Cyclopalladation of (S)-4-tert-Butyl-2-methyl-2-oxazoline: An Unprecedented Case of (sp³)C–H Bond Activation Resulting in exo-Palladacycle Formation

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Direct cyclopalladation of (S)-4-tert-butyl-2-methyl-2-oxazoline at the nonactivated tert-butyl group using palladium(II) acetate in acetic acid afforded the first example of an oxazoline-derived exo-palladacycle with an (sp³)C–Pd bond. The structure of the new palladacycle was established using spectroscopic and X-ray studies of the μ-chlorido-dimeric complex 2 and two mononuclear triphenylphosphine derivatives: neutral adduct 4 and its cationic benzonitrile-phosphate analogue 5. Analysis of NMR data for compounds 4 and 5 suggests a highly puckered λ(S) conformation of the palladacycle in solution. The X-ray crystal structure of cationic complex 5 confirmed the same highly puckered λ(S) conformation of the palladacycle in the solid state; in addition, it revealed unusual π–π-interactions between the phenyl rings of the benzonitrile and PPh₃ ligands and a distorted M-propeller configuration of the PPh₃ fragment.

Introduction

The importance of cyclopalladated compounds (CPCs) cannot be overstressed, based on the numerous articles published each year on the subject. The applications are diverse and have been the subject of reviews and numerous papers. One of the most abundant classes of CPCs contains CN-type metallacycle. Many such CN-complexes are derived from imines and other C–N bond-containing compounds, including oxazolines. On the basis of the position of the C=N bond relative to the palladacycle, CPCs can have either endo- or exo-palladacycles (Chart 1). The vast majority of known imine-derived CPCs contain endo-palladacycles with the C=N bond being endo-cycloidal. This preference of C=N

Chart 1. General Structures of endo- and exo-Palladacycles

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and that by direct Pd(II) activation of an (sp³)³C–H bond to form an exo-palladacycle.

During our ongoing investigations,20,21 into the cyclopalladation reactions of 2-oxazolines and applications of their corresponding CPCs, (S)-4-tert-butyl-2-methyl-2-oxazoline (1) was synthesized. In this paper, we report our results of the successful cyclopalladation of compound 1 resulting in the formation of a unique CPC (2) containing an exo-palladacycle accessed by direct Pd(II) (sp³)³C–H activation.

**Experimental Section**

**General Procedures and Instrumentation.** Routine ¹H, ¹³C, and ³¹P NMR (500, 125, and 202 MHz, respectively), DEPT, COSY, and HSQC spectra were recorded in CDCl₃ using TMS as an internal standard or triethyl phosphate as an external standard on a Bruker Avance 500 spectrometer. Spin–spin coupling constants, J, are given in Hz. IR spectra were recorded on an FT-IR Mattson Genesis Series FTIR. Analytical TLC was performed on Whatman precoated 250 μm plates of silica gel (F₂₅₄). Column chromatography and preparative TLC were carried out using Natland silica gel 60 (230–400 mesh). Melting points were measured on a Laboratoy Devices Mel-Temp apparatus and were not corrected.

Optical rotation measurements were performed on a Rudolph Autopol III automatic polarimeter using a 1 dm tube at room temperature. The low-resolution EI-mass spectrum of 1 was obtained on a Hewlett-Packard 5989 Series II gas chromatograph with a J&W Scientific gas chromatography column (30 m long, i.d. = 0.25 mm, film = 0.25 μm) and a Hewlett-Packard 5971 Series mass selective detector. The high-resolution ES-mass spectrum of 5 was recorded on a Bruker microTOF mass spectrometer. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. All reagents were used as received from the supplier (Aldrich Chemical Co., Acros, or Strem), unless otherwise noted. Prior to use, palladium(II) acetate was dissolved in hot benzene and filtered, followed by

**Chart 2. Structures of Palladacycles A and B**

![Chart 2](image_url)
Solvent removal in vacuo. Glacial acetic acid (GFS Chemicals, ACS "Superior Reagent" grade) was used as purchased, or EM ACS reagent grade acid was distilled from KMnO4. All other solvents were purified by standard procedures prior to use.24

Synthesis of (S)-4-tert-Butyl-2-methyl-2-oxazoline (1). Compound 1 was synthesized as described earlier.25 The yield of 1 from 2.7453 g (0.022 mol) of ethyl acetate dichloride and 2.076 g (0.0177 mol) of (S)-tert-leucinol was 1.9740 g (79%): Rf 0.38 (1:2 i-PrOH–MeCN; bp 153–154 °C (lit. 140–145 °C); IR (neat, ν cm−1) 1681 (C=O); 1H NMR (6 ppm) 0.89 (s, 9H, t-Bu), 1.96 (d, 3H, JH–H of Ph3P = 1.4, CH3-N), 3.82 (m, 1H, NCH), 4.01 (dd, 1H, JOCfR–NCfH = 7.8, JOCfR–PF = 8.6, OCH2), 4.15 (dd, 1H, JOCfR–NCfH = 8.6, JOCfR–NCfH = 10.1, OCH2); 13C NMR (δ ppm) 13.9 (CH3CfN), 25.8 (t-Bu), 68.6 (OCH2), 76.0 (NCH), 164.3 (OCfN); EI-MS, m/z 141 (M+), 126 (M–CH3) = 96, 55, 56.

