4900 *Organometallics* **1999,** *18,* 4900−4907

Articles

(Hydroxyalkyl)pyridinooxazolines in Palladium-Catalyzed Allylic Substitutions. Conformational Preferences of the Ligand

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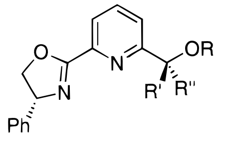
Received July 15, 1999

2-(3′,4′-Dihydro-2′-oxazolyl)-6-(hydroxymethyl)pyridines have been shown by X-ray crystallographic analysis and DFT calculations to exhibit two conformational minima in their complexes with Pd(II) chloride. Theoretical studies of (π-allyl)palladium(II) and (π-olefin)-palladium(0) complexes with 2-(3′,4′-dihydro-2′-oxazolyl)-6-(hydroxymethyl)pyridine revealed two minima in each complex. In contrast, in the calculations of the Pd(II) chloride and Pd-(II) allyl complexes of 2-(3′,4′-dihydro-2′-oxazolyl)-6-(methoxymethyl)pyridine a single conformational minimum was found. NOE studies of complexes in solution were in agreement with the results obtained by the theoretical studies. The knowledge about the conformational preferences of the palladium complexes with (hydroxyalkyl)pyridinooxazolines and (methoxyalkyl)pyridinooxazolines is used to rationalize the results of palladium-catalyzed allylic alkylations employing the two types of ligands.

Introduction

To get access to selective and efficient metal catalysts for use in asymmetric metal catalysis,[1] the design and preparation of chiral ligands surrounding the metal ion are essential.[2] The electronic as well as the steric properties, including the conformational preferences, of the ligands and their metal complexes are the major parameters responsible for the results of the catalytic reactions, and these factors must therefore be carefully considered.

We have previously studied (hydroxyalkyl)pyridinooxazolines (**1**) and (methoxyalkyl)pyridinooxazolines (**2**) as ligands in metal-catalyzed reactions, such as additions of diethylzinc to aldehydes[3] and palladium-catalyzed allylic substitutions.[4] In the free state, the two types of ligands have different conformations. The ether ligands prefer a planar *anti* conformation due to electron pair repulsion and to electron donation from the nitrogen lone pair into the antibonding carbon−oxygen σ-bond,[5] whereas in the alcohols the hydroxy proton takes part in hydrogen bonding to the pyridine nitrogen, resulting in a *syn* planar conformation for these compounds.



1 R=H; R',R''=H, alkyl
2 R=Me; R',R''=H, alkyl
1a R=R'=R''=H
2a R=Me; R'=R''=H

The conformation of the ligands in metal complexes where the oxygen does not take part in coordination to the metal ion has been less well studied.[6] However, as hydrogen bonding to the pyridine nitrogen is excluded in metal complexes with 2-(hydroxymethyl)pyridines, it was expected that, in case the oxygen does not coordinate to the metal ion, metal complexes containing **1** and **2** as ligands would adopt similar conformations. It was therefore surprising to note that the enantioselectivity in palladium-catalyzed allylic alkylations[4a] differed with

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(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis;* Wiley: New York, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(2) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. Tomioka, K. *Synthesis* **1990**, 541.

(3) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549.

(4) (a) Nordström, K.; Macedo, E.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1605. (b) Bremberg, U.; Rahm, F.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3437.

(5) Moberg, C.; Adolfsson, H.; Wärnmark, K.; Norrby, P.-O-; Marstokk, K.-M.; Møllendal, H. *Chem. Eur. J.* **1996**, *2*, 136.

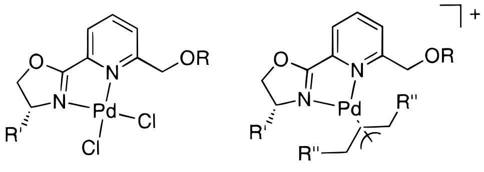
(6) A few crystal structures of such metal complexes have been reported: Garrett, T. M.; Koert, U.; Lehn, J.-M.; Rigault, A.; Meyer, D.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 557. Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205.

