Endo-Effect-Driven Regioselectivity in the Cyclopalladation of (*S*)-2-*tert*-Butyl-4-phenyl-2-oxazoline

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Direct cyclopalladation of (*S*)-2-*tert*-butyl-4-phenyl-2-oxazoline using palladium acetate in acetic acid or acetonitrile provided a mixture of two isomeric compounds, the endo μ-AcO dimeric complex with a C(sp^3)−Pd bond and the corresponding exo derivative with a C(sp^2)−Pd bond, with the former being the major product. The μ-AcO dimeric complexes were converted to the corresponding μ-Cl analogues **3** and **4** by treatment with LiCl in acetone; the latter compounds were transformed to the corresponding PPh_3 adducts **5** and **6**. The NMR data suggested the puckered structure of the endo palladacycle in complexes **3** and **5**, the twisted $\lambda(S)$ conformation of the oxazoline ring in **3**, **4**, and **6**, and the $\delta(S)$ conformation of the heterocycle in complex **5**. The X-ray crystal structure of **5** confirmed the $\delta(S)$ conformation of the oxazoline ring in the solid state and the twisted conformation of the palladacycle and revealed a P-propeller chiral configuration of the PPh_3 ligand. A series of ab initio quantum chemical calculations were performed on two model compounds generated by replacing the PPh_3 ligands with NH_3 in complexes **5** and **6**. The structures and energies of the two model exo and endo isomers were calculated at the RHF, BLYP, and MP2 levels of theory with a 6-31G* basis for the light atoms and LANL2DZ ECP for the palladium and were found to be comparable. Single point coupled cluster calculations, with single double excitations (CCSD), corroborated the results.

Introduction

Regioselectivity in cyclopalladation[1−9] has been observed for a number of substrates; however, factors that govern the direction of metalation appear to depend on many parameters, including hybridization of the carbon to be palladated, the preligand's type and structure, and the palladium source, which ultimately determine kinetic and thermodynamic preferences for palladation. For example, it appears that cyclopalladation of 2-substituted naphthalene derivatives with two competitive C(sp^2) centers for metalation—1-(1-naphthyl)ethylamines,[10] 1-(2-naphthyl)ethylamines,[11,12] and 4,4-dimethyl-2-naphthyl-2-oxazoline[13]—is governed by the greater thermodynamic stability of the formed palladacycles. Regioselectivity in the reactions of dibenzylamine derivatives with different aryl groups[14] can be predicted on the basis of the electronic properties of the arene substituents and can be governed by changing the solvent polarity, which apparently affects the mechanism and reversibility of cyclopalladation.[14] Surprisingly, prediction of cyclopalladation regioselectivity is not obvious when two possible metalation carbons have different hybridizations: sp^2 (aromatic carbon) and sp^3 (aliphatic or benzylic). It is well accepted that activation of aromatic C(sp^2)−H bonds is generally favored over that of benzylic C(sp^3)−H and especially aliphatic C(sp^3)−H bonds.[15] However, in certain cases, palladation of the C(sp^3) atom can successfully compete with the C(sp^2) center to give palladacycles with a C(sp^3)−Pd bond either as the exclusive product[16−21] or as a mixture with the alternative metallacycle.[22]

The direction of cyclopalladation also depends on specific structural features of the preligands. Imines, including oxazolines, show a strong preference for the formation of endo complexes with the C═N bond included in the metallacycle over the alternative exo derivatives (so-called endo effect; Chart 1).

In this work, we compare the endo effect and aromatic vs aliphatic C−H bond activation in the cyclopalladation of (*S*)-

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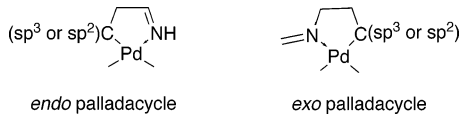
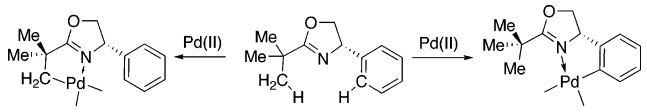
Chart 1. General Structures of Five-Membered Endo and Exo Palladacycles



endo palladacycle *exo* palladacycle

Scheme 1



endo-palladacycle (*S*)-2-*tert*-butyl-4-phenyl-2-oxazoline, **1** *exo*-palladacycle

Scheme 2

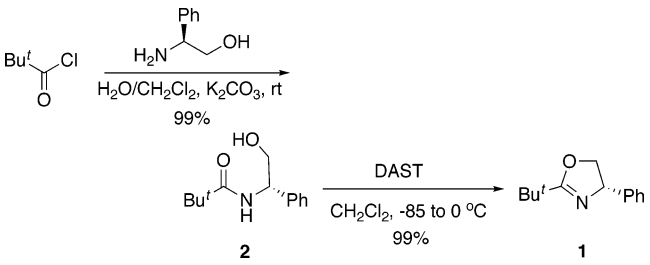


Table 1. Cyclopalladation of (*S*)-2-*tert*-Butyl-4-phenyl-2-oxazoline (1)

run	reagent	solvent	*T*, °C	time, h	**3**:**4** ratio	yield, %
1	$Pd(OAc)_2$	MeCN	80	2	2:1	53
2	$Pd(OAc)_2$	MeCN	80	7	3:1	45
3	$Pd(OAc)_2$	MeCN	80	13	5:1	56
4	$Pd(OAc)_2$	MeCN	20	120	5:2	29
5	$Pd(OAc)_2$	AcOH	60	12	10:1	59

2-*tert*-butyl-4-phenyl-2-oxazoline (**1**). This preligand was chosen for study because of the possible formation of both endo and exo palladacycles (Scheme 1). The former is favored by the endo effect, while the latter is favored by the hybridization type of the carbon atom to be metalated. We wish to report the regioselectivity of (*S*)-2-*tert*-butyl-4-phenyl-2-oxazoline cyclopalladation and to shed light on possible reasons of metalation preference using experimental and theoretical data.

Results and Discussion

1. Synthesis. (a) Preligand Preparation. (*S*)-2-*tert*-Butyl-4-phenyl-2-oxazoline (**1**) was obtained in two steps from commercially available (*S*)-2-phenylglycinol using known procedures[23] (Scheme 2).

(b) Cyclopalladation of (*S*)-2-*tert*-Butyl-4-phenyl-2-oxazoline (1). Reaction of the preligand **1** with $Pd(OAc)_2$ in glacial AcOH at 60 °C, followed by treatment with LiCl, provided a mixture of the desired complexes **3** and **4**, which were then separated by column chromatography (Table 1 and Scheme 3). The cyclopalladation also took place in MeCN at 20−80 °C. Attempts to improve the yield and regioselectivity by using different palladation methods failed. In particular, conversion of the coordination complex **8** ($Pd(HL)_2Cl_2$, HL = oxazoline **1**) to cyclopalladated derivatives **3** and **4** using the procedures reported for other preligands was unsuccessful.[24,25] Cyclopalladated ligand exchange reactions[26−30] with bis(μ-chloro)bis-[2-((dimethylamino)methyl)phenyl-*C*,*N*]dipalladium(II) also did not result in the preparation of desired complexes.

In order to convert **1** to the exocyclic complex **4**, the following reaction sequence was attempted: (i) ortho-directed lithiation of **1** using lithium 2,2,6,6-tetramethylpiperidide (LTMP) or *n*- or *sec*-BuLi in Et_2O or THF at −78 °C, (ii) quenching of the reaction mixture with ICH_2CH_2I or Me_3SiCl, and (iii) reaction of the resulting ortho-substituted derivative with $Pd_2(dba)_3$. In all cases, no characteristic signals of the oxazoline ring protons were found; instead, NMR data suggested the addition of the organolithium reagents across the C═N bond. Similar data were reported by the Richards group for lithiation of C_2-symmetric tridentate Pybox ligands with 4-Ph and 4-Bn substituents.[31]

For subsequent spectral studies, the dimeric complexes **3** and **4** were transformed into their respective mononuclear phosphine derivatives, **5** and **6** (Scheme 3). Compound **5** was further converted into its benzonitrile derivative **7**.

