Diastereoinduction in the Synthesis of Pallada(II)pyrrolidinones: Palladacycles with Two Pd-bonded Stereogenic Carbons

John C. Hershberger, Victor W. Day, and Helena C. Malinakova*

Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045

Received July 4, 2008

Stable palladapyrrolidinones (L-L)Pd-CH(*p*-MeC_6H_4)NBnC(═O)CHPh representing endocyclic carbon-bonded palladium(II) amide enolates with two Pd-bonded sp^3-hybridized stereogenic carbons and bidentate auxiliary ligands (tetramethylethylenediamine (TMEDA), bis(diphenylphosphino)ethane (dppe), and (*S*,*S*)-CHIRAPHOS) were synthesized. The syntheses proceeded with a significant diastereoinduction from the Pd-bonded stereocenter in racemic cationic palladium amide complexes [(L-L)Pd-CH(*p*-MeC_6H_4)NBnC(═O)CH_2Ph]$^+$OTf $^-$ favoring the formation of *cis* diastereomers (denoting the relative stereochemistry of the two sp^3-hybridized carbons in the adjacent positions of the square planar Pd(II) complexes), whereas epimerization of the Pd-bonded stereocenters favoring the formation of the more stable *trans* diastereomers was achieved under basic conditions. Studies of the stereochemical relationships between Pd-bonded stereocenters in palladapyrrolidinones bearing chiral nonracemic auxiliary ligands ((*S*,*S*)-CHIRAPHOS) indicated a lack of double diastereodifferentiation induced by the auxiliary ligands. Molecular structures of the *cis* diastereomers of pallada(II)pyrrolidinones bearing TMEDA and dppe ligands were established by X-ray crystallography.

Introduction

In the past, systematic studies on the structure and reactivity of stable organopalladium complexes have facilitated the development of new Pd-catalyzed reactions important to organic synthesis.[1] The design of palladium-catalyzed protocols for the formation of a bond between two sp^3-hybridized and potentially stereogenic carbons represents one of the frontiers of current organopalladium chemistry.[2] However, explorations of the chemistry of stable isolated organopalladium complexes possessing two Pd-bonded sp^3-hybridized stereogenic carbons[3] remain rare. Aiming to extend our program investigating the chemistry of pallada(II)cycles **I** with a Pd-bonded stereogenic carbon,[4] we became intrigued by related structures of complexes **II** possessing two Csp^3−Pd bonds in *cis* positions of a square planar Pd(II) complex (Figure 1). We envisioned that the first Csp^3−Pd bond would be formed via an oxidative cyclization of acyliminium salts and a Pd(0) source as reported by Arndtsen and co-workers[5] and a subsequent intramolecular nucleophilic attack of an amide enolate at the cationic Pd(II) center would afford the desired complex **II** (Figure 1).[6] Complexes **II** could serve as models for investigating the stereoinduction between the Pd-bonded stereocenters and the chiral nonracemic ligands (L-L).[7]

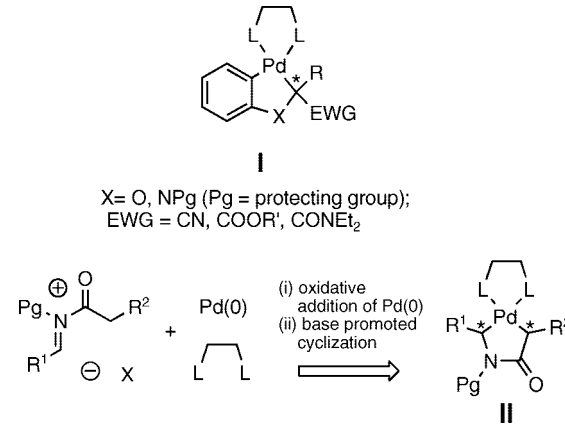


Figure 1

Herein, we describe the preparation of the palladapyrrolidinone complexes **II**, representing rare examples of stable

* To whom correspondence should be addressed. E-mail: hmalina@ku.edu.

(1) (a) Heck, R. F. *Synlett* **2006**, 2855. (b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

(2) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (b) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (c) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691.

(3) (a) Hashimi, A. S. K.; Grundl, M. A.; Bats, J. W.; Bolte, M. *Eur. J. Org. Chem.* **2002**, 1263. (b) Hashmi, A. S. K.; Naumann, F.; Nass Rivas, A.; Degen, A.; Bolte, M.; Bats, J. W. *Chem.*−*Eur. J.* **1999**, *5*, 2836. For additional examples of complexes with two unsubstituted sp^3-hybridized methylene groups bonded to Pd, see. (c) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R, J.; Scott, J. D. *Organometallics* **1988**, *7*, 1363. (d) Diversi, P.; Ingrosso, G.; Lucherini, A.; Lumini, T.; Marchetti, F. *J. Chem. Soc., Dalton Trans.* **1988**, 133.

(4) (a) Lu, G.; Portscheller, J. L.; Malinakova, H. C. *Organometallics* **2005**, *24*, 945. (b) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701. (c) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 8266. (d) Portscheller, J. L.; Lilley, S. E.; Malinakova, H. C. *Organometallics* **2003**, *22*, 2961. (e) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4*, 3679.

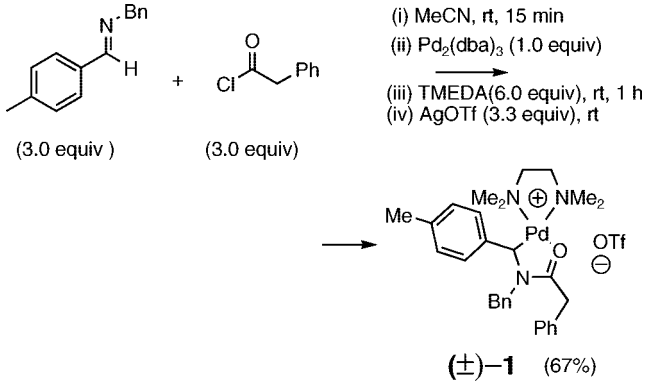
(5) (a) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590. (b) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228. (c) Dghaym, R. D.; Yaccato, K. J.; Arndtsen, B. A. *Organometallics* **1998**, *17*, 4.

(6) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(7) In principle, any stereocenters present in chiral nonracemic auxiliary ligands (L*-L*) in palladium-chelated amide complexes could either enhance or diminish the diastereoselectivity observed for the formation of palladacycles **II** from palladium-chelated amide complexes possessing a single palladium-bonded sp^3-hybridized stereogenic carbon and *achiral* (!) auxiliary ligands (L-L).

10.1021/om800630f CCC: $40.75
Publication on Web 01/15/2009

Scheme 1



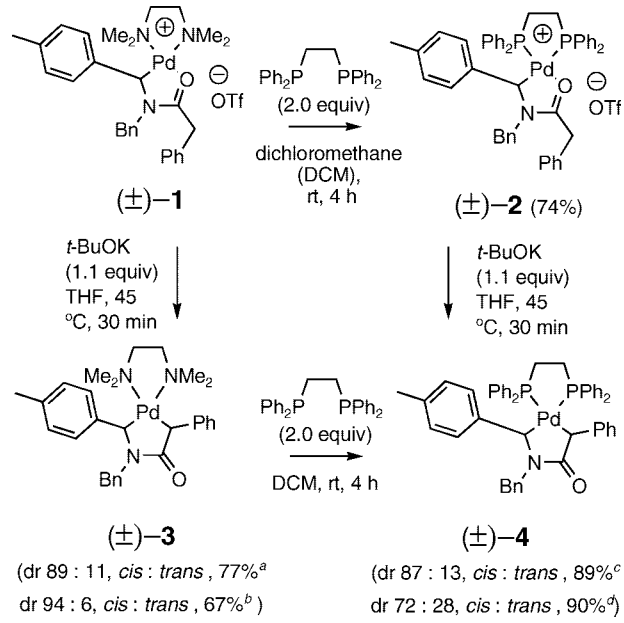
endocyclic carbon-bonded palladium amide enolates[8] with two sp^3-hybridized stereogenic carbons attached to the palladium(II) center, and investigations of the effects of chiral nonracemic auxiliary ligand on the stereoinduction during the formation of the second Pd-bonded sp^3-hybridized stereocenter. Notably, whereas the diastereoinduction from the α-*N*-substituted Pd-bonded carbon in the final step of the synthesis of complexes **II** was found to be substantial providing racemic complexes **II** highly enriched in a single diastereomer (diastereomeric ratio, dr = 94:6 or 87:13), the chiral nonracemic auxiliary ligands (L-L) present in palladapyrrolidinones did not induce significant double diastereodifferentiation.

Results and Discussion

Reasoning that oxidative cyclization of *N*-acyliminium ions with a stoichiometric Pd(0) source would provide an effective alternative to Csp^3-H activation or Csp^3-X activation[9] for the generation of a sterically encumbered Pd-bonded stereocenter, cationic palladium-chelated amide complex (±)-**1** was synthesized by a modification of the protocol reported by Arndtsen et al.[5b] (Scheme 1).

Establishing a sufficient concentration of the acyliminium ion resulting from the equilibrium between the imine and the acyl chloride relative to the concentration of palladium(0) proved to be critical to achieving a high conversion of the Pd_2dba_3 limiting reagent. The difficulties encountered in our initial attempts to isolate the unstable cationic palladium-chelated amide complexes bearing the nucleophilic chloride counterion were circumvented by a final anion metathesis induced by the addition of silver triflate (3.3 equiv) (Scheme 1). Racemic complex (±)-**1** was conveniently isolated as a yellow solid in 67% yield by column chromatography over silica. When the tetramethylethylenediamine ligand (TMEDA) was replaced with bis(diphenylphosphino)ethane (dppe), the isolation of the corresponding palladium amide was complicated by a difficult separation of the product from the complex of the residual dppe ligand with Ag^+ salt. Thus, a yellow solid of the racemic cationic palladium amide (±)-**2** bearing the dppe ligand was obtained via a high-yielding ligand exchange reaction of complex (±)-**1** and was fully characterized (Scheme 2).

Scheme 2



[a] Longer reaction times result in lower yields. [b] Run for 5 h at rt. [c] From (±)-**3**. [d] From (±)-**2**.