10.1021/om990552u CCC: $18.00

the two ligand types. For example, ligand **1** with R′ = H/R″ = *t*-Bu, R′ = H/R″ = neomenthyl, R′ = *t*-Bu/R″ = H, and R′ = neomenthyl/R″ = H yielded products with 95, >99, 90, and 39% ee, respectively, and ligands **2** with R′ = H/R″ = *t*-Bu and R′ = *t*-Bu/R″ = H yielded products in 15 and >99% ee, respectively; that is, for **1** isomers with *R**,*R** configuration resulted in higher selectivity, whereas for **2** those with *R**,*S** configuration were more successful. This was a strong indication of different conformations of the two types of ligands also in their metal complexes, which was indeed corroborated by preliminary NOESY data.[4a] We herein present a more thorough study of the conformation of the ligands in palladium complexes and the conformational change during reaction, as shown by X-ray crystallography, DFT calculations, and NMR spectroscopy.

Results

X-ray Crystallography. The palladium(II) chloride complex of alcohol **1a** (**3**) was first selected and studied as a simple model for a catalytically active intermediate.



3 R=H; R'=Ph
4 R=R'=H
5 R=Me; R'=H
10 R=Me; R'=Ph

6 R=Me; R'=R"=H
7 R=R'=R"=H,
8 R=R'=H; R"=Ph
11 R=R"=H; R'=Ph
12 R=Me; R'=Ph; R"=H

The X-ray analysis revealed two crystallographically independent complexes in the asymmetric unit (molecules A and B). These two complexes exhibit similar conformations; there are only minor variations in the orientation of the C(41)···C(46) phenyl substituent and also in the planarity of the oxazoline rings (Figure 1, Table 2). Interestingly enough, the alcoholic O(2″)−H(2″) group has two distinct orientations in each of the two crystallographically independent molecules. The two major and the two minor conformations, respectively, are similar (Table 2) but have different probabilities (i.e. site occupation factors). Accordingly, the observed N−C−C−O dihedral angles are (with their probabilities given in brackets) 159.5(4)° [91.5%] and −94.3(4)° [8.5%] for A and 159.1(4)° [79.4%] and −92.7(5)° [20.6%] for B. The major orientation opens the possibility for the intermolecular hydrogen-bond interactions O(2″a)−H(2″a)···Cl(1b) and O(2″b)−H(2″b)···Cl(1a) (Table 3), whereas the minor conformations lead to intramolecular H-bonds from O(2#)−H(2#) to Cl(2) in both complexes. The intermolecular hydrogen bonds link the molecules into endless chains, running parallel in the crystallographic *x* direction. The packing of the chains is supported by several C−H···Cl and C−H···O interactions (Table 3), thus giving rise also to relatively short contact distances between the two palladium ions of the asymmetric unit (Pd(1a)···Pd(1b) = 3.6906(6) Å) (Figure 2).

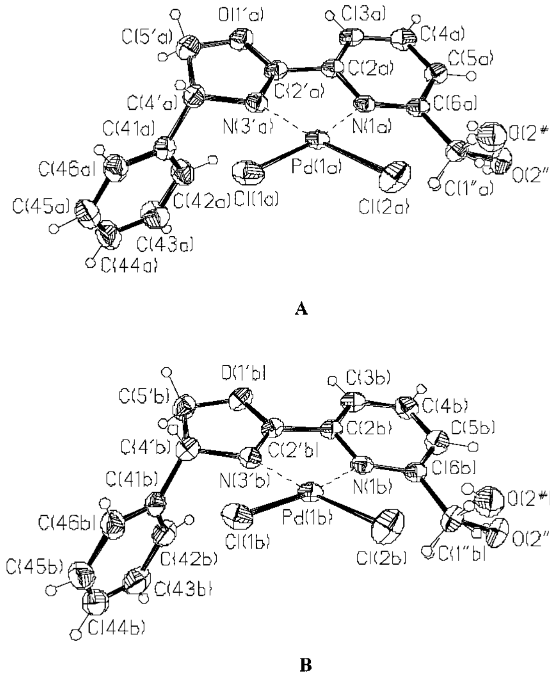


Figure 1. Perspective view of molecules A and B of **3**. The non-hydrogen atoms and disorder sites, labeled as in the text, are represented by their displacement ellipsoids drawn at the 30% probability level.