Synthesis of (S,S)-Di-α-chlorobis[(2-(2-methyl)oxazolin-4-yl)-2,2-dimethylallyl-C,N]dipalladium(II) (2). Compound 1 (206.3 mg, 1.461 mmol) was dissolved in 20 mL of glacial acetic acid. Pd(OAc)2 (484.1 mg, 2.156 mmol) was then added to the stirred solution of oxazoline 1. The reaction mixture was stirred at 80–85 °C for 50 h. The solvent was removed on a rotary evaporator; LiCl (127.8 mg, 3.015 mmol) and anhydrous acetone (30 mL) were added, and the resulting solution was stirred overnight at room temperature. After solvent removal in vacuo, the brown dark crude product was suspended in 1:2 hexanes–CH2Cl2 and purified by flash chromatography (SiO2, d = 4 cm, h = 18.5 cm) using gradient elution (1:2 hexanes–CH2Cl2, 1:5 hexanes–CH2Cl2; 10:50:1 hexanes–CH2Cl2–EtOAc, 5:25:1 hexanes–CH2Cl2–EtOAc, and 1:5 EtOAc–CH2Cl2). The yield of pure complex 2 was 112.2 mg. A second column was done to purify fractions not adequately separated by the first chromotographic column. The second separation was done using a Biotage "Flash 121" chromatographic system equipped with a prepared 12 × 150 mm SiO2 column. The elution was done using 1:1 hexanes–CH2Cl2. The yield of pure complex 2 from the second column was 63.1 mg; the total yield of pure product was 175.3 mg (43%). mp 172 °C (dec); Rf 0.46 (1:2 EtOAc–CH2Cl2); [α]D–201.8°; [α]D–247.7°; [α]D–174.3°; [α]D–555.1° (c 0.022, CH2Cl2); IR (Nujol, ν cm−1) 1658 (C=O); 1H NMR (δ ppm) 0.84 and 0.91 (two s, 6H, OCH2Cl2), 2.18 (three overlapping signals, 5H, CH2CfN and PdCl2), 3.98 (m, 2H, OCH2), 4.27 (m, 1H, NCH); 13C NMR (δ ppm) 13.6 (H2COCO), 23.1 and 23.3 (C1H2O3), 49.0 (CH2Pd), 41.5 (CfCH2), 68.6 (OCH2), 79.4 (NCH), 169.6 (OCfN). Anal. Caled for C26H29CP2N4Pd2: C, 54.06; H, 4.76; N, 4.00. Found: C, 53.81; H, 5.05. N, 4.03. F, 38.33; S, 1.81; P, 5.05. N, 4.03.

Synthesis of Dichlorobis(5)-4-tert-butyl-2-methyl-2-oxazoline palladium(II) (3). PdCl2 (32.1 mg, 0.181 mmol) and (S)-4-tert-butyl-2-methyl-2-oxazoline (54.5 mg, 0.386 mmol) were dissolved in 10 mL of anhydrous methanol. The solution was stirred overnight, and then the solvent was removed in vacuo. The crude product was purified using dry-column vacuum chromatography26 with gradient elution (SiO2 h = 0.5, d = 2.5 cm). The yield of purified product was 48.2 mg (58%): mp 185–190 °C (dec); Rf 0.42 (1.9 EtOAc–PhMe); [α]D–1062°; [α]D–372°; [α]D–289°; [α]D–224° (c 0.20, CH2Cl2); IR (Nujol, ν cm–1) 1649 (C=O); 1H NMR (δ ppm) 1.33 (s, 9H, t-Bu), 2.65 (s, 3H, CH3CfN), 4.09 (m, 1H, NCH), 4.30 (m, 2H, OCH2); 13C NMR (δ ppm) 16.3 (H2CfCfN), 26.4 (CfCH2), 34.0 (CfCH3), 70.1 (OCH2), 74.0 (NCH), 170.4 (OCfN). Anal. Caled for C56H56CP2N4O2Pd: C, 41.80; H, 6.58; N, 6.00. Found: C, 41.93; H, 6.70; N, 6.00.

Synthesis of Chloro[(2-(2-methyl)oxazolin-4-yl)-2,2-dimethylallyl-C,N](triphenylphosphine)palladium-


refined using SHELXS-97 software. Systematic absences and intensity statistics were used to determine the space-group as P212121. A direct-methods approach provided the locations of most non-hydrogen atoms from the electron density map; however, full-matrix least-squares/difference Fourier cycles were used to locate the remaining non-hydrogen atoms. Hydrogens were placed in ideal positions and were refined as riding atoms with relative isotropic displacement parameters. Chirality was established by anomalous dispersion effects in the diffraction data.

Crystallographic data for 5 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-262111. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk].

Results and Discussion

Direct Palladation of (S)-4-tert-Butyl-2-methyl-2-oxazoline (1). Compound 1 was synthesized by cyclization of the corresponding imidate hydrochloride and (S)-tert-leucinol using a procedure previously reported for this compound (Scheme 1).

Two aspects of oxazoline 1 offer significant challenges to cyclopalladation. First, its structure permits only formation of an exo-type palladacycle (see Introduction). In addition, the aliphatic (sp3)C–H bond that must be acted upon by palladium is not activated by any adjacent functional groups. As one would expect based on these limitations, a series of initial attempts met with little success.

Diverse combinations of palladation agent, solvent, base, and temperature regime were tested in reactions with oxazoline 1, including the mild reagent Na2[PdCl4], cationic reagent [Pd(NCMe)4](BF4)2,28 (in MeCN or THF, in the presence of K2CO3, Cs2CO3, or Ag2CO3 for both palladating agents), and the very electrophilic complex Pd(CF3CO2)2,29 (in TFA at room temperature or 65 °C, in the presence of CF3CO2Na or without it). However, no desired CPCs were detected under these conditions (TLC and 1H NMR data). In the case of Pd(CF3CO2)2, formation of Pd(0) was observed along with complete oxazoline 1 decomposition. In the reactions of compound 1 (HL) with [Pd(NCMe)4](BF4)2 and Na2[PdCl4], only coordination complex [Pd(HL)2Cl2] (3) was isolated (21–79%). The same result was obtained in attempts to employ a solid-phase reaction of 1 with Pd(OAc)2: only coordination complex 3 was observed in the resulting mixture (TLC and 1H NMR data).