2. Spectral Characterization of Complexes. The structures of the obtained complexes **3**−**8** were supported by NMR (^1H, ^{13}C, ^{31}P, COSY, DEPT, and HSQC) and IR spectroscopy. Strong evidence of cyclopalladation at the *tert*-butyl group of **1** to produce **3** was provided by the following: (i) the nine-proton singlets of the *tert*-butyl group at δ 1.31 and 1.36 ppm in the spectra of compounds **1** and **8**, respectively, were replaced with two three-proton singlets of diastereotopic methyl groups at δ 1.20 and 1.28 ppm, (ii) there was the appearance of two one-proton doublets at δ 1.86 and 2.02 ppm in the spectrum of **3** for the diastereotopic Pd-bonded methylene protons, and (iii) the DEPT135 spectrum of **3** contained two additional signals: one for a methylene carbon and the other for a methyl carbon. The five-proton aromatic signals at δ 7.22−7.33 and 7.35−7.44 ppm in the spectra of compounds **1** and **8** were replaced by four one-proton aromatic signals. A signal assigned to one of the aromatic CH carbons in the DEPT135 spectrum of the preligand **1** was replaced with a signal of a quaternary aromatic carbon in the spectrum of **4**. A strong band in the IR spectrum of complex **4** at ν 737 cm^{-1} supported the presence of a disubstituted aromatic ring. The two observed bands at ν 757/700, 738/702, and 735/699 cm^{-1}, in the IR spectra of compounds **1**, **3**, and **8**, respectively, are typical for monosubstituted benzenes. The formation of N→Pd bonds in complexes **3**−**8** was supported by the shift of the C═N stretching bands to shorter wavenumbers ($\Delta\nu$ = 13, 32, 10, 19, 17, and 36 cm^{-1}, respectively) in their IR spectra, relative to that at ν 1657 cm^{-1} for the free oxazoline **1**.

Values of coupling constants in the ^1H NMR spectra of the oxazoline preligand **1** and complexes **3**−**8** in $CDCl_3$ were used to determine the oxazoline ring conformations in these compounds. The values of the torsion angles H^S−C(O)−C(N)−H and H^R−C(O)−C(N)−H were estimated using the computer program MestRe-J, which calculates the torsion angles by applying the Haasnoot−de Leeuw−Altona equation.[32] Using values of the coupling constants $^3J_{OCH^S,NCH}$ = 10.1 and $^3J_{OCH^R,NCH}$ = 7.7 for the free oxazoline **1**, values of 5−6 and

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Scheme 3

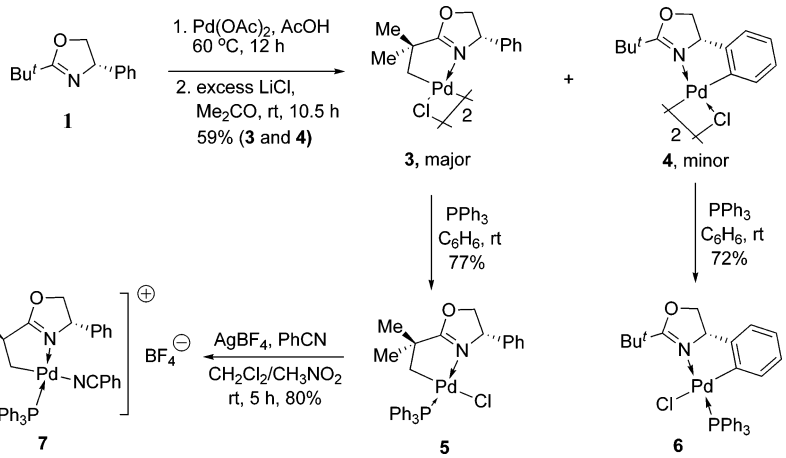


Chart 2. Two Possible Chiral Twisted ($\delta(S)$ and $\lambda(S)$) Conformations of the Oxazoline Ring in Preligand 1 and Complexes 3−7

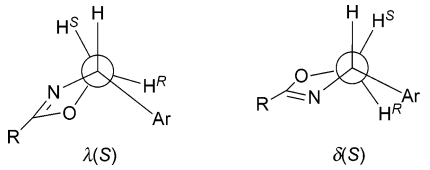
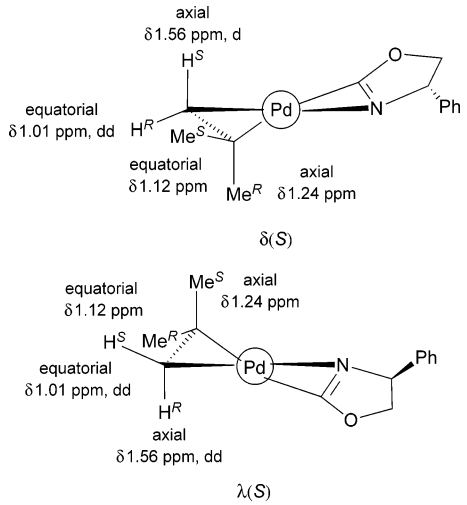


Chart 3. Two Possible Conformations, $\delta(S)$ and $\lambda(S)$, for the Endo Palladacycle in 5



133−134° were obtained for the H^S−C(O)−C(N)−H and H^R−C(O)−C(N)−H torsion angles, respectively. This suggested the slightly twisted $\delta(S)$ conformation for the preligand **1** (Chart 2). The same twisted $\delta(S)$ solution conformation is predicted for dimer **3** (torsion angles H^S−C(O)−C(N)−H and H^R−C(O)−C(N)−H ca. 21 and 124°). Complexes **4**, **6**, and **7** also have the $\delta(S)$ conformation, although the values of the torsion angle H^S−C(O)−C(N)−H are very small: 4−6°. The oxazoline ring conformation in coordination complex **8** can be considered achiral, with no twist to either direction. The PPh_3 adduct **5** has the alternative slightly twisted $\lambda(S)$ conformation in solution, with estimated values of the torsion angles H^S−C(O)−C(N)−H and H^R−C(O)−C(N)−H of ca. 3 and 118°, respectively. The heterocycle's $\lambda(S)$ conformation and the torsion angle values are in good agreement with the data obtained from the X-ray diffraction study of the same compound (vide infra).

The presence of only one signal in the ^{31}P NMR spectra of complexes **5**−**7** (δ 32.9, 40.9, and 32.3 ppm, respectively) indicates that these compounds exist as only one isomer. In complexes **5**−**7**, the coordination sphere of the Pd is expected to have a trans(P,N) geometry, due to the greater trans influence of carbon.[2] The chemical shift of δ 32.9 ppm for compound **5** is very similar to the value of δ 32.4 ppm reported for a C,N-mononuclear cyclopalladated complex with a C(sp^3)−Pd bond and proven trans(P,N) geometry.[33] The NOESY spectrum obtained for complex **6** showed a cross-peak between the signals of the ortho hydrogens of the PPh_3 ligand and the C(6) hydrogen of the aryl ring fused to the palladacycle; such interactions can be observed only in the case of the trans(P,N) geometry of the compound.

The endo palladacycle's conformation in complex **5** in solution (Chart 3) was evaluated using NMR spectroscopy. The ^1H NMR signal of the PdCH group with a chemical shift of δ 1.01 ppm, which appeared as a doublet of doublets due to the interactions with the P atom, must belong to the proton positioned in or close to the PdCNPCl plane. The other signal of the PdCH fragment at δ 1.56 ppm appeared as a doublet, suggesting an orthogonal position with respect to the PdCNPCl plane. These considerations allowed the assignment of the axial and equatorial hydrogens, but not the $PdCH^S$ and $PdCH^R$ groups. In the NOESY spectrum, the ortho protons of the PPh_3 group have a cross-peak with only one of the two Me groups (δ 1.24 ppm) in the palladacycle; this group must be in the axial position. The second CH_3 group (δ 1.12 ppm), which is expected to be in the equatorial position, exhibits weak NOE interactions only with the axial hydrogen of the $PdCH_2$ fragment. No other NOESY cross-peaks were helpful. It is noteworthy that the signals of both $PdCH^{ax}$ and $CH_3{}^{ax}$ groups have higher chemical shifts compared to those in the equatorial position, as expected on the basis of the fact that these groups, which are positioned above and below the PdCNPCl plane, are under the influence of the Pd atom's magnetic anisotropy.[34] Unfortunately, although these data confirm that the palladacycle's conformation is twisted, it was impossible to distinguish between the two possible forms (Chart 3).

