar, as expected. The bond lengths and bond angles about the Pd atom are comparable to those reported for similar prolinate palladium(II) complexes, except for the N(2)−Pd(1) distance of 2.180(2) Å, which is significantly longer than the reported values of 1.973−2.065 Å.[11] It appears that the lengthening of this bond is the result of a large trans influence of the C donor atom of the palladacycle. However, the repulsive interaction between the C(13) atom of the prolinate moiety and the NMe group C(11) should not be excluded, because the distance between the two C atoms is 3.456 Å, which is much less than the sum of the van der Waals radii, 4.0 Å. The tetrahedral distortion of the palladium coordination environment is minimal, with the dihedral angle between the {Pd(1)N(1)C(1)} and {Pd(1)N(2)O(1)} planes being 7.0°. The organopalladium five-membered ring adopts the expected δ conformation, with the α-methyl group C(10) being axially disposed. The geometric parameters of the prolinate moiety of this diastereomer are mainly in a range typical of (*S*)-prolinate palladium(II) complexes.[11,12]

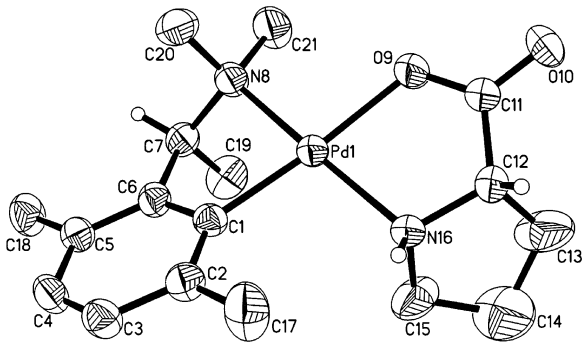


Figure 3. Molecular structure and absolute stereochemistry of (S_C,$S_C$$S_N$)-**8**.

Table 3. Selected Bond Lengths and Bond Angles of Complex (S_C,$S_C$$S_N$)-**8**

Bond Lengths (Å)			
Pd(1)−C(1)	2.003(3)	Pd(1)−O(1)	2.105(2)
Pd(1)−N(8)	2.072(2)	Pd(1)−N(16)	2.068(2)
C(18)−C(19)	3.659(5)	C(17)−H(16)	2.581(5)
C(18)−H(7)	2.598(5)	C(17)−N(16)	3.233(5)
Bond Angles (deg)			
C(1)−Pd(1)−N(16)	102.68(10)	C(1)−Pd(1)−O(9)	175.29(10)
N(8)−Pd(1)−O(9)	94.80(9)	C(1)−Pd(1)−N(8)	80.97(10)
N(16)−Pd(1)−O(9)	81.84(9)	N(16)−Pd(1)−N(8)	169.44(10)