Table 1. Crystal Data and Details of the Data Collection and of the Final Structure Refinement Calculation for 3

identification code	**3**
empirical formula	$C_{30}H_{28}Cl_4N_4O_4Pd_2$ (2 ($C_{15}H_{14}N_2O_2{\cdot}PdCl_2$))
fw	863.16
temperature	293(2) K
radiation/λ	Mo $K\alpha$/0.710 73 Å
cryst syst	orthorhombic
space group	$P2_12_12_1$
unit cell dimens	$a = 9.1540(10)$ Å $b = 14.406(2)$ Å $c = 24.510(6)$ Å
unit cell volume	3232.2(10) Å^3
Z	4 ($Z' = 2$)
density (calcd)	1.774 Mg/m^3
linear abs coeff	1.403 mm^{-1}
F(000)	1712
cryst size	0.577 × 0.046 × 0.069 mm
θ range for data collecn	2.38−25.91°
index ranges min/max h,k,l	−10 to +10, 0−17, 0−30
no. of rflns collected	6120
no. of indep rflns	6120
refinement method	full-matrix least squares on F^2
no. of data/restraints/params	6120/0/417
goodness of fit on F^2	0.979
final R indices[a] ($I > 2\sigma(I)$)	R1 = 0.030, wR2 = 0.052[b]
no. of rflns with $I > 2\sigma(I)$	4761
R indices[a] (all data)	R1 = 0.052, wR2 = 0.059[b]
Flack abs structure param	−0.07(3)
largest diff peak and hole	0.55 and −0.95 e/Å^{-3}

[a] R1 is calculated using the F values; wR2 is based on F^2.[19] [b] The weights of the structure factors were assumed to be $w = [\sigma^2(F_o^2) + 0.017P)^2\,]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$.[19]

DFT Calculations. The presence of two conformations of **3** in the solid state prompted us to investigate the conformational preferences of the ligand theoretically. For this purpose hybrid DFT calculations (B3LYP) were performed on an analogous achiral complex, **4**. Two conformational minima were indeed found, the lowest one having an N−C−C−O dihedral angle of −73° (C,

Table 2. Selected Geometrical Features[a] in Molecules A and B of 3

	molecule A	molecule B
Selected Torsion Angles (deg)		
Cl(1)−Pd(1)−N(1)−C(2)	−2.0(9)	−3.2(1.0)
Cl(2)−Pd(1)−N(1)−C(2)	−161.7(3)	−159.3(3)
Cl(1)−Pd(1)−N(3′)−C(2′)	164.2(3)	162.6(3)
Cl(2)−Pd(1)−N(3′)−C(2′)	77.2(1.4)	73.4(1.3)
N(1)−C(6)−C(1″)−O(2″)	159.5(4)	159.1(4)
N(1)−C(6)−C(1″)−O(2#)	−94.3(4)	−92.7(5)
C(5)−C(6)−C(1″)−O(2″)	−18.6(5)	−17.3(6)
C(5)−C(6)−C(1″)−O(2#)	87.6(5)	90.9(5)
N(1)−C(2)−C(2′)−N(3′)	−1.1(6)	0.8(6)
N(1)−C(2)−C(2′)−O(1′)	−179.8(4)	−177.1(4)
N(3′)−C(4′)−C(41)−C(42)	−48.2(7)	−64.0(6)
N(3′)−C(4′)−C(41)−C(46)	136.6(5)	116.9(5)
C(5′)−C(4′)−C(41)−C(42)	66.9(7)	52.3(7)
C(5′)−C(4′)−C(41)−C(46)	−108.3(6)	−126.7(6)
Coplanarity of Atoms (Å)		
ring atoms of N(1)⋯C(6) pyridine ring	0.044	0.047
ring atoms of C(41)⋯C(46) phenyl ring	0.025	0.018
ring atoms of O(1′)⋯C(5′) H_2−oxazole ring	0.138	0.013
N(1), N(3′), Pd(1), Cl(1), Cl(2)	0.120	0.127
Dihedral Angles Formed by Least-Squares Planes through Planar Moieties (deg)		
pyridine ring and phenyl ring	87.8(2)	87.8(2)
pyridine ring and H_2−oxazole ring	1.8(2)	5.1(2)
pyridine ring and N(1), N(3′), Pd(1), Cl(1) and Cl(2)	17.2(1)	19.4(1)
phenyl ring and H_2−oxazole ring	87.8(2)	92.2(2)
phenyl ring and N(1), N(3′), Pd(1), Cl(1) and Cl(2)	104.3(2)	104.3(2)
H_2−oxazole ring and N(1), N(3′), Pd(1), Cl(1) and Cl(2)	17.7(1)	17.5(1)
Conformation Parameters[b,c] of the Puckered H_2−Oxazole Ring in Molecule A		
puckering amplitude[b] (Å)	0.098(5)	
phase coordinate ϕ[b] (deg)	142(3)	
low value asymmetry param[c] (Å)	$\Delta C_s = 0.002(3)$ at C(5′A)	
Conformation of the H_2−Oxazole Ring in A		
	"near envelope"	