Success in cyclopalladation of compound 1 has been achieved only using Pd(OAc)2 as the palladation agent in acetic acid solution. The desired CPC 2 was isolated in the reaction of Pd(OAc)2 with 1 in the presence of AcONa (with metal–oxazoline–base 1:1:1–5 ratios) in acetic acid at 60–75 °C, followed by treatment with LiCl. The low yields of the dimer 2 (typically 6–18%) using these conditions prompted us to seek some routes to improve this method. The reactant stoichiometry was not found to exert a significant influence on palladation efficiency: the yield of dimer 2 remained constant (ca. 23%) in two reactions performed with metal–oxazoline 2:1 and 1:2 ratios. Surprisingly, the experimental workup was found to make a significant impact on the product yield. In our previous studies,20,21,23 inorganic impurities were removed from the crude product by simple aqueous extraction; however, removing this step and using only chromatographic purification gave a substantial increase in yield of the desired CPC 2 (to 35%).

Reactions using Pd(OAc)2 as the palladation reagent generated a large amount of Pd(0), especially if the reaction temperature was not carefully maintained under 90 °C. It was found, however, that the extent of palladium reduction could be somewhat decreased by exclusion of the base NaOAc from the reaction mixture. Contrary to our findings for another 2-oxazoline,20 the product yield was increased to 43% when NaOAc was eliminated from the reaction mixture and no aqueous workup was done (Scheme 2).

In all reactions of compound 1 (HL) with Pd(OAc)2, a significant amount (20–50%) of the coordination complex Pd(HL)2Cl2 (3) was found. For comparison, this complex was also obtained in a yield of 58% by reacting PdCl2 with oxazoline 1 in a ratio of 1:2 in methanol.

It is noteworthy that dimeric complex 2 is soluble not only in CHCl3 and CH2Cl2 but also in acetone and benzene. A similar exo-dimer derived from (R)-2-methyl-4-phenyl-2-oxazoline is only sparingly soluble in CHCl3 and CH2Cl2. For comparison, the μ-Cl dimer of endo-cyclopalladated (S)-4-tert-butyl-2-phenyl-2-oxazoline is highly soluble in CHCl3, but the corresponding complex of 2-phenyl-2-oxazoline is practically insoluble in CH2Cl2. The same trend has been observed for analogous complexes of benzylamines: their solubility in CHCl3 depends on the number and the size of alkyl groups. It has been found that an increase in the size and number of alkyl groups in the ligand increases the solubility of the corresponding μ-Cl dimers in CHCl3.

For subsequent characterization studies, dimeric CPC 2 was converted to its mononuclear PPh3 adduct 4;
Scheme 2). Complex 4 was further transformed into an ionic benzonitrile complex using AgBF₄ (5; Scheme 2).

Spectral Characterization of Complexes. Spectral characterization of the obtained complexes (2–5) was done using NMR (¹H, ¹³C, ³¹P, DEPT, HSQC, and COSY) and IR spectroscopy. Complex 5 was analyzed by NOESY spectra as well.

Metatation at the tert-butyl group of oxazoline 1 becomes quite evident from comparison of the ¹H NMR spectra of compound 1 and coordination compound 3 with spectra of cyclometalated complexes 2, 4, and 5. The nine-proton singlet of the tert-butyl group in the spectra of oxazoline 1 and the monodentate N-bonded oxazoline moiety in coordination complex 3 (near δ 0.9 and 1.3 ppm, respectively) is replaced in the spectra of compounds 2, 4, and 5 by signals for two diastereotopic methyl groups (2, 4, and 5) and two signals from the diastereotopic palladium-bonded methylene protons (4 and 5). Unfortunately, in the case of dimer 2 signals resulting from the diastereotopic PdCH₂ protons were not well resolved in CDCl₃ or C₆D₆ solutions. These signals, as well as the signal of the methyl group located at the 2-position of the oxazoline ring, were overlapped to give a multiplet at ca. δ 2.2 ppm with integral intensity corresponding to five protons. However, the HSQC spectrum clearly showed that the multiplet at ca. 2.2 ppm belongs to the protons attached to two different carbons. Furthermore, the DEPT135 spectrum indicated that protons having a signal at δ 2.2 ppm correlated to a methylene carbon.

In the IR spectra of complexes 2–5, the C=N stretching frequencies were shifted to lower wavenumbers (Δν = 23–35 cm⁻¹) compared to that of compound 1 (1681 cm⁻¹). This shift indicated that the imine nitrogen is coordinated to the palladium center.⁷,²⁰,²¹

Mononuclear complexes 4 and 5 are best suited for further analysis of new palladacycle conformation because they contain phosphorus, which can provide valuable stereochemical data, and have better ¹H NMR signal resolution. For both phosphine derivatives, standard cis(P,C)-geometry of the palladium coordination sphere has to be expected, since carbon has a greater trans-influence.⁵² This assumption is confirmed by the NOESY spectrum recorded for compound 5: there were no NOESY cross-peaks observed between the singlet of the oxazoline 2-methyl group (δ 2.31 ppm) and the δ 7.63 ppm multiplet, as would be expected for a putative trans(N,N),trans(P,C)-complex. The latter downfield multiplet has to be considered as the result of overlapping of signals from the ortho hydrogens of the PPh₃ rings and the para hydrogen of the PhCN ligand, on the basis of the COSY spectrum of 5, the [7H] integral intensity, previously reported data for triphenylenephosphine complexes of other cyclopalladated oxazolines,⁷,²⁰,²¹ and known spectral data for free benzonitrile.⁵³ By contrast, a rather strong cross-peak was found between the same multiplet at δ 7.63 ppm and the singlet at δ 0.92 ppm assigned to one of the two diastereotopic methyl groups of the oxazoline ligand. Considering that for either geometry of the palladium environment in complex 5 the para proton of the PhCN ligand will be too far from any palladacycle protons to display NOE enhancement, this effect may be attributed only to phosphate ortho- H interaction with one of the CMe₂ groups, which may be evidence of the cis(N,N)-geometry of this complex. This conclusion was confirmed by X-ray study of complex 5 (vide infra). Similarities in the spectral features (signal chemical shifts in ¹H, ¹³C, and ³¹P NMR and multiplicities in ¹H NMR spectra) for complexes 4 and 5 may be considered as evidence of the PPh₃ ligand position trans to the oxazoline nitrogen atom in both compounds. The ³¹P NMR spectra of 4 and 5 contain one peak, revealing that both complexes exist in solution as only one geometric isomer.