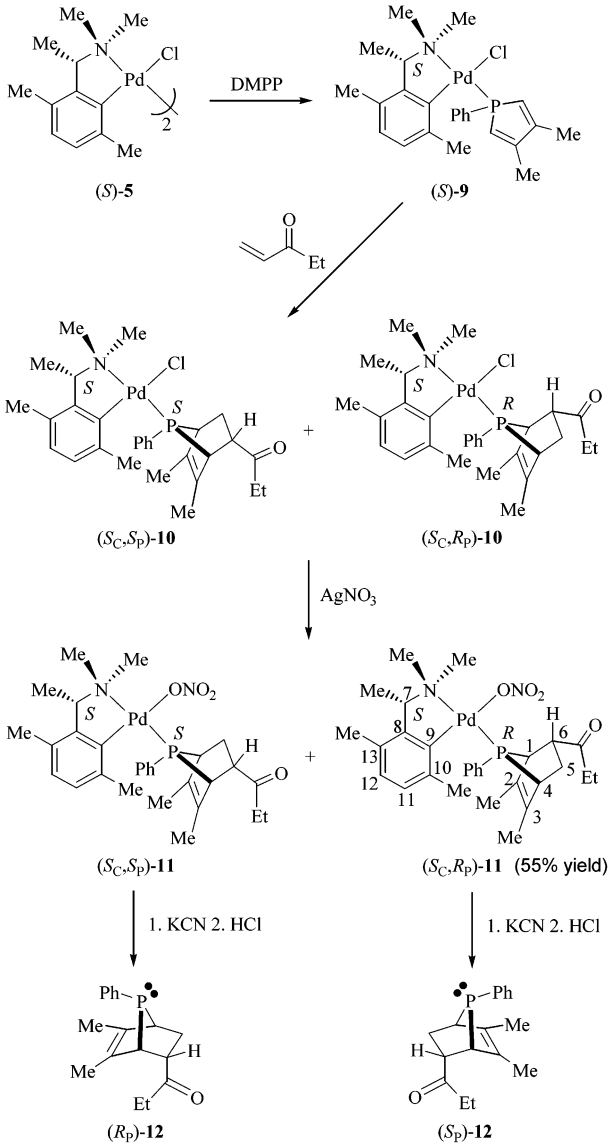
For the more-soluble diastereomer (S_C,$S_C$$S_N$)-**8**, pale-yellow crystals suitable for X-ray crystallography were obtained from acetonitrile−diethyl ether. Figure 3 shows the molecular structure of the complex, and Table 3 lists selected bond lengths and bond angles. The X-ray crystallographic study reveals that the absolute configuration about the α-carbon stereocenter of the palladacycle is *S*, with the α-methyl group occupying the axial position. The conformation of the five-membered palladacycle is λ. In contrast to (R_C,$S_C$$S_N$)-**8**, this complex adopts a trans-(*N*,*N*) arrangement, as with other similar prolinate complexes.[11,12] The distortion of the square planar palladium coordination geometry is also minimal, because the dihedral angle between the two coordination planes {Pd(1)C(1)N(8)} and {Pd(1)N(16)O(9)} is 10.5°. The bond lengths about the central Pd atom are all in the normal range. However, a slight widening of the angle, C(1)−Pd(1)−N(16) (102.7(1)°), is observed, in comparison to an angle of 99.9(1)° for a similar benzylamine derivative.[11] This phenomenon can be attributed to the presence of the spacer methyl group C(17), which imposes a repulsive force onto the adjacent pyrrolidine ring.

Asymmetric Diels−Alder Reaction between the DMPP Complex and Ethyl Vinyl Ketone. In an effort to evaluate the efficiency of the new chiral auxiliary in asymmetric Diels−Alder reactions, the palladium phosphole complex (*S*)-**9** was prepared in quantitative yield from the cleavage reaction between (*S*)-**5** and DMPP (Scheme 5). The structure of this complex was investigated by X-ray crystallography (Figure 4). Single crystals were obtained by slow evaporation of a solution of dichloromethane and hexane. Selected interatomic distances and angles are tabulated in Table 4.

(11) Urban, R.; Kramer, R.; Mihan, Sh.; Polborn, K.; Wagner, B.; Beck, W. *J. Organomet. Chem.* **1996**, *517*, 191. Dunina, V. V.; Razmyslova, E. D.; Kuz'mina, L. G.; Churakov, A. V.; Rubina, M. Y.; Grishin, Y. K. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3147.

(12) Ito, T.; Marumo, F.; Saito, Y. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1971**, *B27*, 1062. Patel, R. P. *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 605.

Scheme 5



The coordination geometry about the Pd(II) ion is distorted square planar with the phosphole coordinated trans to the amine nitrogen. The bond lengths and bond angles around the Pd(1) atom are all comparable to those of other DMPP derivatives of orthopalladated arylamines.[13] As expected, the five-membered palladacycle adopts the λ configuration, with the α-methyl group C(10) axially disposed.

When (*S*)-**9** was treated with excess ethyl vinyl ketone in chloroform at 50 °C, the reaction was found to be complete in 27 h. Prior to purification, the ^{31}P NMR spectrum of the crude reaction mixture in $CDCl_3$ exhibited a sharp singlet at δ 119.9. This product could not be crystallized from a variety of solvents and was subsequently converted to the nitrato analogue, **11**, by treatment with silver nitrate (Scheme 5). Unexpectedly, the ^{31}P NMR spectrum of the resultant complex mixture showed two singlets, at δ 119.9 (major) and 119.1 (minor), in a ratio of 3.5:1, revealing that the initial

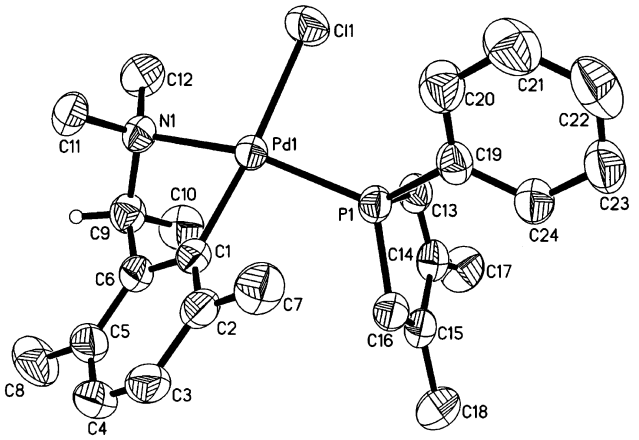


Figure 4. Molecular structure of (*S*)-**9**.