Comparison of the ^1H NMR spectra of compound **5** at −55 °C, room temperature, and +55 °C in $CDCl_3$ revealed that although the chemical shifts of $PdCH^{ax}$ and $PdCH^{eq}$ are slightly shifted (Δ−0.08 and +0.06 ppm (−55 °C) and +0.02 and −0.02

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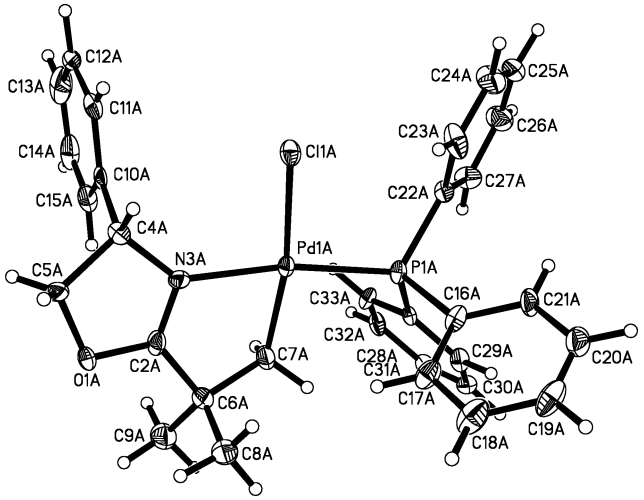

Figure 1. Molecular structure of one of the four unique molecules of compound **5** drawn with ellipsoids at the 50% probability level.

ppm (+55 °C)), their multiplicity remained the same. This suggests that the endo palladacycle adopts only one conformation in the range of −55 to +55 °C in $CDCl_3$.

3. X-ray Structural Analysis of Complex 5. The endo structure of the palladacycle in compound **5**, as well as its trans configuration, were unambiguously confirmed by the single-crystal X-ray diffraction study. There are four molecules (A−D) in the asymmetric unit along with one molecule of water. The water donates both hydrogen atoms to two chlorine atom acceptors on different unique molecules. There is also one nonclassical C−H···O (water) hydrogen bond found as well. The molecular structure of one of the four molecules in the unit cell is presented in Figure 1.

The average Pd−C bond length in compound **5** is 2.05 Å. This value is very similar to that reported for the exo palladacycle **14** (2.04 Å; Chart 4), with the C(sp^3)−Pd bond obtained from (*S*)-4-*tert*-butyl-2-methyl-2-oxazoline.[35] The Pd−N bond length in **5** (2.072 Å) is slightly longer than in two known PPh_3 adducts of oxazoline-derived cyclopalladated complexes with the endo palladacycles (**9a** and **10**; Chart 4) containing a C(sp^2)−Pd bond (2.060 and 2.062 Å);[27,36] however, this bond is shorter compared to that found in the aliphatic exo palladacycle **14** (2.098 Å).[35] The value of the Pd−P bond length in **5** (2.256 Å) is in agreement with those reported for the PPh_3 adducts of cyclopalladated oxazolines[27,36] and benzylamines[33,37,38] (2.235−2.256 Å).

Quite surprisingly, the unit cell has one molecule of water, which forms hydrogen bonds with two chlorine atoms of molecules A and C. In addition, there is a nonclassical C−H···O hydrogen bond between the water's oxygen atom and one of the two ortho H atoms of the 4-phenyl substituent on the oxazoline ligand in molecule B. It appears that the hydrogen bonds affect the configurations of the palladacycle and oxazoline rings. Thus, molecules A and C have a chiral $\lambda(S)$ palladacycle configuration, whereas the two remaining molecules display the alternative $\delta(S)$ configuration (see Chart 3). The degree of the palladacycle's puckering is not as high as in other palladacycles with a C(sp^3)−Pd bond. For example, the averages of the absolute values of intrachelate torsion angles in the molecules A−D are 18.6, 20.3, 18.9, and 21.4°, respectively. These values are lower than those reported for the exo palladacycle **14** (34.2°) and other C,N-palladacycles with the aliphatic chain (28.3−37.8°).[35]

The oxazoline ring of all four molecules exhibit a $\lambda(S)$ configuration[35,36,39] (see Chart 2) with a small twist: the values of the torsion angles H^S−C(O)−C(N)−H, H^R−C(O)−C(N)−C^{ipso}(Ph), H^S−C(O)−C(N)−C^{ipso}(Ph) and H^R−C(O)−C(N)−H are 5.18−19.36, 8.83−23.26, 129.39−144.41, and 101.79−115.38°, respectively. Therefore, the heterocycle adopts the same $\lambda(S)$ configuration in both the solution and solid state.

The coordination environment of the palladium atom in each of the four molecules A−D is square planar. However, one of the molecules (D) displays a tetrahedral distortion with the angle between the NPdC and ClPdP planes equal to 10.0°, while the three other molecules have a pyramidal distortion.

4. Theoretical Calculations. In an effort to understand better the preference for the formation of the endo isomer over the exo isomer of the direct cyclopalladation of oxazoline, a series of ab initio quantum chemical calculations were performed on model compounds. Models of compounds **5** and **6** were generated by replacing the PPh_3 groups with NH_3. Full geometry optimizations were performed on the model compounds at the restricted Hartree−Fock (RHF) level, at the generalized gradient approximation (GGA) to density functional theory (DFT) with Becke exchange[42] and Lee−Yang−Parr correlation functions (BLYP),[43,44] and using the second-order Møller−Plesset (MP2) perturbation theory description of dynamic electronic correlation corrections to mean field. The 6-31G* basis set[45] was used for all atoms, except for palladium. In order to account for relativistic effects in palladium with modest computational costs, the Los Alamos effective core potential with doubly split outer orbitals was used (i.e., the so-called LANL2DZ basis set[46]). All calculations were performed using the C.02 revision of Gaussian03[47] running on an IRIX SGI Origin 300 computer. To obtain accurate theoretical values for thermochemical predictions,

Chart 4. Structures of Representative Endo Palladacycles (5 and 9−12), Exo Palladacycles (13−15) and Coordination Complexes 16

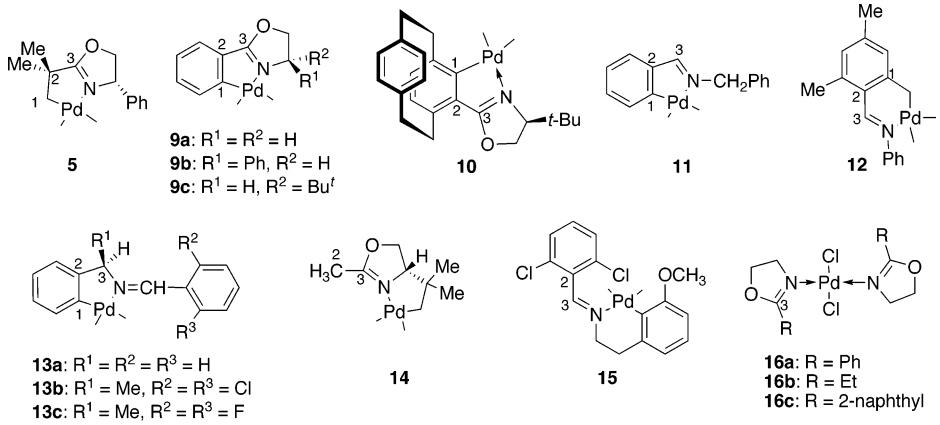

Table 2. Energies (hartree) of Model Endo (5) and Exo Isomers (6) Calculated at Various Levels of Theory and the 6-31G* Basis

isomer	RHF	BLYP	MP2	CCSD//RHF
endo	−1 272.515 502	−1 278.125 783	−1 274.961 166	−1 275.070 262
exo	−1 272.513 813	−1 278.127 377	−1 274.968 791	−1 275.077 018

single-point energy calculations were performed using the coupled cluster approximation, including single and double excitations (CCSD).[48]

As can be seen in Table 2, RHF calculations predict that the endo isomer is slightly lower in energy than the exo isomer, although the energy is small (4.4 kJ/mol). Similarly, theoretical methods that include electron correlation predict small energy separations (4.2 kJ/mol, BLYP; 20.0 kJ/mol, MP2; 17.7 kJ/mol, CCSD//RHF), but with the exo isomer lower than the endo. Since theoretical calculations of the thermochemistry for compounds that do not benefit from a strong cancellation of errors are not generally accurate to more than ca. ±20 kJ/mol (unless a relatively computational expensive multicomponent method such as G3[49] is used), the theoretical calculations are inconclusive, beyond the observation that the two isomers are quite close in energy.

In contrast with the rather ambiguous thermochemical results from the theoretical calculations, the results of the geometry optimizations are in good agreement with the X-ray structure for the known endo isomer. For instance, the bond length of the N═C bond is predicted to be 1.265 Å (RHF/6-31G*), which compares well to the 1.267 Å distance observed by X-ray studies. Likewise, the Pd−N bond length is predicted to be 2.081 Å and compares well to the observed 2.063 Å; the Pd−C bond has a predicted length of 2.062 Å, and is close to the observed 2.075 Å. Angles are also well described theoretically: ∠Pd−N−C is predicted at 114.6° and measured at 114.4°; ∠N−Pd−C is predicted at 81.2°, and the X-ray measurement gives 79.2°.