High-resolution mass spectral characterization of complex 5 gave a base peak of m/z = 508.1030, which corresponds to the C₅N-oxazoline and the triphenylphosphane ligands attached to a palladium (mass accuracy 0.8 ppm). Facile loss of the benzonitrile ligand under rather gentle conditions of the positive ESI method is indicative of its weak coordination with the palladium atom, which may be a consequence of the very strong trans-influence of an (sp³)-carbon.

As reference points for differentiation of diastereotopic protons/groups of the palladacycle we have chosen the protons of the oxazoline ring of known S absolute configuration. Assignment of the oxazoline ring signals in ¹H and ¹³C NMR spectra was done using standard analysis of their HSQC and DEPT135 spectra. Due to the presence of a chiral center, oxazoline derivatives with substituents at the 4-position usually display separate ¹H NMR signals for each of the three heterocycle hydrogens.⁷,²⁰,²¹ Unfortunately, in the ¹H NMR spectra of dimer 2 and its phosphane adduct 4 (measured in CDCl₃) the signals of two of three oxazoline hydrogens were overlapped to give two multiplets near δ 4.0 [2H] and 4.3 ppm [1H] corresponding to the OCH₂ and NCH protons of the oxazoline ring, which is in accordance with previously reported values.⁷,²⁰,²¹,³³ In the ¹H NMR spectrum of cationic complex 5 taken at room temperature in CDCl₃, signals of two hydrogens at δ 4.09 and 4.13 ppm are only partly overlapped. The HSQC spectrum proved that the two overlapping triplets at δ 4.13 and 4.09 ppm and the triplet at 4.48 ppm belong to the NCH and diastereotropic OCH₂ hydrogens, respectively.

The NOESY spectrum of complex 5 reveals strong cross-peaks between the multiplet centered at δ ~ 4.11 ppm (resulting from the partial overlap of the NCH signal and the signal of one of the OCH₂ hydrogens) and both singlets at δ 0.78 and 0.92 ppm belonging to the diastereotropic CMe₂ groups. Since efficient interaction may be possible only between protons or groups located in the cisoid position relative to the C⁵–C⁴–C³ plane, these two strong NOE responses can be explained as a result of interactions between the NCH and CMe₂, and the OCHR and CMe₂, protons (Figure 1).³⁴ Consequently, the multiplet centered at δ ~ 4.11 ppm has to contain the signal of the OCHR proton, and as a result, these two strong NOE responses can be explained as a result of interactions between the NCH and CMe₂, and the OCHR and CMe₂, protons (Figure 1).³⁴ Consequently, the multiplet centered at δ ~ 4.11 ppm has to contain the signal of the OCHR proton, and as a result, the singlet at δ 0.92 ppm assigned to one of the two diastereotopic methyl groups of the oxazoline ligand. Considering that for either geometry of the palladium environment in complex 5 the para proton of the PhCN ligand will be too far from any palladacycle protons to display NOE enhancement, this effect may be attributed only to phosphate ortho- H interaction with one of the CMe₂ groups, which may be evidence of the cis(N,N)-geometry of this complex. This conclusion was confirmed by X-ray study of complex 5 (vide infra). Similarities in the spectral features (signal chemical shifts in ¹H, ¹³C, and ³¹P NMR and multiplicities in ¹H NMR spectra) for complexes 4 and 5 may be considered as evidence of the PPh₃ ligand position trans to the oxazoline nitrogen atom in both compounds. The ³¹P NMR spectra of 4 and 5 contain one peak, revealing that both complexes exist in solution as only one geometric isomer.
Assignment of diastereotopic methyl groups based on their NOE contacts with the oxazoline ring protons in complex 5.

Figure 2. Newman projections of the palladacycle in 5 along the [Pd(Ph)$_2$CH$_2$] group for the actual chiral $\lambda(S)$ conformation with the observed NOE contacts (a) and for the alternative nontwisted envelope with its expected NOE contacts (b).

The triplet at $\delta$ 4.48 ppm may be assigned to the OCH$_3$ proton. Since the NOESY spectrum of 5 shows a weak cross-signal between this triplet at $\delta$ 4.48 ppm and the singlet at $\delta$ 0.78 ppm of the more distant palladacycle's Me group, it provides a basis for assignment of the latter. The triplet at $\delta$ 0.78 ppm of the more distant palladacycle's Me group is located in proximity to the ortho group of the palladacycle. Consequently, the second singlet at $\delta$ 0.92 ppm in the spectra of complex 5 may reasonably be assigned to the CMe$_2$ group.

Several arguments can be presented in support of the latter assignment: (i) a molecular model of the cis(N,N)-isomer of 5 constructed for chiral envelope-like $\lambda(S)$ conformation of the palladacycle showed that the Me$_S$ group of the palladacycle is located in proximity to the ortho protons of the PPh$_3$ ligand (Figure 2a); (ii) X-ray study of 5 (vide infra) revealed a rather short distance of 2.957 Å between a hydrogen of the Me$_S$ group and one of the ortho-hydrogens of the PPh$_3$, while the distances between the Me$_R$ group and ortho-hydrogens of two different PPh$_3$ rings were significantly larger, 4.412 and 5.151 Å; (iii) the aforementioned strong cross-peak between the signal of ortho-PhP protons and the singlet at $\delta$ 0.92 ppm is in complete accordance with these data; (iv) in the $^1$H NMR spectra of another phosphane adduct 4 the similar low-field signal of the CMe$_2$ group (at $\delta$ 0.84 ppm) appears as a doublet ($^5$J$_{HP}$ 0.6 Hz); such marked $^1$H...$^{31}$P spin–spin coupling through five bonds seems to be very unusual and may be partly explained by direct interaction of these nuclei through space. Therefore, high-field signals at $\delta$ 0.84 or 0.92 ppm in the $^1$H NMR spectra of phosphane adducts 4 and 5, respectively, may be assigned to the Me$_S$ group of the palladacycle.