[a] Calculated with the program PARST.[20] [b] Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354. [c] Nardelli, M. *Acta Crystallogr.* **1983**, *C39*, 1141.

Table 3. Bond Distances (Å) and Bond Angles (deg) in Possible Intermolecular Interactions in 3[a]

		distance			
atoms involved	sym	donor⋯acceptor	D−H	H⋯acceptor	angle ∠D−H⋯A
C(1″a)−H(1″a)⋯Cl(2a)	*x*, *y*, *z*	3.107(3)	0.97	2.67	108
C(1″a)−H(1#a)⋯Cl(2a)	*x*, *y*, *z*	3.107(3)	0.97	2.60	113
O(2#a)−H(2#a)⋯Cl(2a)	*x*, *y*, *z*	2.903(3)	0.82	2.31	130
C(1″b)−H(1″c)⋯Cl(2b)	*x*, *y*, *z*	3.106(4)	0.97	2.63	111
C(1″b)−H(1#c)⋯Cl(2b)	*x*, *y*, *z*	3.106(4)	0.97	2.68	107
O(2#b)−H(2#b)⋯O(2#a)	*x*, *y*, *z*	3.416(5)	0.97	2.96	117
O(2#b)−H(2#a)⋯Cl(2b)	*x*, *y*, *z*	2.800(4)	0.82	2.16	135
C(1″a)−H(1#a)⋯Cl(2a)	*x*, *y*, *z*	3.107(3)	0.97	2.60	113
C(1″a)−H(1″b)⋯O(1′b)	$-x+2, y+0.5, -z+0.5$	3.438(5)	0.97	2.75	129
C(42a)−H(42a)⋯O(2#b)	$-x+1, y+0.5, -z+0.5$	3.468(7)	0.93	2.78	132
O(2″a)−H(2″a)⋯Cl(1b)	$-x+1, y+0.5, -z+0.5$	3.223(3)	0.82	2.42	168
C(44a)−H(44a)⋯O(2#b)	$-x+1.5, -y+2, z-0.5$	3.034(7)	0.93	2.33	133
C(45a)−H(45a)⋯O(2#a)	$-x+1.5, -y+2, z-0.5$	3.045(7)	0.93	2.52	116
C(44a)−H(44a)⋯O(2″b)	$-x+1.5, -y+2, z-0.5$	3.540(8)	0.93	2.71	150
C(4b)−H(4b)⋯Cl(2b)	$x+1, y, z$	3.435(7)	0.93	2.77	129
O(2″b)−H(2″b)⋯Cl(1a)	$-x+2, y-0.5, -z+0.5$	3.187(4)	0.82	2.51	142
C(42b)−H(42b)⋯O(2#a)	$-x+2, y-0.5, -z+0.5$	3.501(7)	0.93	2.64	154
C(44b)−H(44b)⋯O(2″b)	$-x+1.5, -y+1, z-0.5$	3.176(7)	0.93	2.53	127

[a] The esd's, where given, are in parentheses. The H atom positions and disorder sites were not refined (see text).

Figure 3) and, about 9.2 kJ/mol above this minimum, another one with a dihedral angle of 178° (D, Figure 3). The transition state for rotation was found at 18.4 kJ/mol, with a dihedral angle of 149° (E, Figure 3). In accordance with what was found in the solid state, the conformation with the smaller dihedral angle was shown to be stabilized by hydrogen bonding of the hydroxy proton to the chloride ion. The O−H bond in C is indeed slightly elongated (0.02 Å) compared to the O−H bond in D.