Examination of the theoretical calculations provides insight into the structure of the exo isomer, for which an X-ray structure has not yet been determined. RHF/6-31G* calculations predict a Pd−C bond length of 2.031 Å, which is only slightly shorter (0.031 Å) than the corresponding bond in the endo isomer. Conversely, the Pd−N bond is elongated (2.131 Å vs 2.081 Å). ∠N−Pd−C in the exo isomer (79.5°) is slightly smaller than in the endo isomer (81.2°).

5. Discussion. In the literature, several reasons for the successful competition of aliphatic over aromatic palladation have been suggested. For example, specific coordination of bidentate preligands to the Pd atom may direct palladation toward the aliphatic carbon.[16,17,19,50] In some cases, e.g., the *Z* isomer of *tert*-butyl phenyl ketoxime,[20] the molecule's geometry makes cyclopalladation of the aromatic carbon impossible. A case of preference of C(sp^3)−H bond activation over the C(sp^2)−H bond was reported for *N*-phenyl *N*-methyl hydrazone of 3,3-dimethyl-2-butanone. The observed C(sp^2)−Pd bond formation and regiospecific palladation of the *tert*-butyl group are quite unique, because metalation of the *N*,*N*-dimethyl hydrazone of the same ketone exclusively furnished a palladacycle containing an C(sp^3)−Pd bond.[51,52] The preference of the benzylic C(sp^3)−H bond activation to form a six-membered palladacycle over C(sp^2)−H activation leading to exo isomers was shown by Albert et al. in studying reactions of 2,4,6-$(CH_3)_3C_6H_2CH{=}N(CH_2)_nC_6H_5$ (n = 0−2) with $Pd(OAc)_2$ in AcOH.[53]

According to the well-referenced review by Jones and Feher, "it is quite general that activation of the stronger C−H bonds is thermodynamically preferred."[15] The strength of C−H bonds in arenes is estimated at 110 kcal/mol, while primary aliphatic C−H bonds are ca. 10 kcal/mol weaker.[15] Therefore, one could have predicted that the exo palladacycle, with a C(sp^2)−Pd bond in **3** and **5,** is more stable thermodynamically than the alternative endo palladacycle, with a C(sp^3)−Pd bond in **4** and **6**. Since our experimental data indicate the opposite and the theoretical data suggest that the isolated compounds are essentially thermodynamically equally stable, there must be other factors affecting the stability.

It has also been noted that activation of aromatic C−H bonds may be kinetically favored, due to the possible prior π-coordination of the arene moiety to the transition metal.[15] However, in the case of cyclopalladation, the reaction is expected to begin with the coordination of the N atom to the Pd, and the aromatic C−H bonds can turn out to be in an unfavorable position with respect to the metal atom. After the complexation of the Pd atom with the ligand, the C−H bond susceptible to palladation must be in close proximity to the Pd atom and adopt an orientation suitable for the C−H bond activation. For 2-aryl-2-oxazolines (HL), the signal of the ortho H in the coordination complexes $Pd(HL)_2Cl_2$ is significantly shifted downfield ($\Delta\delta$ = 0.85−1.08)[27,34] compared to that in the free ligands, due to the magnetic anisotropy of the Pd atom. This observation

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indicates that the ortho H in the coordinated oxazoline ligand in solution is in close proximity to the metal and is above the PdN_2Cl_2 plane.[54] The X-ray diffraction study of the coordination complex $PdCl_2(HL)_2$ (HL = 2-phenyl-2-oxazoline) determined the same position of the ortho H atoms in the solid state.[27] Chemical shift values for the signals assigned to the ortho H atoms of the 4-phenyl substituent in the ^{1}H NMR spectra of the free oxazoline **1** and the corresponding coordination complex **8** are almost identical, suggesting that the position of the ortho CH moiety in 4-phenyl-2-oxazolines is not as favorable as in the case of 2-aryl-2-oxazolines. Therefore, the geometry of the intermediate formed upon complexation of the Pd atom to the oxazoline ligand appears to favor activation of ortho C−H bonds in oxazoline 2-aryl substituents over that in 4-aryl substituents; this, in turn, will favor endo metalation over exo cyclization. Regiospecific endo palladation of (4*R*)-2,4-diphenyl-2-oxazoline[39] supports this hypothesis.

The regioselectivity of cyclopalladation can also depend on the metal source, reaction temperature, solvent, and specific structural features of preligands. For imines and oxazolines, the position of the C=N bond with respect to the palladacycle appears to be vital. These types of substrates show a strong preference for the formation of endo complexes, with the C=N bond in the metallacycle, over the alternative exo derivatives, with the C=N bond outside the palladacycle (Chart 1). For example, direct palladation of 2,4-diphenyl-2-oxazoline,[39] benzylidenebenzylamines,[53,55−60] and naphthyl-[61] and ferrocenylimines[62] provided exclusively endo isomers, while both endo and exo palladacycles could have been envisaged. As a rule, exo palladation occurs when the formation of an endo palladacycle is impossible[63−67] or is strongly disfavored.[65,68−70] To the best of our knowledge, cyclopalladated complexes with an exocyclic C=N bond were obtained regiospecifically in competition with the alternative endo isomers only from ferrocenyl hydrazones of the general formula (η^5-C_5H_5)Fe{(η^5-C_5H_4)CH=NNHAr};[71] however, in this case, the palladacycles are quite different, because they contain two N atoms instead of one as in imine and oxazoline derivatives.

The preference for endo metallacycle formation is not limited to direct palladation using Pd(II) derivatives. For example, oxidative addition of $Pd(dba)_2$ to three aryl-substituted *N*-(*o*-bromobenzyl)*o*-bromobenzylideneamines furnished exclusively endo metallacycles, although both exo and endo isomers could have been formed.[55]

The reasons for the endo palladation preference in imines and oxazolines have not been understood. The only hypothesis for the preference of endo palladacycle formation that has been mentioned in the literature is the possibility of its aromatic character.[72−74] Obviously, the aromaticity hypothesis is not applicable for the endo palladacycle obtained from preligand **1**, since the metal-containing five-membered ring has only one double bond out of five and is nonplanar. This explanation is more plausible for endo palladacycles with a C(sp^2)−Pd bond, although its aromatic character cannot be considered to be the only reason for the endo metalation preference. According to the X-ray data, the endo palladacycles **9a**−**c**, **10**, and **11** obtained from 2-phenyl-2-oxazolines[27,39,40] and *N*-benzylbenzylideneamine,[55] respectively, are nearly planar: the average value of the intrachelate torsion angle for each of these complexes is less than 3.4°. However, the distortion from planarity in the endo palladacycles derived from 2-ferrocenyl-2-oxazolines is more pronounced and reaches 11.3°.[75] In addition to planarity, the palladacycle's bond lengths could be a decisive factor in the discussion of aromaticity. The value of the C(2)−C(3) bond length between the aryl fragment and the N-heterocycle in $Pd(HL)_2X_2$ (HL = oxazoline ligand, **16**; Chart 4) coordination complexes ranges from 1.466 to 1.483 Å, while it is shorter in five-membered endo palladacycles with a C(sp^2)−Pd bond: i.e., 1.440−1.460 Å (Table 3). For comparison, in the palladacycle of complex **5**, the length of the single C(2)−C(3) bond, 1.474 Å, is within the range reported for the coordination complexes **16**. However, the length of the C(2)−C(3) bond in the six-membered endo palladacycle **12** (Chart 4, Table 3), which cannot be aromatic, is only 1.436 Å, which is even shorter than in the supposedly aromatic palladacycles **9**−**11**. The length of the endocyclic C=N bond in five-membered palladacycles **9**−**11** varies from 1.265 to 1.307 Å, with the highest value being for the paracyclophane derivative **10**. For comparison, the length of the C=N bond in coordination complexes **16a**−**c** is also within this range, albeit near its lower limit. The length of the exocyclic C=N bond in palladacycles **13**−**15** varies significantly and, in general, is not so different from those reported for related endocyclic iminic bonds. It should be noted that the presumably aromatic oxazoline-derived palladacycles are part of tricyclic systems. Also, the imine bond is expected to be in conjugation with the 2-aryl fragment, thus forcing the arene ring and the N-heterocycle to be in one plane and shortening the C(2)−C(3) bond. These structural features can cause or contribute to the near-planar conformation of endo palladacycles with a C(sp^2)−Pd bond. One can conclude that delocalization in the five-membered endo palladacycles with the C(sp^2)−Pd bond might be a contributing, but not decisive, factor in the preference for endo palladation.