Strong NOESY cross-peaks (Figure 2a) observed in the spectra of 5 between the singlet at $\delta$ 0.78 ppm corresponding to the Me$_R$ group with both the triplet at $\delta$ 1.41 ppm and the doublet at 1.73 ppm resulting from the diastereotopic hydrogens of the PdCH$_2$ fragment provide the best evidence of the palladacycle's chiral envelope-like $\lambda(S)$ conformation (Figure 3). For the alternative achiral (nontwisted) conformation, only one very strong cross-peak would be predicted for each pair, PdCH$_R$...Me$_R$ and PdCH$_S$...Me$_S$, located in the eclipsed position (Figure 2b); consequently, this nontwisted conformation (Figure 3) may be excluded from further considerations. The NOE enhancement observed for the triplet at $\delta$ 1.41 ppm, due to interactions of the corresponding PdCH$_2$ hydrogen with the ortho hydrogens of the P–Ph rings, allows us to identify this signal as belonging to the PdCH$_S$ proton.

Analysis of the observed signal multiplicities for the PdCH$_2$ fragment in the $^1$H NMR spectrum of phosphane derivatives 4 and 5 provides additional evidence in favor of the $\lambda(S)$ conformation of the palladacycle. In this conformation, the PdCH$_S$ hydrogen related to the doublet at $\delta$ 1.73 ppm is situated in a pseudo-axial position, and the PdCH$_R$ hydrogen, giving rise to the triplet at $\delta$ 1.41 ppm, occupies the pseudo-equatorial position relative to the mean coordination plane. According to the molecular model, the expected torsion angle for the P–Pd–C–H$_S$ fragment should be close to 80–90°, and due to the orthogonality of the P–Pd and C–H$_R$ bonds, efficient spin–spin coupling would not be expected. For this reason, the signal of the PdCH$_R$ proton appeared as a doublet with the geminal coupling constant $^2$J$_{HR} = 10.1$ Hz. The appearance of the PdCH$_S$ proton signal as a triplet suggests an advantageous torsion angle for the P–Pd–C–H$_S$ fragment (estimated at 30–40° using a molecular model, found by X-ray crystal structure analysis 34.4°). In addition, the PdCH$_S$ hydrogen is in very close proximity (2.76 Å in the crystal structure) to the phosphorus atom. The observed coupling constant $^2$J$_{HR}$ can, therefore, be explained by spin coupling of the two nuclei through three bonds and from through-space interaction. It is noteworthy that the same multiplicity pattern for the PdCH$_3$ fragment was reported for the phosphane derivative of another aliphatic palladacycle.

The conformation of the oxazoline ring in compound 1 and complex 5 in CDCl$_3$ was assessed on the basis of the values of coupling constants for the oxazoline hydrogens. The values of the torsion angles H–C$_4$–C$_5$–H$_S$ and H–C$_4$–C$_5$–H$_R$ in compounds 1 and 5 were estimated using the computer program MastRe-J. The program enabled torsion angles for H–C$_4$–C$_5$–H$_S$ and H–C$_4$–C$_5$–H$_R$ to be calculated using the Haasnoot–de Leeuw–Altona equation relating torsion angle to the Haasnoot$^J$.$^36$ The obtained torsion angle values are provided in Figure 4. The values suggest that the oxazoline ring in both compound 1 and complex 5 has the same slightly twisted $\delta(S)$ conformation. The torsion angle values calculated for complex 5 are in fair agreement with the experimental values (4.4° for the H–C$_4$–C$_5$–H$_S$ torsion angle and 125.6° for the H–C$_4$–C$_5$–H$_R$ torsion angle) from the X-ray diffraction study of 5. It is noteworthy

that the $\delta(S)$ conformation of the heterocycle was also suggested on the basis of spectroscopic data for the only known exo oxazoline-based palladacycle, while the oxazine ring in the corresponding endo complexes adopts the $\lambda(S)$ conformation.

**Molecular Structure of Mononuclear Cationic Phosphane Derivative 5**. The most conclusive evidence for the cyclopalladated structure of complexes 2, 4, and 5 comes from the X-ray diffraction study of the mononuclear cationic derivative 5: the site of cyclopalladation at the tert-Bu group and cis(N,N)-geometry of the coordination sphere are unambiguous. Complex 5 crystallizes in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. The anion BF$_4^-$ is well separated from the complex cation: the shortest contact distance (H$_{24A}$ to F$_1^-$) equals to 2.49 Å exceeds the sum of van der Waals radii of these atoms (2.46 Å). The tetrafluoroborate anion is disordered in the crystal, populating two positions in a ratio of 84:16. The general view of this complex and atom-numbering scheme are presented in Figure 5.