As a comparison, the conformations of the $PdCl_2$ and the Pd(II) allyl complexes of the O-methylated ligand (**5** and **6**) were calculated. In contrast to the above complexes, only one minimum, with an N−C−C−O dihedral angle close to 180°, was found for **5** and **6**.

We then proceeded to the (π-allyl)- and (1,3-diphenyl-π-allyl)palladium(II) complexes of the achiral ligand (**7** and **8**, respectively). In each complex, the ligand exhibited two conformational minima, similar to those found for the $PdCl_2$ complex (dihedral angles of −71 and 179°

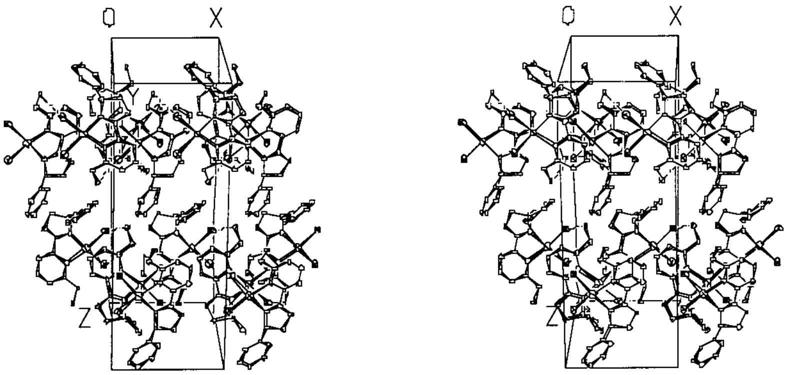


Figure 2. Stereo packing illustration of the crystal structure of **3**. The H atoms and the minor disorder sites of the alcoholic oxygens are excluded for clarity. Intermolecular O(−H)···Cl bonds and short Pd···Pd connections are indicated with dotted lines.

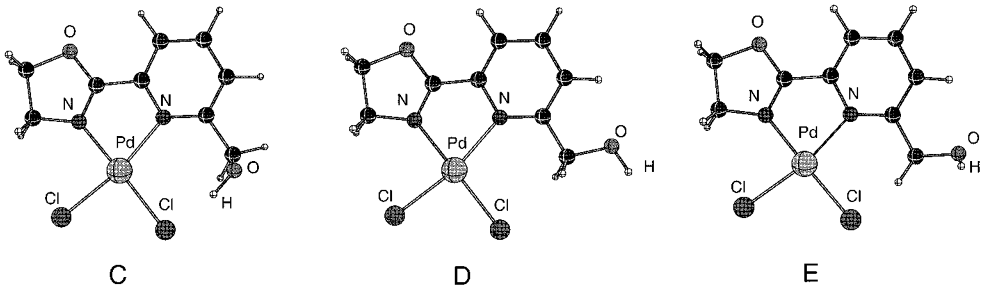


Figure 3. Calculated conformational minima (C and D) and the rotational transition state (E) of complex **4**.

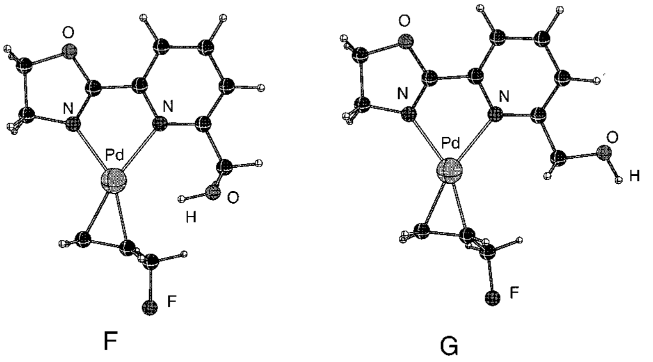
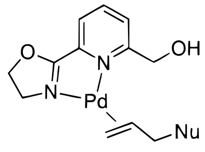


Figure 4. Calculated conformational minima (F and G) of complex **9**.

and of −85 and 178°, respectively). In these complexes, the essentially planar *anti* conformations were found to be more stable by 11.7 and 7.1 kJ/mol, respectively, than the conformation with the smaller N−C−C−O dihedral angle.