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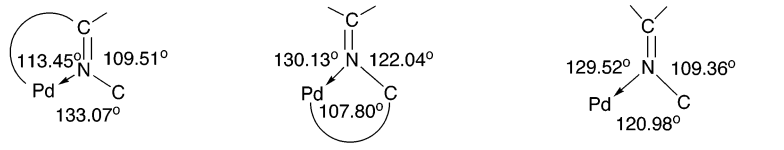
Table 3. Comparison of Structural Parameters for Representative Endo Palladacycles (3, 9−12), Exo Palladacycles (13−15), and Coordination Complexes (16)

	bond length (Å)[a]					bond angle (deg)				torsion angle (deg)	
compd no. (ref)	C(1)−C(2)	C(2)−C(3)	C═N	Pd−C	Pd−N	C═N−Pd	C−N−Pd	C═N−C	C−Pd−N	C−C═N−Pd	C−C═N−C or O−C═N−C
5[b]	1.546	1.490	1.280	2.051	2.072	136.96	114.21	108.67	79.73	6.19	5.32
9a (33)	1.414	1.440	1.265	2.031	2.063	113.40	136.86	109.72	80.67	1.97	0.55
9b (39)	1.423	1.457	1.289	1.993	2.012	114.99	134.90	110.12	80.87	1.99	2.06
9c (40)	1.386	1.460	1.294	1.992	2.031	112.55	137.79	109.35	80.73	11.84	6.06
10 (36)	1.407	1.453	1.307	2.052	2.060	111.44	132.33	108.85	78.57	23.76	3.37
11 (54)	1.409	1.456	1.276	1.944	2.009	114.89	123.49	121.61	81.68	3.69	16.42
12 (52)	1.385	1.436	1.272	2.059	2.137	118.28	123.14	118.58	82.22	1.90	
13a (54)[c]	1.515	1.469	1.275	1.946	2.056	131.65	112.90	115.40	81.54	10.24	9.01
	1.517	1.474	1.276	1.964	2.011	131.65	112.90	115.40	81.54	26.55	0.55
13b (66)		1.516	1.321	2.024	2.104	126.96	107.43	125.59	79.97	13.00	3.49
13c (66)		1.493	1.253	2.004	2.112	132.31	103.93	123.76	80.65	1.56	1.39
14 (35)		1.474	1.273	2.038	2.098	136.94	110.78	108.75	81.71	23.39	1.63
15 (65)		1.479	1.280	2.002	2.124	121.02	118.95	119.95	84.86	3.08	
16a (33)	1.389	1.468	1.271		2.007	130.02	119.90	109.29		10.15	0.29
16b (34)		1.483	1.276		2.010	129.60	121.73	108.65		0.06	1.14
16c (41)		1.466	1.266		2.035	128.94	121.31	109.50		7.95	1.06

[a] See Chart 4 for atom numbers. [b] The values are averages for four unique molecules in the cell. [c] Values are given for two molecules of the same compound with different conformations.

Chart 5. Average Values of Angles Around the N Atom in Five-Membered Endo and Exo Palladacycles with a C(sp^2)−Pd Bond and in the Coordination Complexes Pd(HL)$_2$Cl$_2$



endo-palladacycles **9**–**11** *exo*-palladacycles **13a**–**c** coordination complexes **16a**–**c**

Our experimental data (Table 1) suggest the thermodynamic preference of the endo complex **3** over the exo complex **4**. Palladation of the preligand **1** in MeCN using Pd(OAc)$_2$ resulted in a greater relative amount of the exo dimer **4** with respect to the endo isomer when a lower temperature or a shorter reaction time was used. Two additional experiments were performed to confirm the thermodynamic preference for isomer **3**. First, a sample of the pure exo derivative μ-AcO-**4** was heated in AcOH at 80 °C for 18 h. After treatment of the reaction mixture with LiCl followed by purification using column chromatography, two pure isomers, **3** and **4**, were obtained in 40% total yield and in a ratio of 8.5:1. In another experiment, a sample of pure endo derivative μ-AcO-**3** was heated in AcOH at 80 °C for 3 h (the heating was stopped because of the appearance of black Pd(0)). After addition of LiCl and purification, two isomers, **3** and **4**, were isolated in 90% total yield and in a 10.5:1 ratio. These experiments confirmed that (i) there is an equilibrium between the exo and endo isomers (i.e., intermolecular ligand exchange reaction[26]) and (ii) the endo derivative is thermodynamically preferable. It appears that, in general, endo palladacycles derived from imines, including oxazolines, are more thermodynamically stable than the corresponding exo isomers.

Thermodynamic stability of palladacycles with the endocyclic C═N bond is likely to be a major driving force of endo palladation. The following factors are expected to contribute to this stability: (i) lesser ring strain for five-membered endocyclic systems and (ii) the energy of the new bonds formed, C−Pd and N−Pd.

According to reported experimental[76] and theoretical[77,78] studies, methylenecyclopentane, with an exo C═C bond, has greater ring strain than the corresponding endo isomer. For comparison, the strain in cyclopentene is about the same as that in cyclopentane. The latter minimizes its torsional strain by adopting nonplanar envelope and half-chair conformations, though nonplanarity slightly increases the angle strain. Intuitively, it can be predicted that the same trend is valid for palladacycles. In the case of five-membered endo palladacycles, with an C(sp^2)−Pd bond and two alternating double bonds (cf. palladacycles **10**−**12** in Chart 4), both torsional and angle strain are minimized because of a smaller number of ring substituents and a planar or almost planar geometry. In the aliphatic endo palladacycles, such as those in complexes **3** and **5**, ring puckering is expected to reduce torsional strain but increase angle strain. The puckered conformation of the endo palladacycle derived from oxazoline **1** was confirmed in the solid state by the X-ray crystalographic study of **5** and in solution by the NMR data for **5**.

Comparison of the angles (Table 3) around the N atom in different endo (**5**, **9**−**12**) and exo palladacycles (**13**−**15**), as well as in coordination complexes PdCl$_2$(HL)$_2$ (**16**), reveals significant differences in the values of the angles C═N−Pd and C−N−Pd among these three types of compounds. The values of C═N−Pd, C−N−Pd, and C═N−C angles in coordination complexes **16a**−**c** (129.52°, 120.98, and 109.36°, respectively) indicate a strong distortion of the C═N moiety (Table 3 and Chart 5). In the five-membered endo palladacycles with an C(sp^2)−Pd bond (**9**−**11**), the average value of the C═N−Pd angle is decreased to 113.45°. However, in the case of the five-membered endo palladacycle **5**, the value of the angle is 136.96°, which is closer to that reported for the coordination complexes **16a**−**c**. In the five-membered exo palladacycles with a C(sp^2)−Pd bond (**13a**−**c**), the C═N−Pd angle is outside the metallacycle but its average value is only slightly higher (130.13°) than that reported for the coordination complexes **16a**−**c**. The

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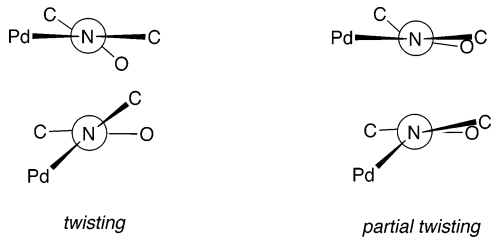
Chart 6. Newman Projections along the C═N Bond Showing Twisting or Partial Twisting Distortions of the π-System in Exo and Endo Palladacycles



average value of the C(sp^3)−N−Pd angle in the exo palladacycles **13a**−**c** is reduced to 107.80°. The aliphatic exo palladacycle **14** has the greatest C═N−Pd angle distortion, but its value is identical with that found in the endo palladacycle **5**. Therefore, angles around the N atom in all three types of complexes are far from the ideal 120°, apparently due to bond dipoles and the large size of the metal atom. Also, because the angle values in five-membered exo palladacycles with C(sp^2)−Pd or even C(sp^3)−Pd bonds are surprisingly close to those reported for coordination complexes **16a**−**c**, the angle distortion around the N atom is unlikely to be a reason for the lesser stability of exo palladacycles.