Taking into account that this structure is the first example of a structurally characterized chiral oxazoline-derived CPC with the (sp$^3$)C--Pd bond, it will be compared with other known complexes including aliphatic palladacycles (Chart 3). Among such structurally characterized analogues, there are two dimers (6a$^{39}$ and 6b$^{39}$), five mononuclear compounds (7a$^{35}$, 7b$^{40}$, 7c$^{41}$, 7d$^{42}$ and 8$^{43}$), and one bis-chelated spiro-complex 9$^{44}$ (Chart 3). All these derivatives contain a five-membered CN-palladacycle with a primary (9), secondary (7a), or tertiary (6a, 7b--d and 8) amino group as the donor fragment. Complex 10 (Chart 3), with a tricyclic structure of the CNNO-type containing a CN-palladacycle with exo-imine N-donor group, has been reported as well.$^{45}$

The coordination environment of the palladium atom in cationic complex 5 may be described as square planar with very slight tetrahedral distortion: the angle between the planes $\{N^3PdC^5\}$ and $\{PPdN^2\}$ is equal to 2.9°. It is of note that almost ideal square-planar geometry is a common feature in pure aliphatic five-membered CN-palladacycles; the tetrahedral distortion angles in complexes 6a, 7b and 7b, 7d fall in the range 1.9--3.1°.$^{38,40,42}$ In the cases of 7a and 9, the metal exists in a very flattened square-pyramidal environment with a slightly twisted base.$^{35,44}$ In comparison, tetrahedral distortions in ortho-palladated derivatives of 2-aryloxazolines and benzylamines fall into much larger ranges, 1.7--15.8° and 2.4--19.3°, respectively.$^{7,22,35}$ Consequently, aliphatic palladacycles due to their pronounced flexibility allow for retention of a square-planar configuration environment, which is optimal for a d$^8$-metal center such as Pd(II).

The Pd--C bond length for complex 5, 2.04 Å, falls in the narrow ranges reported for related CPCs with both (sp$^3$)C--Pd--Cl (1.97--2.05 Å) and (sp$^2$)C--Pd--Cl axes (1.99--2.05 Å), despite the expected difference in the trans-influence of nitrile and chloride ligands. Although this bond is elongated to some extent in the more related cationic complex 10 with (sp$^3$)C--Pd--N=C axis [2.11 Å] and also in the spiro-complex 9 with (sp$^3$)C--Pd--(sp$^3$)C axis [2.16 Å], such Pd--C bond weakening may be a consequence of steric strain in the tricyclic CNNO system of the first model and strong trans-influence of the carbanionic center in the second complex.

The Pd--N(oxazoline) bond length in complex 5, 2.098 Å, is longer than in all known examples of endo-type ortho-palladated oxazolines (1.886--2.085 Å), but is between the normal values of 2.060--2.062 and 2.142--2.188 Å found for phosphane adducts of ortho-palladated oxazolines with an endo-C=N bond$^{39,22}$ and alkylammine CN-palladacycles (8, 7a$^{35,43}$ respectively. Some elongation of the Pd--N bond in the exo-adduct 5 compared to oxazine-derived endo-analogues may be explained as resulting from less efficient palladium bonding with the imino-donor group located in the exocyclic position, due to the absence of intracyclic conjugation with this double bond. This assumption can be supported by similar values of Pd--N bond length.

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(45) Fang, X.; Scott, B. L.; Watkin, J. G.; Kubas, G. J. Organometallics 2000, 19, 4193.
Chart 3. Palladacycles Related to Complex 5 with Reported X-ray Crystal Structures

The Pd–P bond length in cationic complex 5, 2.248 Å, is in good agreement with values (2.234–2.248 Å) reported for neutral exo-imine derivatives 11a,b. These values fall within the ranges found previously for the neutral PPh₃ adducts of ortho-palladated oxazolines of endo-type (2.235–2.256 Å)²¹,²³ and ortho-palladated benzylmines (2.243–2.256 Å).³⁵,⁴⁶,⁴⁷

The weak coordination of the benzonitrile ligand in complex 5 can be seen from the Pd–N² bond length of 2.11 Å. In comparison with the structure of the only known benzonitrile adduct with a CN-palladacycle, 12 (Chart 3), the value of the Pd–N(NCPH) bond is 2.01 Å.⁴⁸ The Pd–N(NCPH) bond length is further decreased to 1.94–1.99 Å in complexes trans-PdX₂(NCPH)₂ [X = Cl (13a), Br (13b)]⁴⁹ and in the 13a component of the crystal Pd₆Cl₁₂-13a-p-xylene.⁴⁹ Such weakening of the Pd–N² bond in complex 5 may reasonably be explained as a consequence of the stronger trans-influence of the alkyl–Pd bond compared to that of the Pd–N bond.³²

As additional support, it can be mentioned that the Pd–N bond lengths in two reported bis(benzonitrile)diphosphane complexes of the [P₂Pd(NCPH)₂] type (14a,b) vary from 2.06 to 2.12 Å in accordance with the rather large trans-influence of the P–Pd bond.³²

The benzonitrile ligand in complex 5 displays nearly linear coordination to the palladium atom with bond angles Pd₁–N²–C⁹ and N²–C⁹–C₁⁰ equal to 171.2° and 179.3°, respectively; these values fall in the ranges 170.2–177.1° and 172.9–180.0° found for benzonitrile complexes 12–14. The length of the N²=C⁹ bond in compound 5 is equal to 1.149 Å, exceeding the value of 1.131 Å reported for analogue 12, and is close to the upper limit of values found for coordination complexes 13a,b and the crystal Pd₆Cl₁₂-13a-p-xylene (1.12–1.16 Å).⁴⁹