To represent the product of the catalytic reaction, the olefin Pd(0) complex **9**, obtained after nucleophilic attack (using F^- as a model of the nucleophile) at the π-allyl ligand, was subjected to calculations. Two minima (F and G, Figure 4) were found for this complex as well, but in contrast to the situation in the π-allyl complexes, the conformation with the smaller N−C−C−O dihedral angle (−57°; F, Figure 4) was now found to be more stable by 9 kJ/mol. It is interesting to note that our calculations predict the conformation with the smaller N−C−C−O dihedral angle to be more stable than the *anti* conformation only for the neutral complexes **4** and **9**. For these more electron-rich metal complexes the interaction between the hydroxy proton and the metal complex is probably stronger.

NMR Analysis. To elucidate the conformation of palladium(II) complexes of ligands of types **1** and **2** in solution, compounds **3** and **10**−**12** were subjected to ^{1}H NMR analysis. The ^{1}H NMR spectra of the chloride complexes **3** and **10** were assigned with the help of COSYgs, HMQCgs, and NOESY using standard pulse sequences. The assignments are shown in Table 4.



9

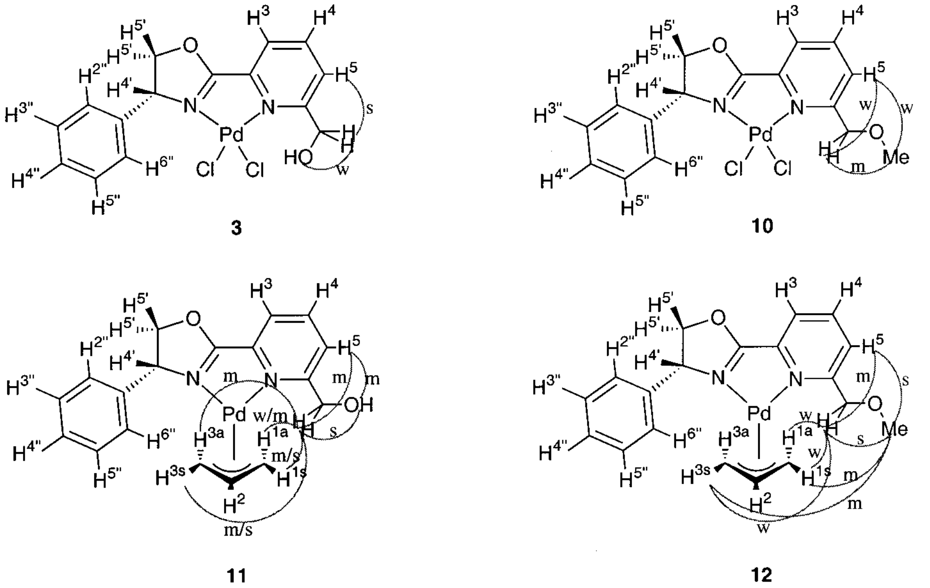
Rapid apparent allyl rotation in the π-allyl complexes **11** and **12** made it necessary to cool the samples in order to avoid coalescence of the signals. TOCSY and COSYgs experiments revealed two sets of five allyl protons in each complex, assumed to originate from two diastereomers, present in a ratio of 1:0.7 in both **11** and **12**. The exchange relationship between the hydrogen atoms in the two rotamers was investigated with EXSY. We were not able to determine the configuration of the major isomer, since interconversion of the two rotamers was rapid in relation to the mixing time in NOESY.

In all four complexes **3** and **10**−**12**, the expected NOEs between the methylene protons in the hydroxymethyl or methoxymethyl substituent and H^5 as well as between the methylene protons and the methoxy protons (in **10** and **12**) or the hydroxy proton (in **3** and **11**) were observed (Figure 5). In **3**, no NOE was observed beween the hydroxy proton and H^5, whereas the corresponding protons in **11** exhibited an interaction of medium intensity, corroborating the different relative stabilities of the two minimum-energy conformations of the two complexes, as observed by DFT calculations. Interactions between the methoxy protons and H^5 in **10**