Values of the C−C═N−Pd and O−C═N−C (or C−C═N−C) torsion angles in Pd(II) complexes indicate that many of them have a π-system distortion in the C═N bond. This distortion can be described as twisting[78] or partially twisting. While coordination complex **16b,** with the least bulky substituent, has essentially no C═N bond π-system distortion, two other Pd(HL)$_2$Cl$_2$ compounds have the Pd−N bond displaced from the C−C═N plane (values of the torsion angle C−C═N−Pd are 7.95° in **16c** and 10.15° in **16a**; see Chart 6, partial twisting distortion). A very small π-system distortion (less than 1.90°) is also found for both six-membered endo and exo palladacycles. The five-membered endo palladacycle **5** exhibits a measurable twisting distortion, with the average values of the torsion angles C−C═N−Pd and O−C═N−C for four molecules being 6.19 and 5.32°. The exo metallacycle **14** displays a significant partial π-system twisting distortion, with a value of 23.39° for the C−C═N−Pd torsion angle. The distortion in both **9a** and **9b** is very small (2.06° or less), while it is more pronounced in **9c** (11.84 and 6.06° for the C−C═N−Pd and O−C═N−C torsion angles, respectively). Apparently, the observed C═N bond twisting distortion in **9c** is to minimize steric interactions due to the presence of the bulky *tert*-butyl group. The highest degree of distortion from planarity is found in one of the two molecules with the exo palladacycle **13a** (26.55° for the C−C═N−Pd torsion angle). However, in the closest α-methyl-substituted derivatives **13b** and **13c**, the degree of the twist is not significant (less than 1.56°). Instead of the π-system twist, these two exo palladacycles have a C(sp^3)−N−Pd angle (107.43 and 103.93°, respectively) much smaller than in other Pd(II) complexes (Table 3) and a significant ring puckering (the C^{Ar}−C^{Ar}−C−N torsion angle in the exo palladacycles **13b**,**c** is 37.53 and 38.16°, respectively).

On the basis of an analysis of the data provided, one can conclude that not just one but a combination of structural features make imine- and oxazoline-derived endo palladacycles more stable than their exo counterparts. For the five-membered endo palladacycles with an C(sp^2)−Pd bond, one such feature is conjugation of the C═N bond with the aryl group, with possible aromatic character of the whole palladacycle. The bond conjugation forces the palladacycles to be planar or near-planar. The planarity, in turn, minimizes the angle strain, while the torsion strain is decreased because of the presence of a single substituent at each carbon in the metallacycle. In oxazoline-based endo palladacycles, distortion of the C═N bond π-system is minimal, unless there is a bulky substituent near the metallacycle. In the case of the endo palladacycle **5,** with a C(sp^3)−Pd bond, its stability is achieved by puckering the ring. Surprisingly, the endo palladacycle **5** and its aliphatic exo counterpart **14** have similar values for the angles around the N atom; however, the exo structure has a much greater distortion of the C═N bond π-system.

Conclusions

The presented data stress the dominant role of the endo effect in the cyclopalladation regioselectivity of imines and oxazolines. Although metalation at sp^2 carbon atoms in general is preferable over that at sp^3 carbon centers, direct cyclopalladation of oxazoline **1** resulted in predominant formation of the endo isomer with an C(sp^3)−Pd bond. The endo complex **3** with a C(sp^3)−Pd bond is thermodynamically favored over the corresponding exo derivative **4** with a C(sp^2)−Pd bond. Relative energies of model exo and endo isomers calculated at the RHF, BLYP, MP2, and CCSD levels of theory are within 20 kJ/mol and do not contradict the hypothesis that C(sp^3)−H bond activation may be favored over that of C(sp^2)−H in the case of the endocyclic position of the C═N bond in the formed palladacycle. The ease of oxazoline cyclopalladation with the formation of five-membered palladacycles decreases in the following order: endo metallacycle with the C(sp^2)−Pd bond > endo with the C(sp^3)−Pd bond > exo with the C(sp^2)−Pd bond > exo with the C(sp^3)−Pd bond.

Experimental Section

General Methods and Materials. All reactions were carried out under a positive pressure of nitrogen. The reaction mixtures were stirred using a magnetic stirrer. Purifications by column chromatography and preparative thin-layer chromatography (TLC) were carried out using Natland silica gel 60 (230−400 mesh). Analytical TLC was performed on Whatman silica gel 60 (F_{254}) 250 μm precoated plates. Compounds were visualized on TLC plates using UV light (254 nm) and/or phosphomolybdic acid (free oxazolines) or iodine stain (complexes). Routine ^{1}H (500 MHz), ^{13}C (126 MHz), and ^{31}P (202 MHz) NMR spectra, as well as DEPT, COSY, HSQC, and NOESY spectra, were recorded on a Bruker AVANCE 500 spectrometer. Spectra were obtained in $CDCl_3$ unless stated otherwise. Chemical shifts are reported in ppm with $SiMe_4$ as an internal standard (^{1}H and ^{13}C) or $P(OEt)_3$ as an external standard (^{31}P). Spin−spin coupling constants, *J*, are given in Hz. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. Melting points were measured on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Optical rotations were measured at room temperature on a Rudolph Autopol III automatic polarimeter. Elemental analyses were carried out by Atlantic Microlabs Inc., Norcross, GA. Benzene was dried by refluxing over K/benzophenone ketyl, distilled under N_2, and kept over 3 Å molecular sieves. Methanol was distilled over Mg turnings activated with iodine. Glacial acetic acid was distilled over $KMnO_4$. Acetone was purified by refluxing with $KMnO_4$, followed by distillation over anhydrous $CaSO_4$. Other solvents were dried by distillation over CaH_2. Prior to use, $Pd(OAc)_2$ was dissolved in hot benzene, followed by filtration and solvent removal in vacuo. All other chemicals were used as purchased without further purification.

(*S*)-2-*tert*-Butyl-4-phenyl-2-oxazoline (1). Compound **1** was obtained as a colorless liquid in quantitative yield from compound **2** (2.40 g, 10.8 mol) and diethylaminosulfur trifluoride (DAST, 1.50

mL, 11.6 mmol) using the procedure reported for its enantiomer.[23] R_f = 0.46 (19:1 CH_2Cl_2−EtOAc). IR (neat, ν, cm^{-1}): 1657 (C═N). $[\alpha]_{633}^{19} = -60.9°$, $[\alpha]_D^{19} = -72.8°$, $[\alpha]_{546}^{19} = -90.8°$, $[\alpha]_{435}^{19} = -173°$ (*c* 2.81, MeOH) (lit.[23] data for the *R* enantiomer: $[\alpha]_D^{23} = +89.2°$ (*c* 4.54, MeOH)). ^{1}H NMR (δ, ppm): 1.31 (s, 9H, *t*-Bu), 4.07 (t, 1H, $^2J_{H^R,H^S} = 8.4$, $^3J_{OCH^R,NCH} = 7.7$, OCH^R), 4.58 (dd, 1H, $^3J_{OCH^S,NCH} = 10.1$, OCH^S), 5.14 (dd, 1H, NCH), 7.22 (m, 2H, *o*-H arom), 7.27 (m, 1H, *p*-H arom) 7.33, (m, 2H, *m*-H arom). ^{13}C NMR (δ, ppm): 28.0 ($C(CH_3)_3$), 33.4 ($C(CH_3)_3$), 69.4 (NCH), 75.0 (OCH_2), 126.5 (*o*-CH arom), 127.5 (*p*-CH arom), 128.7 (*m*-CH arom), 142.9 (*ipso*-C arom), 175.2 (OCN).

(*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2,2-dimethylpropanamide (2). Compound **2** was obtained as a white solid in quantitative yield (2.46 g) from pivaloyl chloride (2.47 g, 20.5 mmol) and (*S*)-2-phenylglycinol (1.52 g, 10.8 mmol) using a procedure reported for this compound.[23] Mp: 133−136 °C. R_f = 0.65 (1:9 *i*-PrOH−CH_2Cl_2). $[\alpha]_{633}^{26} = +70.6°$, $[\alpha]_D^{26} = +83.6°$, $[\alpha]_{546}^{26} = +102°$, $[\alpha]_{435}^{26} = +186°$ (*c* 1.07, MeOH). IR (thin film of CH_2Cl_2 solution, ν, cm^{-1}): 3336 (NH and OH), 1654 (C═O). ^{1}H NMR (δ, ppm): 2.98 (t, 1H, J = 6.0, OH), 3.86 (t, 2H, J = 5.6, OCH_2), 5.03 (br q, 1H, NCH), 6.37 (br d, 1H, $^3J_{NCH,NH} \approx 4.9$, NH), 7.27 (m, 2H, *o*-H arom), 7.31 (m, 1H, *p*-H arom) 7.36, (m, 2H, *m*-H arom). ^{13}C NMR (δ, ppm): 27.6 ($C(CH_3)_3$), 38.8 ($C(CH_3)_3$), 55.8 (NCH), 66.8 (OCH_2), 126.5 (*o*-CH arom), 127.8 (*p*-CH arom), 128.9 (*m*-CH arom), 139.3 (*ipso*-C arom), 179.2 (OCN).