Table 4. Selected Bond Lengths and Bond Angles of Complex (*S*)-**9**

Bond Lengths (Å)			
Pd(1)−C(1)	1.989(3)	Pd(1)−Cl(1)	2.392(1)
Pd(1)−N(1)	2.143(3)	Pd(1)−P(1)	2.227(1)
C(8)−C(10)	3.665(5)	C(10)−C(13)	4.444(5)
C(7)−P(1)	3.436(5)	C(10)−C(16)	4.864(5)
Bond Angles (deg)			
C(1)−Pd(1)−N(1)	79.59(14)	C(1)−Pd(1)−P(1)	94.43(10)
N(1)−Pd(1)−P(1)	157.36(10)	C(1)−Pd(1)−Cl(1)	174.98(10)
N(1)−Pd(1)−Cl(1)	96.53(9)	P(1)−Pd(1)−Cl(1)	90.35(4)
C(16)−P(1)−Pd(1)	121.26(13)	C(13)−P(1)−Pd(1)	106.63(13)
C(19)−P(1)−Pd(1)	121.58(15)		

Diels−Alder reaction mixture contained two diastereomers—(S_C,R_P)-**10** and (S_C,S_P)-**10**—which coincidently exhibit the same ^{31}P NMR chemical shift at δ 119.9.

The major isomer (S_C,R_P)-**11** crystallized readily from ethyl acetate−diethyl ether in the form of pale-yellow prisms with $[\alpha]_D = +75.2°$ (CH_2Cl_2). The molecular structure and the absolute stereochemistry of this major product were determined by X-ray structural analysis (Figure 5). Selected bond distances and bond angles are given in Table 5. Structural investigations revealed that the complex is (S_C,R_P)-**11**, where the endo-cycloadduct coordinates as a typical monodentate ligand via its bridgehead P donor atom to the Pd template trans to the NMe_2 group of the (*S*)-2,5-dimethybenzylamine auxiliary. The absolute configurations of the four newly generated stereogenic centers, at P(1), C(13), C(16), and C(18), are *R*, *S*, *R*, and *S*, respectively, with the carbonyl group orientated in the endo position at C(18). Accordingly, the structural analysis of (S_C,R_P)-**11** confirms that, in the cycloaddition reaction, the diastereomeric products (S_C,R_P)- and (S_C,S_P)-**10** were obtained in the ratio of 3.5:1. Treatment of (S_C,R_P)-**11** with aqueous potassium cyanide gave the known optically active ligand (S_P)-**12**.[7] Thus the P-chiral phosphanorbornene (S_p)-**12** was obtained as the major cycloaddition product when the (*S*)-2,5-dimethylbenzylamine was used as the chiral auxiliary. The apparent inversion of configuration at the stereogenic centers during the liberation process is merely the consequence of the Cahn−Ingold−Prelog sequence rules.[14]

(13) Loh, S. K.; Mok, K. F.; Leung, P. H.; White, A. J. P.; Williams, D. J. *Tetrahedron*: *Asymmetry* **1996**, *7*, 45.

(14) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

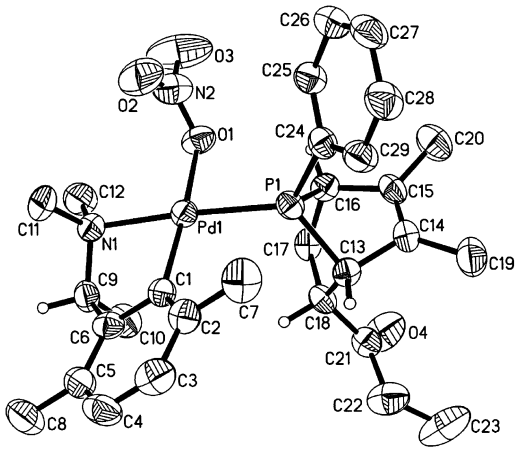


Figure 5. Molecular structure and absolute stereochemistry of (S_c,R_p)-**11**.