Next, racemic palladium amide complexes (±)-**1** and (±)-**2** featuring a single palladium-bonded stereocenter were treated with a base to explore the possibility of creating a second palladium-bonded sp^3-hybridized stereogenic carbon. Mechanistically, the transformation was anticipated to involve an initial deprotonation of the methylene group α to the amide group, generating O-bonded amide enolates,[6] the concentration of which would depend on the choice of base and reaction conditions. Subsequent tautomerization of the O-bonded cationic amide enolates into the endocyclic C-bonded palladium enolates[6,8] would deliver the second palladium-bonded stereocenter in palladacycles **II** (Scheme 2). Thus, the treatment of the racemic complexes (±)-**1** and (±)-**2** with *t*-BuOK at elevated temperatures (45 °C, 0.5 h, THF) afforded good yields of the desired racemic palladacycles (±)-**3** and (±)-**4**, respectively (Scheme 2). ^{1}H NMR spectral data for palladacycles (±)-**3** and (±)-**4** are consistent with the presence of two methine carbons bonded to palladium and indicate that two diastereomers were formed in unequal ratios. Additional evidence supporting the structures of palladacycles (±)-**3** and (±)-**4** with two Pd-bonded sp^3-hybridized carbons, rather than O-bonded Pd-amide enolates, includes IR C═O stretches associated with the amide bonds in palladacycles (±)-**3** and (±)-**4** found at 1617 and 1606 cm^{-1}, respectively, contrasting with the IR C═O stretch signals at 1578 and 1554 cm^{-1} found in the palladium-chelated amide complexes (±)-**1** and (±)-**2**, respectively. Furthermore, ^{1}H NMR spectra of palladacycles (±)-**3** and (±)-**4** are not consistent with the presence of vinylic protons. The signals assigned to the palladium-bonded carbons appear as two pairs of singlets at 4.12 and 3.99 ppm (the major diastereomer) and at 4.13 and 3.94 ppm (the minor diastreomer) in the spectra of complex (±)-**3**, and as two sets of triplets or doublet of doublets at 4.75 ppm (t, J = 7.6 Hz) and 4.40 ppm (dd, J = 8.8 Hz, 6.0 Hz) (the major diastereomer) and 4.78 ppm (t, J = 7.0 Hz) and 4.53 ppm (t, J = 7.0 Hz) (the minor diastereomer) in the spectra of complex (±)-**4**. Notably, ^{31}P NMR spectra recorded at room temperature on complex (±)-**4** revealed the presence of two pairs of broad singlet signals, instead of the anticipated two

(8) For examples of complexes featuring palladium ester and ketone enolate groups, see (a) Campora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Guterrez, E.; Ruiz, C.; Graiff, C.; Tiripicchio, A. *Chem.—Eur. J.* **2005**, *11*, 6889. (b) Albeniz, A. C.; Catalina, N. M.; Espinet, P.; Redon, R. *Organometallics* **1999**, *18*, 5571.

(9) (a) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 4395. (b) Giri, R.; Maugel, N.; Foxman, B. N.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759.

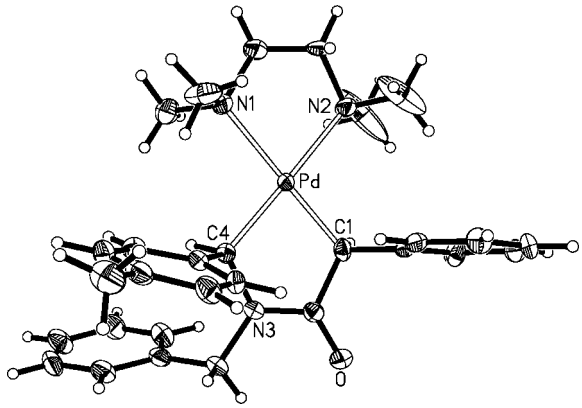


Figure 2. Thermal ellipsoid diagram of complex *cis* (±)-**3**. The ellipsoids are drawn at 50% probability level (for experimental details, see the Supporting Information).

pairs of doublets resulting from the two unequivalent P-atoms.[10] We have observed a similar phenomenon in ^{31}P NMR spectra of palladacycles featuring sterically encumbered fully substituted tertiary sp^3-hybridized Pd-bonded carbon, which we prepared in our prior studies.[11] Conceivably, the steric hindrance at the Pd-bonded stereocenter could cause a facile reversible dissociation of one of the two P-atoms from the Pd-center.[11] To establish the ratios of the diastereomers in palladacycles (±)-**3** and (±)-**4**, the relative integration of the signals for one of the two diastereotopic benzylic protons in the *N*-benzyl group for each diastereomer was employed, revealing that the palladacycle (±)-**3** was produced in dr 89:11 and palladacycle (±)-**4** in dr 72:28.[12]

Diffusion-controlled crystallization of palladacycle (±)-**3** (dr 75:25)[13] from a benzene/pentane mixture afforded yellow single crystals suitable for X-ray crystallographic analysis, which established the molecular structure of the crystalline complex as the *cis* diastereomer[14] (Figure 2). The sample of the crystalline *cis* palladacycle (±)-**3** was subjected to ^{1}H NMR analysis allowing us to assign the chemical shifts to the *cis* and *trans* diastereomers of complex (±)-**3**, revealing that the *cis* diastereomer of palladacycle (±)-**3** was the major product (Scheme 2). Our prior studies[4b,d] indicate that no C−Pd bond breaking

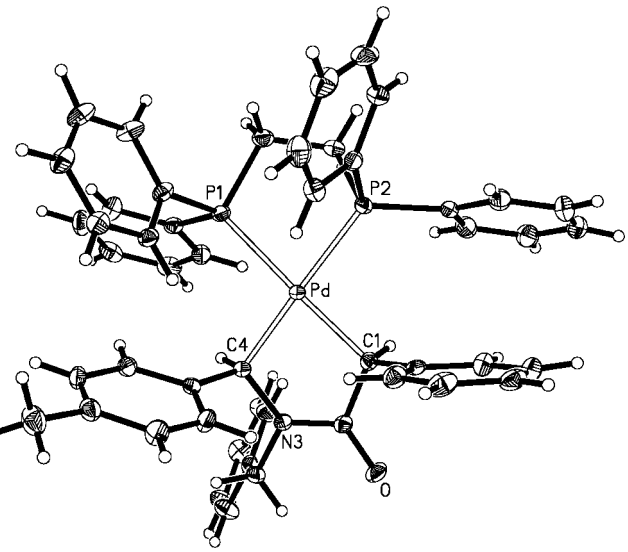


Figure 3. Thermal ellipsoid diagram of complex *cis* (±)-**4**. The ellipsoids are drawn at 50% probability level (for experimental details, see the Supporting Information).

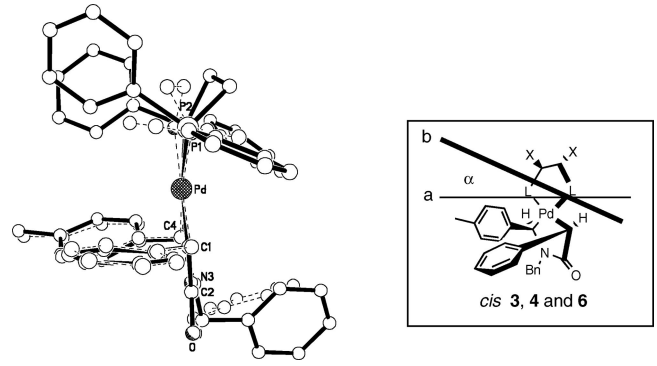


Figure 4. Superimposed molecular structures of *cis* (±)-**3** and *cis* (±)-**4** based on X-ray crystallographic data.

and therefore no change in the diastereomeric composition of palladacycles is expected to occur during a ligand exchange reaction. Accordingly, the treatment of palladacycle (±)-**3** (dr 89:11) with the dppe ligand afforded palladacycle (±)-**4** possessing the corresponding (dr 87:13) ratio of diastereomers, identifying the major diastereomer of palladacycle (±)-**4** as *cis* and the minor as *trans*. The diffusion-controlled crystallization of palladacycle (±)-**4** (dr 86:14) afforded single crystals suitable for X-ray crystallographic analysis, which provided the molecular structure of the *cis* diastereomer of palladacycle (±)-**4** (Figure 3).

The only significant differences in the metrical parameters for the metallacycles of *cis* (±)-**3** and *cis* (±)-**4** involve the bonds to the metal. The Pd−C(1) bond lengths (2.040(4) Å in *cis* (±)-**3** and 2.082(2) Å in *cis* (±)-**4**) in both compounds are slightly shorter than the Pd−C(4) bond lengths (2.048(3) Å in *cis* (±)-**3** and 2.096(2) Å in *cis* (±)-**4**). Additionally, both Pd−C bonds in *cis* (±)-**3** are shorter than either Pd−C bond in *cis* (±)-**4**, presumably due to the greater *trans* influence of phosphines over amines. Notably, the conformations of the five-atom square planar coordination grouping and pyrrolidinone ligands in *cis* (±)-**3** and *cis* (±)-**4** are remarkably similar, causing the 21 nonhydrogen atoms of the two complexes to superimpose with a root-mean-square (rms) deviation of 0.17 Å (Figure 4). The five-atom square-planar coordination groupings, as well as the five nonhydrogen atoms (Pd, O, C(1), C(2),

(10) Temperature dependent ^{31}P NMR spectra of complex (±)-**4** (in d_8-toluene) were recorded ranging the temperatures from −70 to +80 °C. However, a significant sharpening of the signals has not been achieved. For experimental details, see the Supporting Information.

(11) For the discussion of the effects of steric hindrance on the stability of palladacycles of type **I**, see ref 4a.

(12) The ^{1}H NMR signals for the benzylic protons in the spectra of palladacycles (±)-**3** and (±)-**4** allowed for the most precise integration. In the ^{1}H NMR spectrum of palladacycle (±)-**3**, the signals of the benzylic protons that were used for the assignment of dr were found at 4.89 ppm (d, J = 14.8 Hz) for the minor diastereomer and at 4.84 ppm (d, J = 14.5 Hz) for the major diastereomer. In the ^{1}H NMR spectrum of palladacycle (±)-**4**, the signals of the benzylic protons that were used for the assignment of dr were found at 5.12 ppm (dd, J = 14.0 Hz, 1.6 Hz) for the minor diastereomer and at 5.03 ppm (dd, J = 14.4 Hz, 2.0 Hz) for the major diastereomer.