(*S,S*)-Bis(μ-chloro)bis[2-methyl-2-(4-phenyloxazolin-2-yl)propyl-*C,N*]dipalladium(II) (3) and (*S,S*)-Bis(μ-chloro)bis[2-(2-*tert*-butyloxazolin-4-yl)phenyl-*C,N*]dipalladium(II) (4). Compounds **3** and **4** were synthesized by reacting **1** (159 mg, 0.782 mmol) with palladium acetate (195 mg, 0.869 mmol) in glacial acetic acid (4.5 mL) at 60 °C for 12 h. The solvent was evaporated under vacuum, and the brownish residue was dissolved in acetone (4.5 mL). LiCl (99.0 mg, 2.34 mmol) was added, and the mixture was stirred at room temperature for 10.5 h. The solvent was removed in vacuo, and the crude product was purified by dry flash column chromatography (SiO_2, h = 4.5 cm; d = 4 cm) using gradient elution (7:3, 3:2, 1:1, 2:3, 3:7, 1:4, 1:9 hexanes−CH_2Cl_2 and CH_2Cl_2) to obtain a mixture of **3** and **4** in a ratio of 13:1 (160 mg, 59% total yield). Anal. Calcd for $C_{26}H_{32}Cl_2N_2O_2Pd_2$: C, 45.37; H, 4.69; N, 4.07. Found: C, 45.56; H, 4.81; N, 4.04. Data for compound **3** are as follows. Mp: 180 °C dec. R_f = 0.46 (3:7 hexanes−CH_2Cl_2). $[\alpha]_D = +227°$, $[\alpha]_{546} = +278°$, $[\alpha]_{633} = +189°$ (*c* 0.0750, CH_2Cl_2). IR (thin film of CH_2Cl_2 solution, ν, cm^{-1}): 1644 (C═N). ^{1}H NMR (δ, ppm): 1.20 and 1.28 (two s, 3H each, $C(CH_3)_2$), 1.86 and 2.02 (two d, 1H, $^2J_{H,H} = 8.2$, $PdCH_2$), 4.31 (dd, 1H, $^3J_{OCH^R,NCH} = 5.8$, $^2J_{OCH^S,OCH^R} = 8.7$, OCH^R), 4.69 (br t, 1H, $^3J_{OCH^S,NCH} \approx 9.2$, OCH^S), 5.30 (br s, 1H, NCH), 7.20 (m, 2H, *o*-H arom), 7.3 (m, 1H, *p*-H arom), 7.4 (m, 2H, *m*-H arom). ^{13}C NMR (δ, ppm): 26.9 (CH_3), 27.0 (CH_3), 28.2 ($PdCH_2$), 41.2 ($C(CH_3)_2$), 66.0 (NCH), 76.9 (OCH_2), 126.9 (*o*-CH arom), 128.4 (*p*-CH arom), 129.0 (*m*-CH arom), 140.1 (*ipso*-C arom), 183.9 (OCN). Data for compound **4** are as follows. Mp: 140 °C dec. R_f = 0.49 (3:7 hexanes−CH_2Cl_2). $[\alpha]_D = -82.2°$, $[\alpha]_{546} = -104°$, $[\alpha]_{435} = -224°$ (*c* 0.208, CH_2Cl_2). IR (thin film of $CDCl_3$ solution, ν, cm^{-1}): 1625 (C═N). ^{1}H NMR (δ, ppm): 1.51 (s, 9H, *t*-Bu), 4.38 (br t, 1H, $^3J_{OCH^R,NCH} \approx 8.3$, $^2J_{OCH^S,OCH^R} \approx 8.7$, OCH^S), 4.69 (dd, 1H, $^3J_{OCH^S,NCH} \approx 10.2$, OCH^S), 5.75 (br t, 1H, NCH), 6.65 (br d, 1H, $^3J \approx 7.2$, H(6) arom), 6.89 (br t, 1H, $J \approx 7.2$, H(4) arom), 7.01 (br t, 1H, $J \approx 6.8$, H(5) arom), 7.17 (br d, 1H, $J \approx 7.8$, H(3) arom). ^{13}C NMR (δ, ppm): 28.8 ($C(CH_3)_3$), 34.0 ($C(CH_3)_3$), 72.0 (OCH_2), 74.9 (NCH), 119.4 (HC(6)), 125.1 (C(5)), 125.8 (C(4)), 134.1 (C(3)), 139.2 (C(2)), 146.9 (PdC(1)), 179.0 (OCN).

(*S*)-Chloro[2-methyl-2-(4-phenyloxazolin-2-yl)propyl-*C,N*]-(triphenylphosphane)palladium(II) (5). Triphenylphosphine (44.0 mg, 0.168 mmol) was added to a stirred solution of **3** (56.8 mg, 0.0825 mmol) in benzene (7.5 mL). The pale yellow mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the crude product was washed several times with hexanes to afford 77 mg (77%) of the pure product as a white solid. Mp: 178−180 °C. R_f = 0.57 (9:1 CH_2Cl_2−EtOAc). $[\alpha]_D = +118°$, $[\alpha]_{546} = +150°$, $[\alpha]_{633} = +99.9°$ (*c* 0.0950, CH_2Cl_2). IR (thin film of CH_2Cl_2 solution, ν, cm^{-1}): 1647 (C═N). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.01 (dd, 1H, $^2J_{H,H} = 9.7$, $^3J_{HP} = 8.6$, $PdCH^{eq}$), 1.12 (s, 3H, CH_3^{eq}), 1.24 (s, 3H, CH_3^{ax}), 1.56 (d, 1H, $PdCH^{ax}$), 4.53 (dd, 1H, $^2J_{OCH^R,OCH^S} = 8.8$, $^3J_{OCH^R,NCH} = 4.8$, OCH^R), 4.76 (dd, 1H, $^3J_{OCH^S,NCH} \approx 9.9$, OCH^S), 5.62 (dd, 1H, NCH), 7.29−7.42 (m, 14H, overlapping signals of 4-Ph and *m*- and *p*-CH of PPh_3), 7.64−7.68 (m, 6H, *o*-CH of PPh_3). ^{1}H NMR (C_6D_6, δ, ppm): 1.04 (s, 3H, CH_3^{eq}), 1.07 (dd, 1H, $^2J_{HH} = 9.9$, $^3J_{HP} = 8.0$, $PdCH^{eq}$), 1.20 (s, 3H, CH_3^{ax}), 1.63 (d, 1H, $PdCH^{ax}$), 3.84 (br t, 1H, $^2J_{OCH^R,OCH^S} = 8.9$, $^3J_{OCH^S,NCH} = 9.8$, OCH^S), 3.92 (dd, 1H, $^3J_{OCH^R,NCH} \approx 4.7$, OCH^R), 5.64 (dd, 1H, NCH), 6.96−7.02 (m, 9H, *m*- and *p*-CH of PPh_3), 7.07 (m, 1H, *p*-CH of 4-Ph), 7.19 (m, 2H, *m*-CH of 4-Ph), 7.52 (m, 2H, *o*-CH of 4-Ph), 7.84−7.88 (m, 6H, *o*-CH PPh_3). ^{13}C NMR (δ, ppm): 27.5 (CH_3^S), 28.7 (CH_3^R), 36.5 ($PdCH_2$), 41.6 ($C(CH_3)_2$), 64.5 (br d, $^3J_{CP} = 2.3$, NCH), 77.8 (d, $^4J_{CP} = 2.9$, OCH_2), 126.9 (*o*-CH arom of 4-Ph), 127.8 (*p*-CH arom of 4-Ph), 128.1 (d, $^3J_{CP} = 10.6$, *m*-CH of PPh_3), 128.8 (*m*-CH of 4-Ph), 130.2 (d, $^4J_{CP} = 2.1$, *p*-CH of PPh_3,), 131.3 (d, $^1J_{CP} = 48.9$, *ipso*-C of PPh_3), 134.6 (d, $^2J_{CP} = 11.6$, *o*-CH of PPh_3), 141.4 (*ipso*-C of 4-Ph), 184.2 (OCN). ^{31}P NMR (δ, ppm): 32.9. Anal. Calcd for $C_{31}H_{31}ClNOPPd$: C, 61.40; H, 5.15; N, 2.31. Found: C, 61.18; H, 5.14; N, 2.33.