Table 5. Selected Bond Lengths and Bond Angles of Complex (S_c,R_p)-**11**

Bond Lengths (Å)			
Pd(1)−C(1)	2.016(3)	Pd(1)−O(1)	2.148(2)
Pd(1)−N(1)	2.125(2)	Pd(1)−P(1)	2.249(1)
Bond Angles (deg)			
C(1)−Pd(1)−N(1)	81.31(10)	C(1)−Pd(1)−P(1)	101.35(8)
C(1)−Pd(1)−O(1)	172.92(11)	N(1)−Pd(1)−P(1)	169.74(8)
N(1)−Pd(1)−O(1)	92.65(9)	O(1)−Pd(1)−P(1)	83.97(7)

It should be noted that when the (*S*)-naphthylamine auxiliary was employed for the analogous Diels−Alder reaction between DMPP and ethyl vinyl ketone at 70 °C, the cycloadducts (S_P)- and (R_P)-**12** were obtained, in the ratio of 1:1.[7] However, in this present study, this ratio was found to be 1:3.5. Clearly, the 2,5-dimethylbenzylamine complex exhibits a better selectivity than its naphthylamine counterpart for this class of intermolecular cycloaddition reaction. Efforts are underway in our laboratory to develop further new orthopalladacycles, which can enhance the stereoselectivity of asymmetric transformations.

Experimental Section

Reactions involving air-sensitive compounds were performed under a positive pressure of purified nitrogen. Proton NMR spectra were recorded at 300.1 or 500.1 MHz on Bruker model ACF300 or model AMX500 NMR spectrometers. All the ^{31}P NMR spectra were recorded at 120 MHz on a Bruker ACF300 NMR spectrometer. Melting points were determined on Büchi model B-545 melting point equipment and were uncorrected. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter. Elemental analyses were performed by the Elemental Analysis Laboratory of the Department of Chemistry, National University of Singapore.

Synthesis and Complexation of the Ligand, 1-(2′,5′-Dimethylphenyl)ethylamine, (±)-6. A mixture of 1-acetyl-2,5-dimethylbenzene (17.0 g, 0.115 mol) and ammonium formate (28 g, 0.444 mol) was heated at 180 °C for 4 h, cooled to room temperature, and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with water (30 mL) before the solvent was removed. The residual oil in toluene (20 mL) was then treated with concentrated HCl (20 mL) at 100 °C for 3 h and the aqueous portion was separated, diluted with water (50 mL), washed with toluene (30 mL), and treated with NaOH (15 g) in water (30 mL). The liberated amine was extracted into benzene (30 mL × 3) and dried (using Na_2SO_4), and then the solvent was removed. The pale-yellow residue was distilled under reduced pressure to give the product as a colorless oil: 13.2 g (77%), bp 123−125 °C (20 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.34 (d, ^3J = 6.4 Hz, 3H, Me7), 2.31 (s, 3H, Me2), 2.35 (s, 3H, Me5), 4.33 (q, ^3J = 6.4 Hz, 1H, H_7), 6.94 (d, ^3J = 8 Hz, 1H, H_4), 7.02 (d, ^3J = 8 Hz, 1H, H_3), 7.28 (s, 1H, H_6). MS (M^+), *m*/*z* (%): 149 (12), 148 (48), 134 (100), 117 (86), 107 (90), 91 (86), 85 (72), 77 (80), 51 (83), 44 (86).