(13) An inappropriate choice of the elution system for the chromatographic purification of complex (±)-**3** causes decomposition of the major diastereomer of the complex (±)-**3** during the separation. The sample of (±)-**3** with dr 75:25 was obtained in our initial studies using a relatively weak elution system (low gradient of ethyl acetate in hexane).

(14) Herein, the designation "*cis*" and "*trans*" diastereomer of palladacycles (±)-**3**, (±)-**4**, and **6a**−**d** refers to the relative stereochemistry at the palladium-bonded sp^3-hybridized stereogenic carbons. In the *cis* diastereomers, the two aryl substituents attached to the Pd-bonded sp^3-hybridized carbons are both located on the same face of the square planar palladium(II) complex. In the *trans* diastereomers, the two aryl substituents are bonded to the opposite faces of the square planar palladium(II) complex.

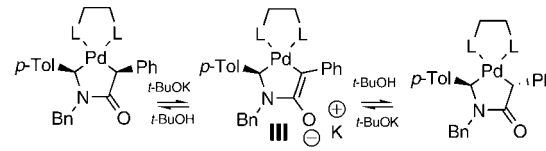
N(3) and C(4)) in both *cis* (±)-**3** and *cis* (±)-**4** palladacycles, are coplanar to within 0.05 Å.

Interestingly, a distinct folding, defined by the dihedral angle (α) between the normals to the mean planes of the five-atom square planar coordination groupings (plane labeled a in Figure 4) and the six-atom **L···L** groupings containing the two heteroatoms and their four methyl or phenyl carbons (plane labeled b in Figure 4), was observed in the solid phase structures of complexes *cis* (±)-**3** and *cis* (±)-**4**. Thus, the pyrrolidinone ligands "fold" by 6° or 9° along the C(1)···C(4) polyhedral edge, and the TMEDA and dppe (**L···L**) ligands "fold" by 13° or 25° along their respective N(1)···N(2) and P(1)···P(2) polyhedral edges away from the pyrrolidinone ligands. As expected, both the "fold" angles are larger for the complex *cis* (±)-**4**. Experiments reported in Scheme 2 showed that, in the presence of both types of auxiliary ligands (TMEDA and dppe), the formation of the *cis* diastereomer of palladacycles (±)-**3** and (±)-**4** from palladium-chelated amide complexes (±)-**1** and (±)-**2** was favored (Scheme 2). Conceivably, this "folding" of the pyrrolidinone and the **L···L** ligands is sterically induced by nonbonded interactions between atoms in the secondary coordination sphere, and if preserved in the solution-phase structures it may play a significant role in inducing the initial preponderance of the *cis*-isomers as the kinetically favored products (vide infra).

The treatment of palladium amide complex (±)-**1** with *t*-BuOK for longer time periods afforded complex (±)-**3** in reduced yields (67%) but increased levels of diastereoselectivity (dr 94:6, *cis*:*trans*). However, variations in the choice of the base (potassium hexamethyldisilazide, KHMDS, or lithium diisopropyl amide, LDA) and conditions (time, temperature) used for the ring-closure reactions of complexes (±)-**1** and (±)-**2** led only to minimal variation in the ratios of diastereomers found in complexes (±)-**3** and (±)-**4**.[15]

The palladium bonded stereocenter corresponding to the α-carbon in the palladium amide enolate possesses an acidic hydrogen potentially rendering the stereocenter configurationally unstable under basic conditions. The pathway to epimerization could involve deprotonation yielding complex **III** (Table 1) followed by reprotonation delivering the epimeric palladacycle. Indeed, palladacycles (±)-**3** (dr 90:10, *cis*:*trans*) and (±)-**4** (dr 87:13, *cis*:*trans*) underwent epimerization when treated with 1.1 equiv of *t*-BuOK in THF at room temperature. Complex (±)-**3** proved to be sensitive to decomposition, and prolonged reaction times led to low recovery yields. Regardless, within 30 minutes, significant epimerization was observed favoring the formation of the *trans* diastereomer of palladacycle (±)-**3** (dr 78:22, *cis*:*trans*, Table 1). In a similar fashion, the more stable palladacycle (±)-**4** (dr 87:13, *cis*:*trans*) underwent epimerization, reaching an equilibrium ratio of dr 42:58 (*cis*:*trans*) in 1 h with a recovery yield greater than 90% (Table 1). Experiments described in Scheme 2 indicate that the existing stereocenter in cationic complexes (±)-**1** and (±)-**2** significantly differentiates the activation energies for the formation of *cis* and *trans* palladacycles (±)-**3** and (±)-**4**, allowing for a more rapid (kinetic control) formation of the *cis* diastereomer of (±)-**3** and (±)-**4** (Scheme 2). Data in Table 1 demonstrate that the *trans* diastereomers of complexes (±)-**3** and (±)-**4** are more thermodynamically stable. Notably, the equilibration of the *cis* and *trans* isomers apparently requires the presence of a sufficient concentration of base to allow for the deprotonation. Thus, treatment of the solutions of complex (±)-**3** (dr 90:10, *cis*:*trans*) with 0.1 equiv or 0.5 equiv of *t*-BuOK at room temperature for 1 h did not produce any change in the *cis*:*trans* ratios detectable by ^{1}H NMR. No epimerization in the sample of palladacycle (±)-**3** (dr 88:12, *cis*:*trans*) has been observed upon heating of a solution of complex (±)-**3** in THF at 45 °C for 3 h in the absence of a base (recovery yield 92%). Heating of a solution of complex (±)-**4** (dr 91:9, *cis*:*trans*) in THF at 45 °C for 3 h in the absence of a base led to minimal epimerization and afforded the recovered (yield 90%) complex (±)-**4** in dr 83:17 (*cis*:*trans*). The results suggest that an alternative pathway to epimerization involving a reversible interconversion of the *cis* and *trans* C-bonded Pd-amide enolates via the O-bonded Pd-enolates as intermediates does not operate to a significant extent.[16]

Table 1



ligand L-L	*cis*: *trans* ratio in the substrate	time (min)	*cis* : *trans* ratio in the recovered compound	recovery[a] (%)
	(±)-**3**			
TMEDA	90 : 10	5	88 : 12	83
		30	78 : 22	82
	(±)-**4**			
dppe	87 : 13	60	42 : 58	91
		180	42 : 58	92

[a] A solution of the palladacycles in THF was treated with 1 equiv of *t*-BuOK (1 M in THF). The yield of the palladacycle recovered after flash chromatography is indicated in the last column.

Our earlier studies of the diastereocontrol in the synthesis of palladacycles of type **I** bearing chiral nonracemic bidentate ligands indicated that high levels of stereoinduction at the palladium-bonded sp^3-hybridized α-carbon in exocyclic ester and amide enolates can be achieved.[4b,d] In this context, the cationic chelated amide complexes described above provide us with a unique opportunity to investigate how stereocenters present in the auxiliary ligand sphere of the complex may interact with the existing palladium-bonded sp^3-hybridized stereogenic carbon to either reinforce, diminish, or override the preference for the formation of *cis* diastereomers of palladacycles of type **II** (Figure 1, Scheme 2, and Table 1).

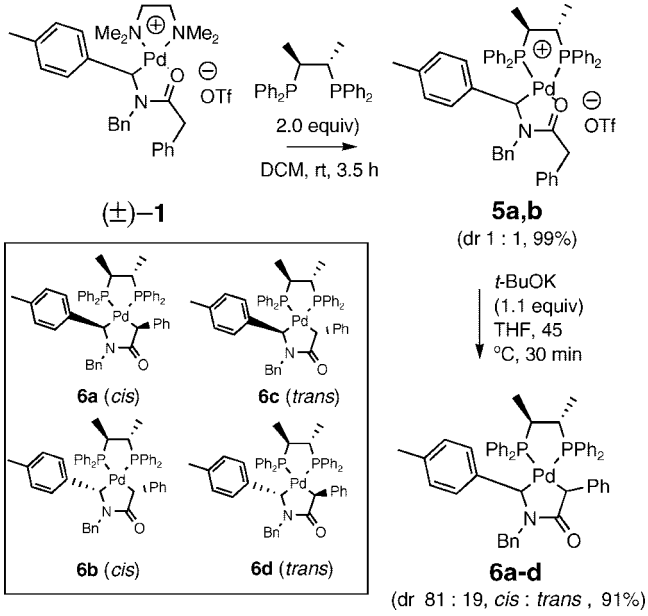
A C_2 symmetric bidentate phosphine ligand (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane ((*S*,*S*)-CHIRAPHOS) was selected for these studies. Formation of a tight five-membered chelate ring including the P−Pd−P bonds was anticipated to provide favorable conditions for maximum stereoinduction.[4b] Thus, ligand exchange reaction of the racemic complex (±)-**1** with (*S*,*S*)-CHIRAPHOS (2.0 equiv) afforded the anticipated equimolar mixture of two diastereomeric cationic complexes (*S*,*S*,*S*)-**5a** and (*R*,*S*,*S*)-**5b** in a quantitative yield (Scheme 3). Characteristic signals in ^{31}P NMR that allow us to differentiate the two diastereomers include doublets at 59.7 ppm (J = 45.4 Hz) and at 47.5 ppm (J = 45.4 Hz) for **5a** and doublets at 57.6 ppm (J = 50.2 Hz) and at 42.9 ppm (J = 50.2 Hz) for **5b**. However, in the absence of X-ray crystallographic analyses[17]

(15) For the details of the additional experiments, see the Supporting Information.