Table 4. ^{1}H NMR^a

	3 (J_{H-H})	**10** (J_{H-H})	**11**, major (J_{H-H})	**11**, minor (J_{H-H})	**12**, major (J_{H-H})	**12**, minor (J_{H-H})
H^3	7.78 (7.9, 1.4)	8.05 (8.2)	8.24 (4.6)	8.24 (4.6)	8.04 (7.9)	8.04 (7.9)
H^4	8.14 (7.7)	8.15 (7.8)	7.97 (4.5)	7.97 (4.5)	8.28 (7.8)	8.28 (7.8)
H^5	7.89 (7.6, 1.3)	7.86 (7.4, 1.3)	8.24 (4.6)	8.24 (4.6)	8.02 (7.9)	8.02 (7.9)
C$\mathbf{H}_2$OH/Me	5.00 + 4.93 (13.9, 8.1)	5.20 + 4.95 (17.1)	4.83 (6.0)	4.81 (6.0)	4.57 + 4.53 (15.0)	4.57 + 4.53 (15.0)
OCH_3		3.49 (s)			3.57 (s)	3.57 (s)
OH	4.50 (8.1)		3.40 (5.5)	3.39 (6.0)		
$H^{4'}$	5.75 (10.1, 5.2)	5.72 (10.1, 5.2)	5.47 (9.7)	5.59 (9.8)	5.57 (9.7)	5.69 (9.7)
$H^{5'}$	5.27 (10.1, 9.1)	5.27 (10.0, 9.1)	5.36 (10.2)	5.38 (9.9)	5.40 (10.2)	5.42 (11.5)
$H^{5'}$	4.88 (8.9, 5.3)	4.87 (9.0, 5.2)	4.77 (9.0)	4.72 (9.1)	4.76 (8.9)	4.69 (9.0)
$H^{2''+6''}$	7.46−7.31 (m)	7.44−7.35 (m)	7.41 + 7.30 (7.5)	7.41 + 7.30 (7.5)	7.4 + 7.31 (7.5)	7.4 + 7.31 (7.5)
$H^{3''+4''+5''}$	7.46−7.31 (m)	7.44−7.35 (m)	7.5 (m)	7.5 (m)	7.49 + 7.36 (m)	7.49 + 7.36 (m)
H^{1s}			4.63 (6.1)	3.33 (3.8)	4.45 (7.1)	3.38 (6.2)
H^{1a}			3.21 (12.7)	3.03 (12.4)	3.15 (12.2)	3.17 (8.0)
H^2			5.50 (m)	5.29 (m)	5.53 (m)	5.32 (m)
H^{3s}			3.79 (7.0)	4.65 (5.9)	3.91 (6.3)	4.48 (7.5)
H^{3a}			2.36 (12.6)	3.32 (11.1)	2.39 (12.7)	3.29 (12.6)

^{a} The shifts are in ppm relative to TMS, and coupling constants J_{H-H} (in parentheses) are in Hz. The spectra were measured at 500 MHz in $CDCl_3$, at 25 °C for **3**, −15 °C for **10**, −10 °C for **11**, and −33 °C for **12**.



3 **10** **11** **12**

Figure 5. NOEs of complexes **3** and **10**−**12** represented as gray curves, their relative strengths being denoted with s (strong), m (medium), or w (weak). To normalize the NOE integrals, signals were compared to the NOE signal between H^4 and $H^{5/3}$ present in all complexes. Signals as large as or larger than this signal are denoted (s), those larger than half of this signal (m). Only NOE correlations to the methylene and the hydroxy/methoxy moieties are shown.

and **12** are in accordance with the preferred planar *anti* conformations suggested by the theoretical investigation.

A common feature of the two π-allyl complexes **11** and **12** is the interaction between protons in the hydroxymethyl and methoxymethyl groups, respectively, with both termini of the allylic moiety, indicating apparent allyl rotation.[7] This interconversion was rapid enough to cause coalescence of signals at room temperature in both **11** and **12** (Figure 6), and therefore all measurements had to be perfomed with cooling. The activation enthalpy for apparent allyl rotation was estimated by measuring the coalescence temperature of protons in the two complexes and was shown to be significantly higher (7.4 kJ/mol) for **11** than for **12**. As **11** differs from **12** only by the presence of a hydroxy instead of a methoxy moiety, the difference in apparent allyl rotation is assumed to be related to an interaction between the allyl and the hydroxy/methoxy units. This interaction may be related to the different conformational preferences