***N*,*N*-Dimethyl-1-(2′,5′-Dimethylphenyl)ethylamine, (±)-7.** A solution of 1-(2′,5′-dimethylphenyl)ethylamine (10.0 g, 67.1 mmol) in formic acid (12.5 mL, 326 mmol) and formaldehyde (37%, 14.3 mL, 197 mmol) was heated at 95−100 °C for 6 h, and concentrated hydrochloric acid (20 mL) was added after the solution was cooled to room temperature. After removal of the solvent, the residual oil was treated with aqueous NaOH (10 M, 30 mL) and the liberated amine extracted into dichloromethane (50 mL × 3) and dried (using Na_2SO_4), and then the solvent was removed. The crude product was distilled under reduced pressure to give the amine as a colorless oil: 9.3 g (78%), bp 122−124 °C (20 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.30 (d, $^3J_{HH}$ = 6.4 Hz, 3H, Me_7), 2.23 (s, 6H, NMe), 2.30 (s, 3H, Me_2), 2.31 (s, 3H, Me_5), 3.38 (q, $^3J_{HH}$ = 6.4 Hz, 1H, H_7), 6.93 (d, $^3J_{H3H4}$ = 7 Hz, 1H, H_4), 7.01 (d, $^3J_{H3H4}$ = 7 Hz, 1H, H_3), 7.26 (s, 1H, H_6). MS (M^+), *m*/*z* (%): 177 (46), 162 (88), 146 (40), 133 (83), 117 (74), 105 (69), 91 (71), 72 (100), 51 (64), 44 (73).

(±)-Di-μ-chlorobis[1-[1-(dimethylamino)ethyl]-2,5-dimethyl-6-phenyl-*C*,*N*]dipalladium(II), (±)-5. A mixture of dichlorobis(acetonitrile)palladium(II) (2.59 g, 10 mmol) and silver perchlorate (4.14 g, 20 mmol) in acetonitrile (30 mL) was stirred in darkness for 1 h. The precipitate (AgCl) was filtered off, and the filtrate was added dropwise into a stirred mixture of *N*,*N*-dimethyl-1-(2′,5′-dimethylphenyl)ethylamine (1.77 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in dichloromethane (30 mL). The resulting mixture was stirred at room temperature for 20 h and then filtered through Celite. The filtrate was evaporated, and the residue in dichloromethane (100 mL) was stirred vigorously with HCl (1 M, 50 mL) for 1 h. The organic layer was separated, washed with water (50 mL × 2), dried (using Na_2SO_4), and concentrated to ca. 5 mL. Dilution of the solution with hexane precipitated the racemic dimer in the form of yellow prisms: 2.70 g (85.0%), mp 171−173 °C (dec). Anal. Calcd for $C_{24}H_{36}N_2Cl_2Pd_2$: C, 45.31; H, 5.70; N, 4.40. Found: C, 44.87; H, 5.56; N, 4.05. ^{1}H NMR ($CDCl_3$): δ 2.13 (d, *J* = 6.4 Hz), 2.17 (s), 2.44 (s), 2.44 (s), 2.48 (s), 2.52 (s), 2.58 (s), 2.60 (s), 2.66 (s), 2.68 (s), 3.49 (m), 6.59 (m), 6.63 (m).

Alternative method: The silver perchlorate (4.14 g, 20 mmol) used in the previously described preparation can be replaced by the nonhygroscopic and less-expensive silver nitrate, with the overall yield being 87%.

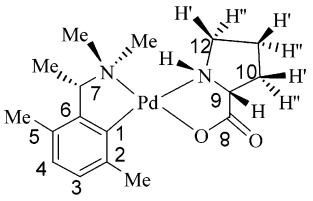
Optical Resolution of the Orthopalladated Complex (±)-5. (R_C,$S_C$$S_N$)-Prolinato-[1-[1-(dimethylamino)ethyl]-2,5-dimethyl-6-phenyl-*C*,*N*]palladium(II), (R_C,$S_C$$S_N$)-8. A solution of sodium prolinate (1.55 g, 11.3 mmol) in CH_3OH (30 mL) was added to the racemic dimer (±)-**5** (3.00 g, 4.72 mmol), which was suspended in the same solvent (30 mL). The mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with water (20 mL × 2), and dried (using Na_2SO_4), and then the solvent was removed to give the diastereomeric mixture in the form of a pale-yellow powder (3.60 g, 96%). The addition of hexane to the solution of this diastereomeric mixture in dichloromethane (10 mL) slowly precipitated the less-soluble diastereomer (R_C,S_C,S_N)-**8** in the form of pale-yellow flakes: 1.32 g (73.3%, based on half of the mixture used), mp >170 °C (dec), $[\alpha]_D$ +36.1° (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{17}H_{26}N_2O_2Pd$: C,

Table 6. Crystallographic Data for Complexes of (±)-**5**, (R_C,$S_C$$S_N$)-**8**, ($S_C$,$S_C$$S_N$)-**8**, (*S*)-**9**, and (S_c,R_p)-**11**