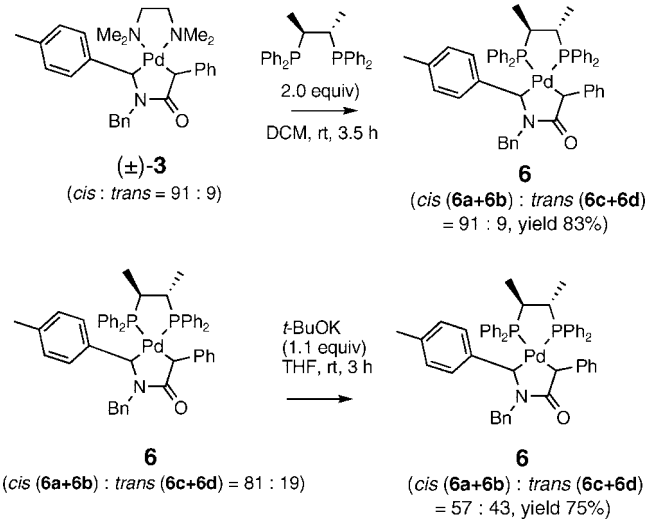
(16) The slow epimerization of complex (±)-**4** upon heating in the absence of base (from dr 91:9 to 83:17, *cis*:*trans*) could be rationalized by a reversible interconversion of the C-bonded and O-bonded palladium amide enolate forms of palladacycle (±)-**4**.

(17) Despite numerous attempts at the diffusion-controlled crystallization of mixtures of diastereomeric complexes **5a** and **5b**, we were unable to obtain a single crystal suitable for X-ray crystallographic analyses.

Scheme 3



Scheme 4

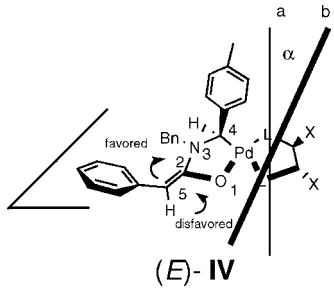


that would yield molecular structures of the individual complexes, the assignment of absolute configurations of complexes **5a** and **5b** (see above) to specific spectral (^{31}P NMR) signals remains purely arbitrary. The mixture of diastereomers of complex **5** (dr 1:1) was treated with *t*-BuOK under the conditions identical to those in the ring-closure protocols employed for the synthesis of palladacycles (±)-**3** and (±)-**4** (compare Schemes 2 and 3). As anticipated, the reaction afforded the palladacycle **6** as a mixture of four diastereomers in unequal ratios. In principle, the reaction can afford four diastereomers **6a**−**d** with structures shown in the inset of Scheme 3, complexes **6a** and **6b** corresponding to palladacycles with *cis* relative stereochemistry[14] at the two palladium-bonded stereocenters, and complexes **6c** and **6d** with *trans* relative stereochemistry[14] at the palladium-bonded stereogenic carbons. Accordingly, ^{31}P NMR of the isolated complex **6** indicated the presence of seven broad signals (singlets, one representing an overlap of signals for two different P atoms),[18] apparently divided into two groups of four signals according to relative integration. In the first group corresponding to the major product(s), the four ^{31}P NMR singlet signals had approximately equal intensity (peak areas in relative ratios of 1:1.3:1.3:1). The four ^{31}P NMR signals in the second group represented the minor products and had peak areas in relative ratios of approximately 2:2:1:1 (for details, see Supporting Information). Overall, the combined integrated ^{31}P NMR signal areas for the four signals comprising each of these two groups were found to be in the ratio of 81:19.[18] In order to assign the signals in the ^{31}P NMR spectra of complex **6** to either *cis* or *trans* diastereomers, palladacycle (±)-**3** with known unequal ratio of *cis*:*trans* diastereomers (dr 91:9, *cis*:*trans*) was subjected to a ligand exchange reaction with an excess of the chiral nonracemic ligand (*S*,*S*)-CHIRAPHOS (Scheme 4). On the basis of prior studies,[4d] we were anticipating that the *cis* diastereomer of complex (±)-**3** will afford a 1:1 mixture of *cis* diastereomers **6a** and **6b** and the *trans* diastereomer of complex (±)-**3** will afford a 1:1 mixture of diastereomers *trans* **6c** and **6d**. Indeed, the ^{31}P NMR spectrum of the isolated palladacycle **6** revealed the presence of two groups of four broadened signals[11] with equal peak areas with the groups, and the ratio of the combined peak areas of the two groups of peaks 91:9, thus identifying the signals in the dominant group as those arising from *cis* palladacycles **6a**,**b** and the signals comprising the minor group as those arising from the *trans* palladacycles **6c**,**d**. On the basis of these data, we were able to assign the ^{31}P NMR signals for the two *cis* diastereomers **6a** and **6b** and for the *trans* diastereomers **6c** and **6d**. The signals (broad singlets) in ^{31}P NMR (162 MHz) of complex **6** assigned to the *cis* complexes **6a** and **6b** are found at 45.1, 42.8, 38.8, and 36.0 ppm. The signals (broad singlets) in ^{31}P NMR (162 MHz) of complex **6** assigned to the *trans* complexes **6c** and **6d** are found at 46.3, 42.8, 41.7, and 39.7 ppm. Despite our attempts at crystallization of palladacycle **6**, we were unable to secure X-ray quality crystals of pure diastereomers **6a**−**d**, and therefore, the assignment of the ^{1}H and ^{31}P NMR signals for the specific diastereomers **6a** versus **6b** and **6c** versus **6d** could not be realized. Data acquired in this experiment were employed to analyze the ^{31}P NMR signals of complex **6** prepared via the ring-closure reaction reported in Scheme 3, revealing that the *cis* diastereomers **6a** + **6b** were generated in approximately equal ratio and represent the dominant diastereomers in the mixture consisting of 81% *cis* diastereomers **6a** + **6b** and 19% *trans* diastereomers **6c** + **6d**, which were generated in approximately 2:1 ratio.

It is notable that the ring-closure reactions of racemic cationic amide complex (±)-**2** (Scheme 2) as well as of the equimolar mixture of diastereomers of cationic amide complex **5** (Scheme 3) proceed with almost identical *cis*:*trans* selectivity, regardless of the presence of stereogenic centers in the chiral nonracemic auxiliary phosphine ligand in complexes **5a**,**b**.[19] Apparently, the chiral nonracemic auxiliary ligand does not exert a significant amplifying (matched pair) or diminishing (mismatched pair) effect on the stereocontrol realized by the palladium-bonded stereogenic sp^3-hybridized carbon present in the cationic amide complexes **5** during the base-mediated conversion of the in situ formed O-bonded palladium amide enolates into the C-bonded palladium amide enolates (the palladacycles **6**).

(18) The ^{31}P NMR (162 MHz) signals found in the mixture of four diastereomers **6a**−**d** were as follows: 46.3 ppm (s br, 0.12 P), 45.1 ppm (s br, 0.38 P), 42.8 ppm (s br, 0.55 P, signal for two distinct overlapping P's), 41.7 ppm (s br, 0.063 P), 39.7 ppm (s br, 0.067 P), 38.8 ppm (s br, 0.44 P), 36.0 ppm (s br, 0.38 P).

(19) Analogous experiments to those reported in Scheme 3 but involving an enantiomer of the chiral nonracemic ligand, for example, (*R*,*R*)-CHIRAPHOS, would afford a mixture of four diastereomers **6a′**−**d′**, each of which would represent an enantiomer of the complexes **6a**−**d** shown in the insert of Scheme 3. Thus, identical ratios of diastereomers would be expected to arise from these experiments.



(*E*)- **IV**

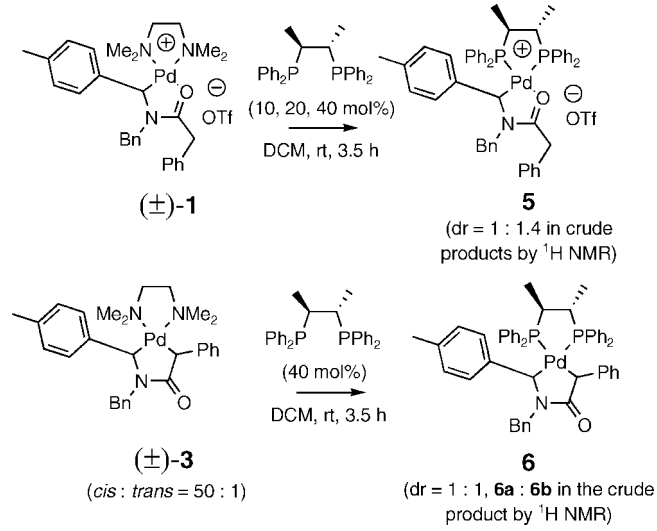
Figure 5

To evaluate the effect of the chiral nonracemic auxiliary ligands on the thermodynamic stability of the palladacycles, the mixture of diastereomeric palladacycles **6** obtained in the ring closure reaction of complex **5a**,**b** described in Scheme 3 (**6a**:**6b**:**6c**:**6d** = 5.9:7.3:2.0:1.0; *cis*:*trans* 81:19) was treated with *t*-BuOK (1.1 equiv) under the conditions identical (3 h, rt, THF) to the conditions used in entry 4, Table 1 (Scheme 4). As anticipated, the ^{31}P NMR analysis of the recovered palladacycle **6** (75% recovery yield) indicated a significant increase in the content of both the *trans* diastereomers **6c**,**d**, reaching the ratio of **6a**:**6b**:**6c**:**6d** = 1.1:1.6:1:1; *cis*:*trans* 57:43) (Scheme 4). Conceivably, the preference for the initial formation of the *cis* palladacycles (±)-**3**, (±)-**4**, and **6** could be rationalized based on an interesting structural feature elucidated by the comparison of the molecular structures of *cis* (±)-**3** and *cis* (±)-**4** established by X-ray crystallography (see Figure 4, vide supra). Assuming that similar features are found in the solution phase structures of the relevant complexes, we can envision that nonbonded interactions between the phenyl substituent attached to the palladium-bonded carbon C(4) and the ligand sphere (**L**···**L**) force the ligand **L**···**L** to fold away from the C(4) phenyl along the N(1)···N(2) or P(1)···P(2) polyhedral edge as indicated by the angle α between the normal plane **a** and the "fold" plane **b** highlighted in the structure of the O-bonded Pd enolate intermediate **IV** (Figure 5). The formation of the (*E*)-enolate, which presumably arises via the deprotonation of the cationic amide complexes (±)-**1**, (±)-**2**, and **5** (Figure 5), is anticipated to be favored due to minimized steric interactions between the phenyl substituent and the ligand sphere (**L**···**L**).