Another structural peculiarity of complex 5 is the nearly coplanar orientation of the benzonitrile phenyl ring and one of the PPh₃ phenyl rings (A) (Figure 6) characterized by the torsion angle C₈–Pd–P–C₁₅₀ of −174.6° and an interplanar angle between these two aromatic rings of 16.5°. Noncovalent attractive interactions between π–π-systems are invoked to account for stabilization and orientation in many systems.⁵¹,⁵² In recent theoretical studies of intermolecular π–π stacking in simple arene dimers, three geometries are most commonly discussed: sandwich (D₀₋), parallel-displaced (C₂h, “slipped sandwich”), and T-shaped (C₂ᵥ, “point-to-face”).⁵⁰–⁵³ In structure 5, the orientation of the PhCN and P–Ph⁴ rings resembles the parallel-displaced geometry of two arenes. The closest contact distance between the two aromatic rings is 3.5 Å (C₁⁰–C₃²), which is in accord with experimental values of 3.4–3.6 Å found to be the average interplanar spacing in...
porphyrin aggregates. \(^5^1\) For comparison, a study of substituent effects on \(\pi-\pi\) interactions performed by Sinnokrot and Sherrill\(^5^2\) found a vertical displacement of 3.6–3.8 Å for a sandwich benzene-benzonitrile dimer. Due to the restricted geometry of the arene moieties in \(5\), horizontal displacement of the two arenes is 1.39 Å (Figure 6; defined as the distance between the Ph A-centroid to C\(^{31}\)), which is slightly shorter than the calculated horizontal displacements for benzene dimers (1.54–2.10 Å).\(^5^2,^5^3\) Since the geometric parameters of complex \(5\) are in good agreement with both theoretical and experimental values for systems with known \(\pi-\pi\) interactions, one can reasonably interpret the nearly coplanar orientation of the two arene rings in complex \(5\) as due to intramolecular \(\pi-\pi\) interactions.

The stereochemistry of the coordinated PPh\(_3\) ligand in complex \(5\) is of special interest since its propeller-like rotameric states can provide additional chirality.\(^5^4–^5^6\) The Ph\(_3\)P-M fragment remains achiral only if all P-Ph rings are positioned either parallel (“parallel” conformation) or orthogonal (“orthogonal” conformation) to the \(C_3\) axis of the PPh\(_3\) moiety (Figure 7).\(^5^4\) Between the two extremes lie the rotameric states that result from synchronous twisting of the three P-Ph rings (starting from the orthogonal conformation) about the P-C\(^{ipso}\) axes.\(^5^4\) Rotation can be either clockwise or counterclockwise (Figure 7), which generates the chiral propeller-like configurations \(P\) (plus) and \(M\) (minus), respectively. Unfortunately, studies of the influence of other chirality elements on PPh\(_3\) stereochemistry have been mainly restricted to cyclopentadienyl compounds with planar chirality and an asymmetric metal center.\(^5^5–^5^7\) Recently, a detailed analysis\(^5^8\) of available X-ray structure data for PPh\(_3\) derivatives of \(C^*-\) and \(N^*-\)chiral benzylamine palladacycles has shown that the spirality (helicity) of the phosphane ligand is dependent upon both the palladacycle conformation and the nature of the N-donor atom.

The rotameric states of the aromatic rings in the phosphane ligand (relative to the corresponding P-C\(^{ipso}\) bonds) in complex \(5\) were estimated using averaged values of the pair of torsion angles that include the

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\(^{58}\) Kataeva, N. A. Ph.D. Dissertation, M. V. Lomonosov Moscow State University, Moscow, Russia, 2002.
ortho-Ph carbons, i.e., Pd–P–C$_1$$_{p}$$_{o}$$_{p}$–C$_7$$_{o}$$_{h}$$_{th}$ (ω$_{1}$) and Pd–P–C$_{p}$$_{o}$$_{p}$–C$_7$$_{o}$$_{h}$$_{th}$, according to the known equation ω$_{1}$ = (ω$_{11}$ + ω$_{12}$ + 180°)2. The torsion angle range of 0°–90° is indicative of the P propeller configuration, while the range 90°–180° corresponds to the M configuration. For complex 5, the angles ω$_{1}$–ω$_{2}$ are equal to 90.3°, 141.0°, and 177.4° for PPh$_3$ rings A (C$_{p}$–C$_{p}$ = C$_{p}$), B (C$_{p}$–C$_{p}$ = C$_{p}$), and C (C$_{p}$–C$_{p}$ = C$_{p}$), respectively (Figure 6). These data allow us to describe the PPh$_3$ conformation as an M propeller, distorted due to interaction of ring A with the PhCN ligand.

For comparison, the PPh$_3$ ligands also adopt a helical conformation in related phosphate adducts (S$_{C}$,S$_{P}$)$_{2}$–[C$_7$H$_3$]$^{+}$,7a and (S)$^{+}$–8, which contain a Pd–CH$_2$ bond, as well as in the phosphate derivative of the ortho-palladated oxazoline (S$_{C}$,S$_{P}$)$_{2}$-1522 (Chart 3). In the structures of these three complexes, two or three values of ω$_{1}$–ω$_{2}$C angles (119.6°, 158.5°, and 132.9° for 7a; 174.0°, 101.7°, and 129.6° for 8; 85.9°, 138.1°, and 167.8° for 15) correspond to the M propeller configuration of the phosphine ligand. In all reported X-ray data for PPh$_3$ derivatives of chiral benzylamine palladacycles,58 only two PPh$_3$ rings exist in the twisted state, while the third P–Ph ring adopts a nearly parallel disposition, presumably due to secondary interactions that were not investigated.

The crystal structure of complex 5 has provided valuable information to support the conclusions made from spectral data regarding the geometry of the two phosphane derivatives 4 and 5. The analysis of the phosphorus atom environment in adduct 5 has revealed its very close proximity to one of two hydrogen atoms in the CH$_2$Pd fragment, with the H$_{C}$–P–P distance equal to 2.8 Å, which is significantly shorter than the sum of van der Waals radii of these atoms (3.0 Å2).7b This short contact is most likely responsible for efficient through-space 3P–H spin–spin coupling, in addition to through-bond interaction, which is also large due to the advantageous H$_{C}$–C$_7$–P–P torsion angle of 34.4°. The values of these geometric parameters found in the X-ray crystal structure are in complete accordance with the very large value of the J$_{HP}$ constant (~10.1 Hz) observed for only one of the PdCH$_2$ protons, H$_5$. The other PdCH$_2$ proton (H$_7$) is farther from the phosphorus atom [the H$_{C}$–P–P distance equal to 3.27 Å], and its orientation [with the H$_{C}$–C$_7$–P–P torsion angle equal to ~84.7°] is not suitable for efficient through-bond coupling. For these reasons, no coupling between the phosphorus and the second PdCH$_2$ proton was detected.