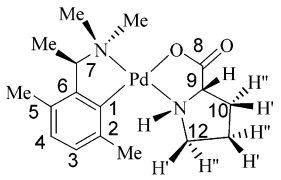
	(±)-**5**	(R_C,$S_C$$S_N$)-**8**	(S_C,$S_C$$S_N$)-**8**	(*S*)-**9**	(S_c,R_p)-**11**
formula	$C_{24}H_{36}Cl_2N_2Pd_2$	$C_{17}H_{26}N_2O_2Pd$	$C_{17}H_{26}N_2O_2Pd$	$C_{24}H_{31}ClNPPd$	$C_{29}H_{39}N_2O_4PPd$
mw	636.25	396.80	396.80	506.32	616.99
space group	$P2_1/n$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
cryst syst	monoclinic	orthorhombic	monoclinic	orthorhombic	orthorhombic
a/Å	11.7472(2)	8.0740(15)	6.8729(1)	8.788(1)	11.5788(7)
b/Å	15.9525(3)	8.6042(16)	9.0444(2)	12.523(2)	15.6471(9)
c/Å	14.9517(3)	24.7412(45)	14.4899(1)	21.617(3)	16.0232(9)
β/°	109.307(1)	90	103.420(1)	90	90
V/Å^3	2644.3(1)	1718.8(5)	876.1(1)	2378.9(6)	2903.0(3)
Z	4	4	2	4	4
T/K	293(2)	293(2)	293(2)	223(2)	223(2)
λ/Å	0.71073	0.71073	0.71073	0.71073	0.71073
μ/mm^{-1}	1.575	1.088	1.067	0.969	0.730
R1 (obs. data)[a]	0.0328	0.0232	0.0212	0.0462	0.0460
wR2 (obs. data)[b]	0.0669	0.0542	0.0556	0.0485	0.0471
Flack parameter		0.03(3)	0.02(3)	0.01(2)	−0.01(2)

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

51.46; H, 6.61; N, 7.06. Found: C, 51.49; H, 6.57; N, 7.09. ^{1}H NMR ($CDCl_3$): *δ* 1.75 (m, 2H, H11), 1.85 (d, $^3J_{H7Me7}$ = 6.4 Hz, 3H, Me7), 1.94 (m, 1H, H10″), 2.19 (s, 3H, Me5), 2.32 (s, 3H, Me2), 2.54 (m, 1H, H10′), 2.60 (s, 3H, NMe(eq)), 2.70 (s, 3H, NMe(ax)), 3.34 (m, 1H, H12″), 3.38 (b, 1H, NH), 3.52 (q, $^3J_{H7Me7}$ = 6.4 Hz, 1H, H7, overlapped with the weak multiplet of H12′ at the same chemical shift), 4.21 (m, 1H, H9), 6.68 (d, $^3J_{H3H4}$ = 7.6 Hz, 1H, H3), 6.70 (d, $^3J_{H3H4}$ = 7.6 Hz, 1H, H4).



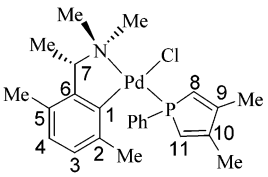
(S_C,$S_C$$S_N$)-Prolinato-[1-[1-(dimethylamino)ethyl]-2,5-dimethyl-6-phenyl-*C*,*N*]palladium(II), (S_C,$S_C$$S_N$)-8. The previously described mother liquor of (R_C,$S_C$$S_N$)-**8** was evaporated to dryness, and the residue was dissolved in acetonitrile (10 mL). Dilution of this solution with diethyl ether resulted in the precipitation of the other diastereomer, (S_C,$S_C$$S_N$)-**8**, in the form of pale-yellow prisms: 1.27 g (70.5%), mp >170 °C (dec), $[\alpha]_D$ +236° (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{17}H_{26}N_2O_2Pd$: C, 51.46; H, 6.61; N, 7.06. Found: C, 51.33; H, 6.59; N, 7.08. ^{1}H NMR ($CDCl_3$): *δ* 1.66 (m, 1H, H11′), 1.92 (d, $^3J_{H7Me7}$ = 6.4 Hz, 3H, Me7), 2.06 (m, 1H, H11″), 2.19 (s, 3H, Me5), 2.23 (m, 1H, H10′), 2.32 (m, 1H, H10″), 2.36 (s, 3H, Me2), 2.61 (s, 3H, NMe(ax)), 2.68 (s, 3H, NMe(eq)), 3.16 (m, 1H, H12′), 3.26 (m, 1H, H12″), 3.52 (q, $^3J_{H7Me7}$ = 6.4 Hz, 1H, H7), 4.01 (b, 1H, NH), 4.06 (m, 1H, H9), 6.67 (d, $^3J_{H3H4}$ = 7.6 Hz, 1H, H3), 6.70 (d, $^3J_{H3H4}$ = 7.6 Hz, 1H, H4).