The methine carbon C(5) in the intermediate **IV** can replace the oxygen in the Pd coordination sphere by rotating ∼180° about the C(2)−N(3) bond. The amount of steric hindrance will be different for the different directions of rotation and will be determined by the order in which the hydrogen and phenyl substituents are moved past the nearest methyl or phenyl groups of the **L**···**L** ligands (TMEDA, dppe, or (*S*,*S*)-CHIRAPHOS). If the predominant conformation for the **L**···**L** ligands in the intermediate **IV** is similar to the one observed in the solid phase structures for *cis* (±)-**3** and *cis* (±)-**4**, the *cis* isomers would be expected to be formed preferentially. Notably, this mechanism for the transfer of the stereochemical information is independent of the absolute configuration of the of the stereocenters present in the auxiliary ligand (*S*,*S*)-CHIRAPHOS, since only the angle of the "fold" is controlling the diastereoselectivity of the process, and the presence of additional methyl groups in (*S*,*S*)-CHIRAPHOS would be expected to have little additional influence, being distant from the important nonbonding interactions. Equilibration of the *cis* palladacycles via reversible deprotonation yielding the C-bonded Pd-enolate **III** (Table 1) allows the phenyl ring to move along a less sterically encumbered plane ultimately providing the more stable *trans* palladacycles.

Finally, we explored possible approaches to enantiomerically pure or enriched complexes **5** and **6**. In agreement with

Scheme 5



observations of Arndtsen et al.,[5a] our attempts at modifying the synthetic protocol for the preparation of cationic palladium-chelated amide complexes to introduce auxiliary ligands prior to the formation of the palladium-bonded stereocenter were unsuccessful.[20] Thus, we considered kinetic resolution of racemic palladium-chelated amide complex (±)-**1** and an essentially pure *cis* diastereomer of racemic palladacycle (±)-**3** via ligand exchange reactions with substoichiometric quantities of chiral nonracemic ligand (*S*,*S*-CHIRAPHOS) (Scheme 5).

Palladacycle (±)-**3** with the ratio of *cis*:*trans* diastereomers dr > 20:1 was obtained by precipitation of complex (±)-**3** in the final stages of the concentration of the ethyl acetate eluent from column chromatography following the preparation of complex (±)-**3** according to the method described in Scheme 2 (vide supra). Thus, complex (±)-**1** was treated with either 10, 20, or 40 mol % of the (*S*,*S*)-CHIRAPHOS ligand at room temperature. ^{1}H NMR analyses of the crude reaction mixtures indicated that complete conversion of the phosphine ligand to the two diastereomers of the cationic palladium−amide complexes **5a**,**b** occurred.[21] Only low levels of differentiation between the rates of the ligand exchange reactions involving the enantiomers of complex (±)-**1** were realized providing an approximately 1.4:1 ratio of the two diastereomers of the cationic complex **5** in all three experiments. The *cis* diastereomer of palladacycle (±)-**3** (dr > 20:1, *cis*:*trans*) reacted with 40 mol % of the (*S*,*S*)-CHIRAPHOS ligand to afford the corresponding two *cis* diastereomers **6a** and **6b** in an essentially equal molar ratio as established by the analysis of the ^{1}H NMR spectrum of the crude reaction mixture.[22] These experiments indicate a lack of noticeable differentiation in the reaction rates of the enantiomers of complexes (±)-**1** and *cis* (±)-**3** with chiral nonracemic ligand (*S*,*S*)-CHIRAPHOS.

Conclusions

In conclusion, the results described herein yielded insights into features controlling the stereochemical relationships in unique organopalladium(II) complexes featuring two Pd-bonded stereocenters as well as chiral nonracemic bidentate ligands. Significant stereoinduction between the two sp^3-hybridized Pd-bonded stereocenters has been observed and utilized to obtain racemic complexes (±)-**3** and (±)-**4** highly enriched (dr 94:6 or 87:13) in the kinetically favored *cis* diastereomer. The molecular structures of the *cis* diastereomers in complexes bearing TMEDA and dppe auxiliary ligands were established

by X-ray crystallography. Analysis of the molecular structures of the complexes *cis* (±)-**3** and *cis* (±)-**4** provided insights that allowed us to propose a plausible rationale for the mechanism of transfer of the stereochemical information in the described reaction system. Notably, the formation of C-bonded tautomer of the palladium amide enolates **II** was strongly favored, and epimerization of the Pd-bonded stereocenter corresponding to the α-carbon of the amide functionality could only be induced in the presence of an excess of base, favoring the thermodynamically more stable *trans* isomers of complexes **II**. Furthermore, no effects consistent with the involvement of either stereochemically matched or mismatched pairs have been observed when a chiral nonracemic auxiliary bidentate phosphine ligand ((*S,S*)-CHIRAPHOS) was employed in the preparation of a palladacycle of type **II** (complex **6**), indicating a lack of stereochemical induction from the auxiliary ligand sphere during the formation of the second Pd-bonded sp^3-hybridized stereogenic carbon. Thus, the preparation of enantiomerically pure complexes of type **II** would require an efficient ligand control of the absolute configuration of the Pd-bonded stereocenter generated in the first step, a result consistent with our prior findings on the mechanims of stereoinduction in the formation of chiral nonracemic palladacycles of type **I**.[23] To date, attempts at the formation of enantiomerically enriched palladacycles **6** via kinetic resolution based approaches have not proven to be practical. At present, we are exploring the reactivity of palladacycles (±)-**3** and (±)-**4** in carbon−carbon bond-forming reactions aiming to uncover reaction pathways, which could be utilized toward the development of catalytic reactions.

Experimental Section

Amide Complex (±)-1. To a stirred solution of (*E*)-*N*-(4-methylbenzylidene)-1-phenylmethanamine (0.733 g, 3.503 mmol) in acetonitrile (5 mL) was added neat phenyl acetyl chloride (0.541 g, 3.503 mmol) to afford a pale yellow solution, which was stirred for 15 min at rt under argon. Acetonitrile (25 mL) was added, followed by Pd_2dba_3 (0.529 g, 0.578 mmol), and the reaction mixture was allowed to stir for additional 10 min. Neat TMEDA (0.814 g, 7.006 mmol) was added, and the reaction mixture was stirred for 1 h. Silver trifluoromethanesulfonate (0.990 g, 3.854 mmol) was added, and the reaction mixture was allowed to stir for an additional 1 h. The resulting suspension was filtered through a plug of celite, and the celite was washed with additional acetonitrile until the eluent was colorless. Solvents were removed under reduced pressure, the crude product was triturated with ether and dissolved in dichloromethane, and the dichloromethane solution was filtered through celite. Solvents were removed under reduced pressure to afford a crude product which was purified by flash chromatography over silica eluting with dichloromethane/acetonitrile (3:1) to afford the amide complex (±)-**1** (0.544 g, 67%) as a yellow solid: mp = 54−74 °C; R_f = 0.50 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 6 H), 7.20 (d, *J* = 6.9 Hz, 2 H), 7.08 (br s, 4 H), 6.92 (d, *J* = 6.6 Hz, 2 H), 4.46 (s, 1 H), 4.45 (d, *J* = 16.1 Hz, 1 H), 3.91 (d, *J* = 16.1 Hz, 1 H), 3.77 (s, 2 H), 3.16 (td, *J* = 13.0 Hz, 3.5 Hz, 1 H), 2.73 (td, *J* = 13.9 Hz, 3.15 Hz, 1 H), 2.62 (s, 3 H), 2.61 (s, 3 H), 2.49−2.39 (m, 5 H), 2.25 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 138.0, 137.3, 133.5, 132.3, 129.9, 129.0 128.9, 128.5, 128.2, 127.7, 127.6, 127.0, 120.7 (q, $J(^{13}C - ^{19}F)$ = 320.8 Hz), 65.1, 64.0, 57.2, 52.3, 51.0, 49.9, 47.3, 46.7, 39.4, 21.1, several signals account for more than one carbon; ^{19}F NMR (376 MHz) δ −76.84 (s, 3 F); IR (thin film, cm^{-1}) 1578 (s), 1153 (s); HRMS (ES^+) calcd for $C_{29}H_{38}N_3OPd$ [$(M-CF_3SO_3)^+$], 550.2050; found, 550.2038. Anal. Calcd for $C_{30}H_{38}F_3N_3O_4PdS$: C, 51.47; H, 5.47; N, 6.00. Found: C, 52.34; H, 5.29; N, 5.66.