Comparable data were obtained for the Pd–CH$_2$ fragment in related phosphate derivatives 8 and 7a; the two CH$_2$–P–P distances are equal to 3.30 and 2.88 Å for 8 and 3.01 and 3.38 Å for 7a. An analogous significant difference in the values of two corresponding torsion angles H–C–Pd–P was observed as well: ~39.1° and 81.7° for 8 and ~40.6° and 83.8° for 7a. In accordance with these X-ray data, only the pseudo-equatorial proton of the PdCH$_2$ fragment in complex 7a reveals efficient 3P–H spin–spin coupling, with J$_{HP}$ = 9.4 Hz.35

The stereochemistry of the palladacycle in complex 5 is in agreement with the predictions derived from the $^1$H NMR data. First of all, the high degree of palladacycle puckering should be mentioned: the average magnitude of the absolute values of intrachelate torsion angles (τ) is equal 34.2°, which is above the range of τ = 28.3–33.2° reported for other related aliphatic CN-palladacycles (6a,b and 7a–d), except the very sterically crowded pentacyclic structure 8 (τ = 37.8°). Such pronounced puckering in the exo-palladacycle of compound 5 is in drastic contrast to the rather small extent of nonplanarity found for endo-palladacycles derived from oxazolines, which are characterized by the τ range 1.7–10.3° for the majority of such complexes. Only in the case of sterically overcrowded oxazoline-based endo-palladacycles with ferrocenylene59 and paracyclophane22 frameworks have τ values increased up to 10.4–16.2°.

The palladacycle conformation in complex 5 may be described as a twisted envelope, with the C$_2$ atom at the apex of the flap and a bend of 36.7° along the line N–N$^\prime$. Similar conformations, with the C$_2$ or C$^\prime$ atom at the top of the flap and the corresponding bend of 42.2–48.8°, are typical for the majority of other complexes with aliphatic palladacycle constituents. As might be expected, the most twisting has been observed for the aliphatic carbon chain of the palladacycle in complex 5, with the greatest values for torsion angles N–C$_{1}$–C$_{1}$–C$_{1}$ and C$_{1}$–C$_{1}$–C$_{1}$–Pd (~54.9° and 48.3°, respectively). These values fall into the corresponding ranges reported for other complexes of this type (44.8–63.8° and 43.2–48.9°, respectively).

The conformation of the palladacycle in complex 5 may be described as λ(S$_{C}$) on the basis of the negative sign of torsion angle N–C$_{1}$–C$_{1}$–C$_{1}$ (~54.91°). In accordance with this stereochemistry, one (C$_{1}$H$_{3}$)$_{2}$ of two Me groups of the CMe$_2$ fragment and the methine hydrogen at the adjacent C$_{1}$–stereocenter (C$_{1}$H$_{1}$A) are in strict trans-axial positions, with the C$_{5}$–C$_{7}$H$_{3}$ and C$_{1}$–H$_{1}$A bonds deviated from the normal to the mean coordination plane (mcpl) by only 0.13° and 3.87°, respectively. In the PdCH$_2$ fragment, deviations of the C$_{8}$–H$_{8}$A and C$_{8}$–H$_{8}$P bonds from the normal to the mcpl equal 12.13° and 61.98°, respectively, which indicates an axial position for the former and a quasi-equatorial orientation for the latter hydrogen.

Unfortunately, available data do not allow prediction of palladacycle stereochemistry based on the configuration of intracyclic stereocenters. The same type of chirality transfer may be found only for the CN-palladacycles bearing one C$_{4}$-stereocenter, namely, λ–(S$_{C}$)$^\prime$–5, (S$_{C}$)$^\prime$–7d, and λ–(S$_{C}$)$^\prime$–6b. In the case of polycyclic structures δ(R$_{C}$–R$_{C}$–)$^\prime$–8 and δ(S$_{C}$)$^\prime$–10 and palladacycles δ(S$_{C}$–R$_{C}$–)$^\prime$–7a and δ(R$_{C}$–R$_{C}$–)$^\prime$–7b bearing several stereocenters, any simple correlation is impossible.

The oxazoline ring in complex 5 adopts a nearly planar conformation, with the average magnitude of the absolute values of intracyclic torsion angles (τ) of 1.5°; this value lies at the lower limit of a rather wide range found for the oxazoline-derived CPCs of endo-type (τ ~ 0.4–14.0°).7b22

**Conclusion**

Despite the unfavorable combination of the reduced propensity of (sp$^3$)C–H bonds to be activated by Pd(II) and disadvantageous exo-position of the C=N bond in the target palladacycle, cyclopalladation of (S)-4-tert-butyl-2-methyl-2-oxazoline was achieved using palladium(II) acetate as metatation agent. This is the first
example of direct cyclopalladation of an oxazoline derivative through the aliphatic group at position 4 of the heterocycle. Spectral investigations of the initial dimeric complex and its mononuclear phosphane derivatives and X-ray diffraction study of an unusual cationic phosphane-benzonitrile derivative confirmed a very high degree of palladacycle puckering and its existence in both the crystal and solution states as the $\lambda(S)$ conformation. This conformation is fixed by the bicyclic structure formed by palladacycle annelation with a chiral oxazoline ring. Peculiarities of the new palladacycle, such as its very pronounced twisting and high conformational stability, create the best conditions for efficient chirality transfer from the carbon stereocenter to other ligands in the palladium environment.

Further research into $(sp^3)C-H$ activation toward formation of optically active CPCs and their applications (estimation of their potential as chirality inductors) is ongoing at this time.

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Supporting Information Available: The crystallographic information file (CIF) for complex 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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