(*S*)-(−)-Di-*μ*-chlorobis[1-[α-(dimethylamino)ethyl]-2,5-dimethyl-6-phenyl-*C*,*N*]dipalladium(II), (*S*)-5. A solution of the diastereomer (S_C,$S_C$$S_N$)-**8** (1.25 g, 3.16 mmol) in CH_2Cl_2 (20 mL) was treated with aqueous HCl (1 M, 15 mL) under vigorous stirring for 30 min. The organic layer was separated, washed with water (10 mL × 2), and dried (using Na_2SO_4), and then the solvent was removed under reduced pressure. The amorphous yellow product was dried further under high vacuum: 0.98 g (98%), mp 130−132 °C, $[\alpha]_D$ +214° (*c* 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): *δ* 2.13 (d, *J* = 6 Hz, 6H), 2.17 (s, 6H), 2.44 (s, 3H), 2.52 (s, 3H), 2.58 (s, 6H), 2.66 (m, 2H), 3.49 (m, 2H), 6.57−6.64 (m, 4H).

The optically pure (*R*)-(+)-dimer (*R*)-**5** was prepared from (R_C,$S_C$$S_N$)-**8** in a similar manner: $[\alpha]_D$ −208° (*c* 0.5, CH_2Cl_2).

Diels−Alder endo-Cycloaddition Promoted by the Palladium Template (*S*)-(−)-Chloro[1-[1-(dimethylamino)ethyl]-2,5-dimethyl-6-phenyl-*C*,*N*]{3′,4′-dimethyl-1′-phenylphosphole-*P*}-palladium(II), (*S*)-9. To a solution of (*S*)-(+)-**5** (0.16 g, 0.25 mmol) in dichloromethane (10 mL) was added a solution of 3,4-dimethyl-1-phenylphosphole (DMPP) (0.10 g, 0.53 mmol) in the same solvent (5 mL). The resulting yellow solution was stirred at room temperature for 30 min, and the solvent was removed under reduced pressure. The residual solid was chromatographed on a silica gel column, using dichloromethane as the eluent, to give a yellow powder, which was recrystallized from dichloromethane−hexane in the form of yellow prisms: 0.21 g (82%), mp 179−181 °C (dec), $[\alpha]_D$ +442° (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{24}H_{31}NClPPd$: C, 56.93; H, 6.17; N, 2.77; P, 6.17. Found: C, 57.17; H, 6.15; N, 3.19; P, 5.86. ^{31}P NMR: *δ* 28.2 (s, 1P). ^{1}H NMR ($CDCl_3$): *δ* 1.79 (d, $^3J_{HH}$ = 6.4 Hz, 3H, Me7), 2.01 (s, 3H, Me10), 2.02 (s, 3H, Me9), 2.17 (s, 3H, Me2), 2.20 (s, 3H, Me5), 2.48 (d, $^4J_{PH}$ = 2.5 Hz, 3H, NMe(ax)), 2.78 (d, $^4J_{PH}$ = 3.5 Hz, 3H, NMe(eq)), 3.54 (qn, $^3J_{HH}$ = $^4J_{PH}$ = 6.4 Hz, 1H, H7), 6.21 (d, $^2J_{PH}$ = 33.0 Hz, 1H, H11), 6.67 (d, $^3J_{HH}$ = 7.4 Hz, 1H, H4), 6.70 (dd, $^3J_{H3H4}$ = 7.4 Hz, $^5J_{PH}$ = 1.0 Hz, 1H, H3), 6.78 (d, $^2J_{PH}$ = 32.5 Hz, 1H, H8), 7.32−7.39 (m, 3H, *p*-Ph, 2 × *m*-Ph), 7.87 (m, 2H, 2 × *o*-Ph).