Amide Complex (±)-2. Amide complex (±)-**1** (0.464 g, 0.663 mmol) and 1,2-bis(diphenylphosphino)ethane (0.528 g, 1.325 mmol) were dissolved in dichloromethane (7 mL). The resulting yellow solution was stirred for 5 h at rt under argon. Solvents were removed under reduced pressure, and the crude product was purified by flash chromatography over silica eluting with dichloromethane/acetonitrile (6:1) to afford complex (±)-**2** (0.479 g, 74%) as a yellow solid: mp = 75−90 °C; R_f = 0.46 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.64 (m, 2 H), 7.50−7.16 (m, 22 H), 7.12 (td, *J* = 7.8 Hz, 2.5 Hz, 2 H), 6.88 (d, *J* = 12.3 Hz, 1 H), 6.87 (d, *J* = 11.3 Hz, 1 H), 6.82 (d, *J* = 6.6 Hz, 2 H), 6.78 (d, *J* = 7.9 Hz, 2 H), 6.30 (br s, 2 H), 4.74 (dd, *J* = 15.5 Hz, 2.8 Hz, 1 H), 4.34 (dd, *J* = 8.2 Hz, 3.5 Hz, 1 H), 4.02 (dd, *J* = 15 Hz, 2 H), 3.95 (d, *J* = 15.8 Hz, 1 H), 2.74−2.44 (m, 3 H), 2.21 (s, 3 H), 2.00−1.84 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0 (dd, $J(^{13}C - ^{31}P)$ = 8.3 Hz, 1.8 Hz), 138.7 (d, $J(^{13}C - ^{31}P)$ = 5.5 Hz), 136.0, 134.0, 133.4 (d, $J(^{13}C - ^{31}P)$ = 11.0 Hz), 132.8, 132.75 (d, $J(^{13}C - ^{31}P)$ = 11.9 Hz), 132.5 (d, $J(^{13}C - ^{31}P)$ = 13.8 Hz), 132.3 (d, $J(^{13}C - ^{31}P)$ = 11.9 Hz), 132.0 (dd, $J(^{13}C - ^{31}P)$ = 31.2, 2.8 Hz), 131.5 (dd, $J(^{13}C - ^{31}P)$ = 14.7, 2.8 Hz), 130.4, 130.1, 129.5, 129.4 (d, *J* ($^{13}C - ^{31}P$) = 15.0 Hz), 129.3, 129.2, 129.1, 129.0, 128.92 (d, *J* ($^{13}C - ^{31}P$) = 11.0 Hz), 128.2, 127.7, 127.3, 127.2, 126.8, 125.2, 124.0, 123.5, 120.9 (q, $J(^{13}C - ^{19}F)$ = 320.8 Hz), 76.8 (dd, *J* ($^{13}C - ^{31}P$) = 99.4 Hz, 5.0 Hz), 52.2 (d, *J* ($^{13}C - ^{31}P$) = 4.6 Hz), 40.0, 31.4 (dd, *J* ($^{13}C - ^{31}P$) = 37.6 Hz, 20.2 Hz), 21.1 (dd, *J* ($^{13}C - ^{31}P$) = 30.0 Hz, 7.3 Hz), 20.9, several signals account for more than one carbon; ^{31}P NMR (162 MHz, $CDCl_3$) δ 51.5 (br s, 1 P), 38.5 (br s, 1 P); ^{19}F NMR (376 MHz) δ −76.8 (s, 3 F); IR (thin film, cm^{-1}) 1554 (s), 1150 (s); HRMS (ES^+) calcd for $C_{49}H_{46}NOP_2Pd$ [$(M-CF_3SO_2)^+$], 832.2089; found, 832.2062. Anal. Calcd for $C_{50}H_{46}F_3NO_4P_2PdS$: C, 61.13; H, 4.72; N, 1.43. Found: C, 61.09; H, 4.39; N, 1.36.

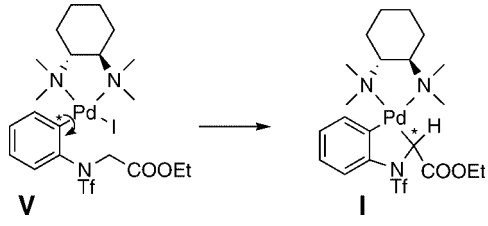
Amide Complex 5a,b. Amide complex (±)-**1** (0.203 g, 0.291 mmol) and (2*S*,3*S*)-bis(diphenylphosphino)butane (0.124 g, 0.291 mmol) were dissolved in dichloromethane (6 mL). The resulting yellow solution was stirred for 3.5 h at rt under argon. Solvents were removed under reduced pressure, and the resulting crude product was purified by flash chromatography over silica, eluting with dichloromethane/MeOH (19:1) to afford complex **5a**,**b** (0.292 g, 99%) (dr 1:1) as a yellow solid: mp = 77−100 °C; R_f = 0.58 (6.5:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.72 (m, 1 H), 7.70−7.45 (m, 13.5 H), 7.44−7.38 (m, 0.5 H), 7.33−7.07 (m, 12 H), 7.02−6.95 (m, 1 H), 6.79 (d, *J* = 7.0 Hz, 1 H), 6.74−6.68 (m, 2 H), 6.66 (d, *J* = 7.88 Hz, 1 H), 6.31 (d, *J* = 6.9 Hz, 1 H), 6.14 (d, *J* = 6.9 Hz, 1 H), 4.64 (dd, *J* = 16.8 Hz, 3.2 Hz, 0.5 H), 4.62 (dd, *J* = 15.8 Hz, 2.8 Hz, 0.5 H), 4.20 (dd, *J* = 8.5 Hz, 2.8 Hz, 0.5 H), 4.01 (dd, *J* = 7.6 Hz, 4.0 Hz, 0.5 H), 3.93−3.77

(20) An attempt to prepare complex **5** via the oxidative cyclization protocol employing Pd_2dba_3 pretreated with dppe ligand (a modified Arndtsen's protocol) proved unsuccessful.

(21) For additional information, see the Supporting Information.

(22) For additional information, see the Supporting Information.

(23) Our prior studies on the mechanism of stereoinduction in the formation of related palladacycles **I** (Figure 1) suggested that the control of the ratio of atropisomers arising from a restricted rotation around the aryl−Pd bonds in complexes **V** (see below) is essential for achieving high levels of diastereoselectivity in the formation of palladacycles **I** (see ref 4b).



(m, 3 H), 2.67−2.56 (m, 0.5 H), 2.32−2.20 (m, 2 H), 2.18−2.10 (m, 0.5 H), 2.09 (s, 1.5 H), 1.90−1.80 (m, 0.5 H), 1.10−0.94 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.93, 181.87, 139.0 (d, $J(^{13}C - ^{31}P) = 6.4$ Hz), 137.4 (d, $J(^{13}C - ^{31}P) = 4.6$ Hz), 136.1 (t, $J(^{13}C - ^{31}P) = 12.0$ Hz), 135.8 (d, $J(^{13}C - ^{31}P) = 1.8$ Hz), 135.4 (d, $J(^{13}C - ^{31}P) = 13.8$ Hz), 135.0 (d, $J(^{13}C - ^{31}P) = 12.8$ Hz), 133.9 (d, $J(^{13}C - ^{31}P) = 16.5$ Hz), 133.1 (d, $J(^{13}C - ^{31}P) = 2.8$ Hz), 132.7, 132.5, 132.3 (d, $J(^{13}C - ^{31}P) = 1.8$ Hz), 132.16, 132.13, 132.11, 132.08, 131.8 (d, $J(^{13}C - ^{31}P) = 11.0$ Hz), 131.6 (d, $J(^{13}C - ^{31}P) = 10.1$ Hz), 131.3, 131.2 (d, $J(^{13}C - ^{31}P) = 2.8$ Hz), 130.3, 129.5 (d, $J(^{13}C - ^{31}P) = 11.0$ Hz), 129.47, 129.42, 129.34, 129.32, 129.26, 129.24, 129.21, 129.18, 129.14, 129.07, 128.9 (d, $J(^{13}C - ^{31}P) = 4.6$ Hz), 128.8 (d, $J(^{13}C - ^{31}P) = 12.5$ Hz), 128.5 (d, $J(^{13}C - ^{31}P) = 11.0$ Hz), 128.3, 128.05 (d, $J(^{13}C - ^{31}P) = 2.8$ Hz), 128.0, 127.7, 127.5 (d, $J(^{13}C - ^{31}P) = 2.8$ Hz), 127.3, 127.2, 127.1, 127.0, 126.9, 126.84, 126.79, 126.7, 126.63, 126.60, 126.5, 126.2, 125.2 (d, $J(^{13}C - ^{31}P) = 54.1$ Hz), 124.1 (d, $J(^{13}C - ^{31}P) = 51.5$ Hz), 123.9 (d, $J(^{13}C - ^{31}P) = 48.6$ Hz), 121.3 (q, $J(^{13}C - ^{19}F) = 319.3$ Hz), 120.1 (d, $J(^{13}C - ^{31}P) = 49.5$ Hz), 76.9 (dd, $J(^{13}C - ^{31}P) = 402.3$ Hz, 6.0 Hz), 76.8 (d, $J(^{13}C - ^{31}P) = 208.0$ Hz, 5.8 Hz), 53.4, 52.3 (dd, $J(^{13}C - ^{31}P) = 12.0$ Hz, 4.3 Hz), 43.9 (dd, $J(^{13}C - ^{31}P) = 35.8$ Hz, 23.8 Hz), 42.6 (dd, $J(^{13}C - ^{31}P) = 34.8$ Hz, 22.9 Hz), 39.9, 31.8, 31.3 (dd, $J(^{13}C - ^{31}P) = 44.0$ Hz, 10.1 Hz), 31.1 (dd, $J(^{13}C - ^{31}P) = 44.0$ Hz, 11.0 Hz), 29.6, 21.0, 20.8, 14.1 (m), 14.08 (dd, $J(^{13}C - ^{31}P) = 54.6$ Hz, 5.5 Hz), 14.01 (d, $J(^{13}C - ^{31}P) = 5.5$ Hz), 14.0 (dd, $J(^{13}C - ^{31}P) = 5.5$ Hz), several signals account for more than one carbon; ^{31}P NMR (162 MHz, $CDCl_3$) δ 59.7 (br s, 1 P), 57.6 (br s, 1 P), 47.5 (br s, 1 P), 42.9 (br s, 1 P); ^{19}F NMR (376 MHz) δ −76.7 (s, 3 F); IR (thin film, cm^{-1}) 1562 (s), 1150 (s); HRMS (ES^+) calcd for $C_{51}H_{50}NOP_2Pd$ [$(M-CF_3SO_2)^+$], 860.2402; found, 860.2389. Anal. Calcd for $C_{52}H_{50}F_3NO_4P_2PdS$: C, 61.81; H, 4.99; N, 1.39. Found: C, 62.36; H, 4.65; N, 1.37.

General Procedure for the Synthesis of Palladacycles via Ring Closure. To a solution of cationic palladium complex (0.1 M) in THF at a given temperature was added a solution of base (*t*-BuOK 1.0 M in THF, KHMDS 0.5 M in toluene, LDA 2.0 M in heptane/THF/ethylbenzene), and the reaction mixture was stirred for the designated time(s) under argon. The suspension was diluted with dichloromethane, and the solvents were removed under reduced pressure. The oily residue was dissolved in dichloromethane and filtered through celite to remove any insoluble materials. Solvents were removed under reduced pressure, and the crude product was purified by flash chromatography over silica eluting with ethyl acetate (EtOAc) and hexane mixtures or with EtOAc to afford the corresponding palladacycles as yellow or orange solids.