(*S*)-Chloro[2-(2-*tert*-butyloxazolin-4-yl)phenyl-*C,N*](triphenylphosphane)palladium(II) (6). Compound **6** was synthesized by following the procedure described for compound **5**, except that the reaction mixture (triphenylphosphine (13.5 mg, 0.00510 mmol) and **4** (15.5 mg, 0.00230 mmol) in benzene (2.0 mL)) was stirred at room temperature for 17 h. Purification of the crude product by preparative TLC using multiple elutions with CH_2Cl_2 gave 19.6 mg (72%) of the pure product as a cream white solid. Mp: 124−126 °C. R_f = 0.54 (9:1 CH_2Cl_2−EtOAc). $[\alpha]_D = -36.5°$, $[\alpha]_{546} = -42.0°$, $[\alpha]_{435} = -75.5°$ (*c* 0.200, CH_2Cl_2). IR (thin film of CH_2Cl_2 solution, ν, cm^{-1}): 1638 (C═N). ^{1}H NMR (δ, ppm): 1.52 (s, 9H, *t*-Bu), 4.53 (dd, 1H, $^3J_{OCH^R,NCH} \approx 7.1$, $^2J_{OCH^S,OCH^R} \approx 8.6$, OCH^R), 4.69 (dd, 1H, $^3J_{OCH^S,NCH} \approx 10.0$, OCH^S), 5.95 (dd, 1H, NCH), 6.27 (t, 1H, $^3J_{HH} \approx {}^4J_{HP} \approx 6.7$, CH(6) arom), 6.35 (t, 1H, $J \approx 7.4$, CH-(5) arom), 6.75 (d, 1H, $J \approx 7.5$, CH(3) arom), 6.85 (t, 1H, CH(4) arom); 7.32 (m, 6H, *m*-CH of PPh_3), 7.40 (m, 3H, *p*-CH of PPh_3), 7.71 (6H, *o*-CH of PPh_3). ^{13}C NMR (δ, ppm): 28.7 ($C(CH_3)_3$), 34.1 ($C(CH_3)_3$), 71.9 (OCH_2), 73.7 (d, $^3J_{CP} = 1.8$, NCH), 120.0 (C(3) arom), 124.0 (C(4) arom), 125.3 (d, $^4J_{CP} = 5.5$, C(5) arom), 127.9 (d, $^3J_{CP} = 10.9$, *m*-CH of PPh_3), 130.5 (d, $^4J_{CP} = 2.5$, *p*-CH of PPh_3), 131.1 (d, $^1J_{CP} = 51.6$, *ipso*-C of PPh_3,), 135.5 (d, $^2J_{CP} = 11.6$, *o*-CH of PPh_3), 137.6 (d, $^3J_{CP} = 10.8$, C(6) arom), 147.5 (d, $^2J_{CP} = 2.6$, PdC(1) arom), 149.0 (C(2) arom), 178.1 (d, $^3J_{CP} = 8.5$, OCN). ^{31}P NMR (δ, ppm): 40.9. Anal. Calcd for $C_{31}H_{31}ClNOPPd$: C, 61.40; H, 5.15; N, 2.31. Found: C, 61.96; H, 5.38; N, 2.30.

(*S*)-(Benzonitrile)[2-methyl-2-(4-phenyloxazolin-2-yl)propyl-*C,N*](triphenylphosphane)palladium(II) Tetrafluoroborate (7). Compound **7** was obtained as an unstable white solid using a reported procedure.[35] $[\alpha]_D = +65.8°$, $[\alpha]_{546} = +81.7°$, $[\alpha]_{633} = +55.8°$, $[\alpha]_{435} = +167°$ (*c* 0.220, CH_2Cl_2). IR (thin film of $CDCl_3$ solution, ν, cm^{-1}): 1640 (C═N), 2260 (C≡N). ^{1}H NMR (δ): 1.25 and 1.31 (two s, 3H, $C(CH_3)_2$), 1.54 (m, 2H, $PdCH_2$), 4.34 (dd, 1H, $^2J_{OCH^R,OCH^S} = 9.0$, $^3J_{OCH^R,NCH} = 7.1$, OCH^R), 5.16 (dd, 1H, $^3J_{OCH^S,NCH} = 10.2$, OCH^S), 5.68 (dd, 1H, NCH), 7.21 (m, 1H, *p*-CH arom), 7.27 (m, 2H, *m*-CH arom), 7.36 (m, 2H, *o*-CH arom), 7.44−7.51 (12H, *m*- and *p*-CH of PPh_3, and *m*- and *p*-CH of PhCN), 7.56−7.60 (8H, *o*-CH of PPh_3 and *o*-CH of PhCN). ^{13}C NMR (δ, ppm): 27.7 and 28.3 ($C(CH_3)_2$), 35.2 ($PdCH_2$), 42.2 ($C(CH_3)_2$), 66.0 (NCH), 78.7 (d, $^4J_{CP} = 3.0$, OCH_2), 126.5 (*o*-CH arom), 129.0 (*p*-CH arom), 128.6 (d, J = 12.1, *p*-CH of PhCN), 128.9 (d, $^3J_{CP}$

= 11.0, *m*-CH of PPh_3), 129.1 (*m*-CH arom), 129.3 (d, $^1J_{CP}$ = 50.2, *ipso*-C of PPh_3), 129.4 (d, *J* = 10.8, *m*-CH of PhCN), 131.4 (d, $^4J_{CP}$ = 2.0, *p*-CH of PPh_3), 132.1 (d, *J* = 9.9, *ipso*-C of PhCN), 132.5 (br s, CN of PhCN), 133.9 (d, *J* = 16.2, *o*-CH of PhCN), 134.1 (d, $^2J_{CP}$ = 12.2, *o*-CH of PPh_3), 140.8 (*ipso*-C arom), 186.4 (d, $^3J_{CP}$ = 2.3, OCN). ^{31}P NMR (δ, ppm): 32.3.

(*S*)-Dichlorobis(2-*tert*-butyl-4-phenyl-2-oxazoline)palladium-(II) (8). Na_2PdCl_4 (39.4 mg, 0.134 mmol) was added to a stirred solution of **2** (54.5 mg, 0.268 mmol) and anhydrous methanol (5.0 mL). The reaction mixture was stirred for 58 h at room temperature, followed by solvent removal in vacuo. The orange residue was dissolved in CH_2Cl_2, and the solution was filtered though a short pad of Celite. Upon evaporation of the solvent, 56 mg (72%) of the pure compound **8** was obtained as orange crystals. Mp: 108 °C dec. R_f = 0.31 (CH_2Cl_2). IR (thin film of $CHCl_3$ solution, ν, cm^{-1}): 1621 (C═N). ^{1}H NMR (δ, ppm): 1.36 (s, 9H, *t*-Bu), 3.99 (dd, 1H, $^2J_{OCH^R,OCH^S}$ = 8.9, $^3J_{OCH^R,NCH}$ = 10.2, OCH^R), 4.59 (dd, 1H, $^3J_{OCH^S,NCH}$ = 10.5, OCH^S), 5.31 (t, 1H, NCH), 7.35−7.44, (m, 5H, CH arom). ^{13}C NMR (δ, ppm): 28.6 ($C(CH_3)_3$), 34.3 ($C(CH_3)_3$), 71.6 (NCH), 74.8 (OCH_2), 128.6 (*o*-CH arom), 128.7 (*p*-CH arom), 129.4 (*m*-CH arom), 138.1 (*ipso*-C arom), 178.5 (OCN). Anal. Calcd for $C_{26}H_{34}Cl_2N_2O_2Pd$: C, 53.48; H, 5.87; N, 4.80. Found: C, 52.86; H, 5.82; N, 4.51.

X-ray Crystallographic Analysis of 5. Microcrystals of complex **5** suitable for X-ray diffraction analysis were grown by slow crystallization from ethyl acetate−benzene−pentane at 5 °C. A white crystal (approximate dimensions 0.03 × 0.02 × 0.02 mm^3) was placed onto the tip of a 0.01 mm diameter glass fiber and mounted on the ChemMatCARS CCD area detector microcrystal diffractometer instrument for data collection at 95(1) K.[79] A preliminary set of cell constants was calculated from reflections harvested from one set of 40 frames. This produced initial orientation matrices determined from 400 reflections. The data collection was carried out using synchrotron radiation (APS 15-ID-A double-diamond monochromator) with λ = 0.495 94 Å, a frame time of 1 s, and a detector distance of 6.0 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.84 Å. Two major sections of frames were collected with 0.60° steps in ω and ϕ as independent scans and a detector position of 0.0° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[80] Final cell constants were calculated from 2700 strong reflections from the actual data collection after integration (SAINT).[81]

The structure was solved using Bruker SHELXTL[82] and refined using Bruker SHELXTL.[82] The space group $P2_12_12_1$ was determined on the basis of systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the *E* map. Full-matrix least-squares/difference Fourier cycles were performed, which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full-matrix least-squares refinement converged to R1 = 0.0397 and wR2 = 0.0877 (F^2, all data).

Crystallographic data for **5** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC-621769. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, int. code +44(1223)-336-033; e-mail, deposit@ccdc.cam.ac.uk).

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Supporting Information Available: Figures giving NMR spectra of compounds **1**−**8** and a CIF file giving crystallographic data for compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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