Asymmetric Diels−Alder Reaction between (*S*)-9 and Ethyl Vinyl Ketone. Synthesis of (S_C,R_P)- and (S_C,S_P)-10 and Isolation of (S_C,R_P)-11. A mixture of the chloro complex (*S*)-**9** (0.60 g, 1.2 mmol) and ethyl vinyl ketone (0.50 g, 6.0 mmol) in chloroform (10 mL) was heated at 50 °C for 27 h and filtered through a layer of Celite, and then the solvent was removed. The ^{31}P NMR ($CDCl_3$) spectrum of the crude product indicated a singlet at *δ* 119.9. This mixture in CH_2Cl_2 (5 mL) was then stirred vigorously with excess

$AgNO_3$ (0.50 g, 2.9 mmol) in water (5 mL) for 1 h in darkness. The precipitate (AgCl) was removed by filtration through a layer of Celite, and then the filtrate was dried (using $MgSO_4$) and the solvent was removed. The crude product was chromatographed on a silica gel column using ethyl acetate/dichloromethane (1:1, v/v) as the eluent to give the diastereomeric mixture of (S_C,R_P)- and (S_C,S_P)-**11** in the form of a yellow powder, which exhibited two ^{31}P NMR signals, at δ 119.9 (major) and 119.1 (minor). Recrystallization of the mixture from ethyl acetate−diethyl ether gave the major isomer (S_C,R_P)-**11** in the form of pale-yellow prisms: 0.40 g (55%), mp 176−178 °C (dec), $[\alpha]_D$ +75.2° (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{29}H_{38}N_2O_4PPd$·: C, 56.47; H, 6.19; N, 4.56; P, 5.01. Found: C, 56.53; H, 6.38; N, 4.60; P, 5.26. ^{31}P NMR ($CDCl_3$): δ 119.9 (s, 1P). ^1H NMR ($CDCl_3$): δ 0.83 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_2CH_3), 1.38 (s, 3H, C=CMe), 1.58 (s, 3H, C=CMe), 1.94−2.06 (m, 1H, H_{5exo}), 2.03 (d, $^3J_{HH}$ = 6.4 Hz, 3H, CH*Me*), 2.10 (m, 2H, CH_2CH_3), 2.21 (s, 3H, Me13), 2.28 (s, 3H, Me10), 2.50 (d, $^4J_{PH}$ = 1.6 Hz, 3H, N$Me_{(ax)}$), 2.61 (d, $^4J_{PH}$ = 3.2 Hz, 3H, N$Me_{(eq)}$), 2.94 (m, 1H, H_{5endo}), 3.08 (m, 1H, H_1), 3.21 (b, 1H, H_4), 3.34 (m, 1H, H_6), 3.61 (qn, $^3J_{HH}$ = $^4J_{PH}$ = 6.4 Hz, 1H, C*H*Me), 6.72 (d, $^3J_{HH}$ = 7.7 Hz, H_{12}), 6.78 (d, $^3J_{HH}$ = 7.7 Hz, H_{11}), 7.38 (m, 3H, *p*-Ph, 2 × *m*-Ph), 7.52 (m, 2H, 2 × *o*-Ph).

X-ray Crystal Structure Determinations of Complexes (±)-5, (R_C,$S_C$$S_N$)-8, ($S_C$,$S_C$$S_N$)-8, (*S*)-9, and ($S_C$,$R_P$)-11. Crystallographic data for complexes (±)-**5**, (R_C,$S_C$$S_N$)-**8**, ($S_C$,$S_C$$S_N$)-**8**, (*S*)-**9**, and (S_C,R_P)-**11** are summarized in Table 6. The diffraction data were collected on a Siemens model SMART CCD diffractometer, using graphite monochromated Mo Kα radiation. SADABS absorption corrections were applied, and all non-hydrogen atoms were refined anisotropically by a full-matrix least-squares procedure, using the SHELXL program.[15] H atoms were introduced at fixed distances from C atoms and assigned fixed thermal parameters.

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Supporting Information Available: For (±)-**5**, (R_C,$S_C$$S_N$)-**8**, ($S_C$,$S_C$$S_N$)-**8**, (*S*)-**9**, and (S_C,R_P)-**11**, tables of crystal data, data collection, solution and refinement, final positional parameters, bond distances and angles, thermal parameters of non-hydrogen atoms, and calculated hydrogen parameters (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

IC030018L

(15) Sheldrick, G. M. SHELXL 93, Program for Crystal Structure Refinement; University of Göttingen: Göttingen, Germany, 1993.