Palladacycle (±)-3. Amide complex (±)-**1** (0.540 g, 0.7710 mmol) was treated with *t*-BuOK (0.85 mL, 0.85 mmol) at 45 °C according to the general procedure described above. Elution with EtOAc/Hex (1:1) and EtOAc followed by trituration with pentane afforded complex (±)-**3** (0.3471 g, 82%) (dr 88:12, *cis*:*trans*) as a light orange powder: mp = 162−170 (dec.); R_f = 0.36 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.0 Hz, 1.8 H), 7.38 (d, J = 7.5 Hz, 0.3 H), 7.33 (d, J = 7.9 Hz, 2 H), 7.30−7.23 (t, J = 7.0 Hz, 1 H), 7.24−7.12 (m, 5.5 H), 7.12−6.97 (m, 3.4 H), 4.89 (d, J = 14.8 Hz, 0.12 H), 4.84 (d, J = 14.5 Hz, 0.88 H), 4.13 (s, 0.12 H), 4.12 (s, 0.88 H), 3.99 (s, 0.88 H), 3.94 (s, 0.12 H), 3.40 (d, J = 14.5 Hz, 0.88 H), 3.34 (d, J = 14.5 Hz, 0.12 H), 2.65−2.56 (m, 0.2 H), 2.50−2.46 (m, 1 H), 2.45−2.34 (m, 5.6 H), 2.33−2.20 (m, 5.2 H), 2.13−2.06 (m, 1 H), 1.55 (s, 2.7 H), 1.44 (s, 2.7 H), 1.40 (s, 0.3 H), 1.35 (s, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (182.5), 182.2, (148.4), 147.4, (144.5), 144.0, (139.0), 138.8, 134.1, (132.5), 130.7, (130.1), (129.8), (129.7), (129.2), 129.1, 128.8, 128.6, (128.5), 127.94, 127.91, 126.3, 124.2, (123.7), (60.6), (60.5), (60.4), 60.23, 60.18, (53.4), (50.5), 50.3, (50.0), (49.5), 49.2, 48.8, 48.6, 47.8, 47.5, 47.0, 46.1, 45.6, (29.7), 21.9, 21.1, 21.0, (minor diastereomer signals in parentheses), some signals account for more than one carbon; IR (thin film, cm^{-1}): 1617 (s); HRMS (ES^+) calcd for $C_{29}H_{38}N_3OPd$ ($M + H^+$), 550.2050; found, 550.2025. Anal. Calcd for $C_{29}H_{37}N_3OPd$: C, 63.32; H, 6.78; N, 7.64. Found: C, 63.38; H, 6.52; N, 6.97.

A sample of complex (±)-**3** highly enriched in the *cis* diastereomer (dr > 20:1 by ^{1}H NMR) was obtained by precipitation and trituration (benzene) of solids obtained directly from the EtOAc eluent after chromatography. Analytical data for complex *cis*-(±)-**3** (dr > 20:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 7.5 Hz, 2 H), 7.32−7.23 (m, 7 H), 7.14−7.09 (m, 3 H), 4.89 (d, J = 14.5 Hz, 1 H), 4.16 (s, 1 H), 4.03 (s, 1 H), 3.43 (d, J = 14.5 Hz, 1 H), 2.56−2.52 (m, 1 H), 2.45 (s, 3 H), 2.42 (s, 3 H), 2.34−2.29 (m, 5 H), 2.17−2.13 (m, 1 H), 1.60 (s, 3 H), 1.50 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 147.5, 144.2, 139.0, 134.0, 130.8, 129.1, 129.0, 127.9, 126.3, 124.2, 60.2, 50.2, 49.2, 48.9, 48.6, 47.8, 47.0, 21.1, several signals account for more than one carbon.

Palladacycle (±)-4. Amide complex (±)-**2** (0.089 g, 0.091 mmol) was treated with *t*-BuOK (0.100 mL, 0.100 mmol) at 45 °C under argon according to the general procedure above. Elution with EtOAc/Hex (1:1) followed by trituration with pentane afforded palladacycle (±)-**4** (0.068 g, 90%) as a yellow powder in dr 72:28, *cis*:*trans*.

Alternatively, palladacycle (±)-**4** was also synthesized via ligand exchange reaction. Thus, complex (±)-**3** (dr 89:11, *cis*:*trans*) (0.396 g, 0.719 mmol) and 1,2-bis(diphenylphosphino)ethane (0.573 g, 1.44 mmol) were dissolved in dichloromethane (10 mL). The resulting yellow solution was stirred for 3.5 h at rt under argon. Solvents were removed under reduced pressure, and the crude product was purified by flash chromatography over silica, eluting with EtOAc/hexane (1:1) to afford palladacycle (±)-**4** (0.534 g, 89%) as a yellow powder (dr 87:13).

Complex (±)-**4** was characterized as a mixture of diastereomers in the ratio dr 91:9, *cis*:*trans* (obtained from an analogous but separate experiment in 89% yield) providing the analytical data below: mp = 150−165 °C (dec.); R_f = 0.50 (2:1 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.56 (m, 2.2 H), 7.54−7.45 (m, 5.8 H), 7.42 (td, J = 7.6 Hz, 1.6 Hz, 2 H), 7.39−7.16 (m, 7 H), 7.12 (td, J = 7.6 Hz, 1.6 Hz, 1.9 H), 7.08 (td, J = 7.6 Hz, 1.6 Hz, 1.9 H), 7.02−6.82 (m, 7.8 H), 6.79−6.61 (m, 5.0 H), 6.58−6.44 (m, 0.4 H), 5.12 (dd, J = 14.0 Hz, 1.6 Hz, 0.09 H), 5.03 (dd, J = 14.4 Hz, 2.0 Hz, 0.91 H), 4.78 (t, J = 7.0 Hz, 0.09 H), 4.75 (t, J = 7.6 Hz, 0.91 H), 4.53 (t, J = 7.0 Hz, 0.09 H), 4.40 (dd, J = 8.8 Hz, 6.0 Hz, 0.91 H), 3.61 (d, J = 14.2 Hz, 0.91 H), 3.55 (d, J = 14.2 Hz, 0.09 H), 2.19 (s, 3H), 2.17−1.85 (m, 3.7 H), 1.78−1.61 (m, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5 (t, $J(^{13}C - ^{31}P) = 6.4$ Hz), (182.2 (t, $J(^{13}C - ^{31}P) = 6.4$ Hz)), 148.2 (t, $J(^{13}C - ^{31}P) = 3.0$ Hz), (146.1 (d, $J(^{13}C - ^{31}P) = 7.3$ Hz)), 145.4 (d, $J(^{13}C - ^{31}P) = 3.0$ Hz), (144.6 (d, $J(^{13}C - ^{31}P) = 4.5$ Hz)), 138.9, (138.7), 134.2 (dd, $J(^{13}C - ^{31}P) = 16.9$ Hz, 14.0 Hz), 133.5 (d, $J(^{13}C - ^{31}P) = 13.8$ Hz), 133.2 (d, $J(^{13}C - ^{31}P) = 13.8$ Hz), 133.0 (d, $J(^{13}C - ^{31}P) = 12.8$ Hz), 132.8 (d, $J(^{13}C - ^{31}P) = 12.8$ Hz), 132.46, 132.35 (d, $J(^{13}C - ^{31}P) = 1.8$ Hz), 132.30 (dd, $J(^{13}C - ^{31}P) = 31.2$ Hz, 1.8 Hz), 132.31, 132.2, 132.19, (131.9), 131.59 (dd, $J(^{13}C - ^{31}P) = 29.3$ Hz, 1.8 Hz), (131.4), (131.15), (131.07), (130.71), (130.61), 130.3 (dd, $J(^{13}C - ^{31}P) = 10.1$ Hz, 1.8 Hz), 129.84, 129.63, (129.55), 129.5 (d, $J(^{13}C - ^{31}P) = 12.5$ Hz), 129.3 (d, $J(^{13}C - ^{31}P) = 15.0$ Hz), 129.26, 128.80, 128.70, 128.67, 128.59, (128.50), (128.46), (128.29), 128.24, 128.17, 127.79, 127.38, 127.3, (126.3), 126.16, 126.0 (d, $J(^{13}C - ^{31}P) = 2.5$ Hz), (125.46), 122.90, (122.31), (64.3), 57.0 (t, $J(^{13}C - ^{31}P) = 3.7$ Hz), 56.7 (dd, $J(^{13}C - ^{31}P) = 70.1$ Hz, 2.8 Hz), 56.3 (dd, $J(^{13}C - ^{31}P) = 86.6$ Hz, 3.7 Hz), 49.1 (d, $J(^{13}C - ^{31}P) = 3.7$ Hz), 29.2 (td, $J(^{13}C - ^{31}P) = 24.7$ Hz, 17.4 Hz), (27.6 (d, $J(^{13}C - ^{31}P) = 16.5$ Hz)), (27.4 (d, $J(^{13}C - ^{31}P) = 16.5$ Hz)), (27.1 (d, $J(^{13}C - ^{31}P) = 16.5$ Hz)), (26.9 (d, $J(^{13}C - ^{31}P) = 16.5$ Hz)), (20.9), 20.8, (signals for the minor diastereomer are in parentheses), some signals account for more than one carbon;^{31}P NMR (162 MHz, $CDCl_3$) δ (39.5 (br s, 0.05

P)), (35.9 (br s, 0.05 P)), 34.8 (br s, 0.45 P), 32.7 (br s, 0.45 P), (signals for the minor diastereomer in parentheses); IR (thin film, cm^{-1}): 1607 (s); HRMS (ES^+) calcd for $C_{49}H_{46}NOP_2Pd$ ($M + H^+$), 832.2089; found, 832.2108. Anal. Calcd for $C_{49}H_{45}NOP_2Pd$: C, 70.71; H, 5.45; N, 1.68. Found: C, 70.86; H, 5.34; N, 1.64.

Palladacycle 6a−d. Amide complex **5a**,**b** (dr 1:1) (0.155 g, 0.154 mmol) was treated with *t*-BuOK (0.170 mL, 0.170 mmol) at 45 °C according to the general procedures described above. Elution with EtOAc/Hex (1:1) followed by trituration with pentane afforded complex **6a−d** (0.120 g, 91%) as a yellow powder, dr **6a**:**6b**:**6c**:**6d** = 5.9:7.3:2:1, *cis*:*trans*, 81:19.

Alternatively, palladacycle **6** was also synthesized via a ligand exchange reaction. Thus, complex (±)-**3** (dr 91:9, *cis*:*trans*) (0.082 g, 0.149 mmol) and (*S*,*S*)-CHIRAPHOS (0.095 g, 0.223 mmol) were dissolved in dichloromethane (2 mL). The yellow solution was stirred for 3.5 h at rt under argon. Solvents were removed under reduced pressure, and the crude product was purified by flash chromatography over silica, eluting with EtOAc/hexanes (1:1) to afford palladacycle **6** (0.107 g, 83%) (dr 91:9, **6a**:**6b**:**6c**:**6d** = 4.5:4.5:0.5:0.5, *cis*:*trans*) as a yellow powder after trituration with pentane. Analytical data for this sample of complex **6a−d**: mp = 90−135 °C (dec.); R_f = 0.52 (2:1 EA/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (td, J = 8.2 Hz, 1.6 Hz, 1.9 H), 7.60−7.39 (m, 7.5 H), 7.38−7.09 (m, 11 H), 7.09−6.91 (m, 4.5 H), 6.86−6.55 (m, 8 H), 6.51 (d, J = 7.3 Hz, 1 H), 6.19 (d, J = 7.9 Hz, 0.1 H), 5.10 (dd, J = 14.0 Hz, 2.2 Hz, 0.05 H), 4.97 (d, J = 2.2 Hz, 0.22 H), 4.96 (d, J = 1.9 Hz, 0.23 H), 4.93 (d, J = 2.2 Hz, 0.22 H), 4.92 (d, J = 2.2 Hz, 0.23 H), 4.58 (t, J = 6.3 Hz, 0.05 H), 4.54 (dd, J = 8.1 Hz, 6.7 Hz, 0.45 H), 4.42 (dd, J = 8.8 Hz, 6.0 Hz, 0.05 H), 4.32 (dd, J = 9.5 Hz, 4.0 Hz, 0.45 H), 4.28 (t, J = 8.0 Hz, 0.45 H), 4.17 (dd, J = 9.8 Hz, 4.0 Hz, 0.03 H), 4.08 (t, J = 6.9 Hz, 0.22 H), 3.86 (t, J = 7.6 Hz, 0.45 H), 3.57 (d, J = 14.2 Hz, 0.45 H), 3.53 (s, 0.05 H), 3.49 (d, J = 14.5 H, 0.45 H), 3.44 (d, J = 14.2 Hz, 0.05 H), 2.28 (s, 0.1 H), 2.25−2.18 (m, 1 H), 2.17−2.09 (m, 1.3 H), 2.08−2.02 (m, 0.5 H), 1.68−1.46 (m, 1.0 H), 1.45−1.25 (m, 1.0 H), 1.03−0.93 (m, 3 H), 0.92−0.86 (m, 1 H), 0.84−0.75 (m, 0.4 H), 0.72 (dd, J = 10.0 Hz, 7.0 Hz, 1.3 H), 0.69−0.64 (m, 0.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9 (t, $J(^{13}C - ^{31}P)$ = 7.0 Hz), (182.6 (t, $J(^{13}C - ^{31}P)$ = 6.4 Hz)), 182.1 (t, $J(^{13}C - ^{31}P)$ = 7.0 Hz), (182.0 (t, $J(^{13}C - ^{31}P)$ = 6.4 Hz)), 148.6 (t, $J(^{13}C - ^{31}P)$ = 2.8 Hz), (148.3), 147.0 (t, $J(^{13}C - ^{31}P)$ = 1.8 Hz), (146.0 (d, $J(^{13}C - ^{31}P)$ = 5.5 Hz)), 145.7 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), 145.2 (d, $J(^{13}C - ^{31}P)$ = 4.6 Hz), (143.9 (d, $J(^{13}C - ^{31}P)$ = 7.3 Hz)), (143.3 (d, $J(^{13}C - ^{31}P)$ = 6.4 Hz)), (138.9), 138.8, (138.4), (136.96 (d, $J(^{13}C - ^{31}P)$ = 15.6 Hz)), 136.92 (d, $J(^{13}C - ^{31}P)$ = 14.7 Hz), 136.7 (d, $J(^{13}C - ^{31}P)$ = 14.7 Hz), (135.7 (d, $J(^{13}C - ^{31}P)$ = 13.8 Hz)), (135.4 (d, $J(^{13}C - ^{31}P)$ = 13.2 Hz)), 134.9 (t, $J(^{13}C - ^{31}P)$ = 12.5 Hz), (133.9 (d, $J(^{13}C - ^{31}P)$ = 8.0 Hz)), (133.7 (d, $J(^{13}C - ^{31}P)$ = 8.4 Hz), 133.2 (d, $J(^{13}C - ^{31}P)$ = 12.3 Hz), 132.2 (d, $J(^{13}C - ^{31}P)$ = 16.8 Hz), 132.16, (132.1), 132.04, (132.01), 131.94 (d, $J(^{13}C - ^{31}P)$ = 3.6 Hz), 131.86 (d, $J(^{13}C - ^{31}P)$ = 2.9 Hz), (131.4 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), (131.3 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), 131.0, 130.93, 130.86, 130.80, 130.7 (dd, $J(^{13}C - ^{31}P)$ = 4.6 Hz, 1.8 Hz), 130.6 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), 130.5, 130.4 (d, $J(^{13}C - ^{31}P)$ = 1.8 Hz), 130.3, 130.1 (d, $J(^{13}C - ^{31}P)$ = 4.6 Hz), (130.0 (d, $J(^{13}C - ^{31}P)$ = 1.8 Hz)), 129.8 (d, $J(^{13}C - ^{31}P)$ = 4.6 Hz), 129.7 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), 129.6, 129.5, 129.44, 129.36, 129.2, 129.1 (d, $J(^{13}C - ^{31}P)$ = 1.2 Hz), 129.0 (d, $J(^{13}C - ^{31}P)$ = 3.7 Hz), (128.93), 128.89, 128.87, 128.8, 128.63, 128.58, 128.5, 128.4, (128.3), 128.25, 128.20, 128.18, 128.14, 128.11, (127.84), (127.82), 127.76, 127.7 (d, $J(^{13}C - ^{31}P)$ = 3.7 Hz), 127.6 (d, $J(^{13}C - ^{31}P)$ = 10.0 Hz), 127.4, (127.1), 126.7, (126.6), (126.5 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), (126.4), 126.2 (d, $J(^{13}C - ^{31}P)$ = 3.0 Hz), 126.05, 126.01 (d, $J(^{13}C - ^{31}P)$ = 3.5 Hz), 125.8, (125.7 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), 125.6 (d, $J(^{13}C - ^{31}P)$ = 2.4 Hz), 125.5, (125.33), 125.28, 64.3, 59.0 (dd, $J(^{13}C - ^{31}P)$ = 38.0 Hz, 2.8 Hz), 58.4 (dd, $J(^{13}C - ^{31}P)$ = 28.4 Hz, 1.8 Hz), 57.8 (dd, $J(^{13}C - ^{31}P)$ = 52.2 Hz, 2.8 Hz), (57.4 (dd, $J(^{13}C - ^{31}P)$ = 7.3 Hz, 2.8 Hz)), 57.1 (dd, $J(^{13}C - ^{31}P)$ = 40.0 Hz, 1.8 Hz), 56.9 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), (56.0 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), (49.4 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz)), 49.1 (d, $J(^{13}C - ^{31}P)$ = 3.7 Hz), 49.0 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), (48.9 d, $J(^{13}C - ^{31}P)$ = 3.7 Hz)), 41.8 (d, $J(^{13}C - ^{31}P)$ = 2.8 Hz), 41.71 (dd, $J(^{13}C - ^{31}P)$ = 45.8 Hz, 14.7 Hz), 41.66 (d, $J(^{13}C - ^{31}P)$ = 3.7 Hz), 37.0 (d, $J(^{13}C - ^{31}P)$ = 22.0 Hz, 17.4 Hz), 35.7 (dd, $J(^{13}C - ^{31}P)$ = 23.3 Hz, 18.8 Hz), 34.02, (33.98), 30.5, 22.3, 20.98, (20.94), 20.85 (20.80), 20.7, 19.0, 15.9 (dd, $J(^{13}C - ^{31}P)$ = 15.6, 5.5 Hz), 15.2 (dd, $J(^{13}C - ^{31}P)$ = 15.6, 5.5 Hz), 14.31, 14.26, 14.23, 14.18, 14.12, 14.06, 14.00, (13.39), (13.34), (13.27), (13.20), (13.08), (13.04), (signals for the minor diastereomers are in parentheses), several signals account for more than one carbon; ^{31}P NMR (162 MHz, $CDCl_3$) δ (46.3 (br s, 0.12 P)), 45.1 (br s, 0.38 P), 42.8 (br s, 0.55 P (major + minor), (41.7 (br s, 0.063 P)), (39.7 (br s, 0.067 P)), 38.8 (br s, 0.44 P), 36.0 (br s, 0.38 P), (signals for the minor diastereomers in parentheses); IR (thin film, cm^{-1}): 1607 (br); HRMS (ES^+) calcd for $C_{51}H_{50}NOP_2Pd$ ($M + H^+$), 860.2402; found, 860.2382. Anal. Calcd for $C_{51}H_{49}NOP_2Pd$: C, 71.20; H, 5.74; N, 1.63. Found: C, 71.01; H, 5.59; N, 1.58.

Acknowledgment. Support for this work from the National Science Foundation via CAREER Award (Grant No. CHE-0239123) to H.C.M. is gratefully acknowledged.

Supporting Information Available: Description of the experiments reported in Scheme 4, Scheme 5, and Table 1, description of the assignment of ^{31}P NMR signals for complexes **6a−d**, including printouts of ^{31}P NMR spectra for **6a−d**, temperature dependent ^{31}P NMR spectra of complex **6**, ^{1}H and ^{13}C NMR spectra of all new compounds prepared in this study as well as CIF files providing X-ray crystallographic data for complexes *cis* (±)-**3** and *cis* (±)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800630F