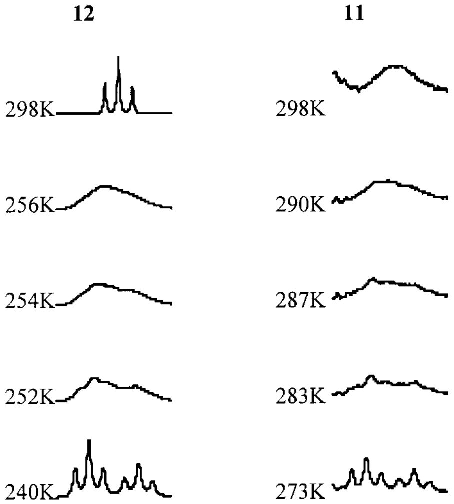


Figure 6. Coalescence of the signals from $H^{5'}$, at δ 4.77/4.72 in **11** and at δ 4.76/4.69 in **12**.

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of the two types of ligands, as deduced by the present calculations.

Discussion

Palladium-catalyzed allylic alkylations are known to proceed via the reversible[8] formation of a (π-allyl)-palladium(II) complex formed by oxidative addition of an allylic substrate, commonly an allylic acetate or carbonate, to Pd(0), followed by nucleophilic attack at the π-allyl fragment on the face *trans* to the metal ion, to form a (π-olefin)palladium(0) complex.[9] A variety of bidentate ligands with phosphorus, nitrogen, and sulfur as donor atoms have been shown to catalyze the reaction.[10] With chiral ligands highly enantioselective formation of products has frequently been achieved.[11] The enantiodiscrimination is related to the type of substrate used and can occur during the oxidative addition or during the nucleophilic attack.[10] With substrates yielding *meso* allyl groups, the enantioselectivity is determined by the regiochemistry of the nucleophilic attack, an event that occurs outside the coordination sphere of the metal ion, distant from the chiral ligand.

With asymmetric (C_1-symmetric) ligands at least two diastereomeric (π-allyl)palladium complexes may form. The relative rate of reaction of the two complexes depends only on the free energy of the transition states leading to product, since the barrier to interconversion of the two diastereomeric complexes is low (Curtin−Hammett conditions).[9] It has been shown that, at least under certain conditions, the reaction is exothermic and that the stabilities of the transition states are reflected in the stability of the diastereomeric reactants and, thus, that the major complex leads to the major product.[9] However, a late transition state has also been suggested to better explain the results under certain conditions,[12] and in a sterically congested system, a strongly rotated allyl ligand “prepared for” a TS having a Pd(0) olefin-like structure was observed by X-ray crystallography.[13] It thus seems relevant to consider the reactivity of the starting π-allyl complex as well as the stability and the structure of the product olefin complex.[14]

With C_2-symmetric ligands the asymmetry in the (π-allyl)palladium complex originates solely in the different steric environments at the two allylic termini, whereas with C_1-symmetric ligands donor atoms with different *trans* influences may be employed, leading to electronic desymmetrization as well. The carbon atom at the allylic terminus with the longer distance to Pd is preferentially attacked by the nucleophile.[15] Steric congestion may lead to different Pd−C distances, and a strong *trans* influence of a donor is manifested in a longer Pd−C bond *trans* to that donor.[16]

Figure 7. Topology of Pd(0) olefin (A) and Pd(II) π-allyl (B) complexes of (hydroxyalkyl)pyridinooxazolines with R^*,R^* absolute configuration.

(Methoxyalkyl)pyridinooxazolines (**2**) with R^*,S^* absolute configuration are expected to adopt a pseudo-C_2 symmetry (A, Figure 7), whereas those with R^*,R^* absolute configuration are assumed to exhibit the conformation shown in B (Figure 7). The former structures lead to high enantioselectivity and the latter to low. In allyl complexes of (hydroxyalkyl)pyridinooxazolines with R^*,R^* absolute configuration the situation is similar to that in (methoxyalkyl)pyridinooxazolines with the same absolute configuration (B). However, as the palladium-catalyzed allylic alkylation proceeds toward the olefin complex, the higher energy conformational minimum becomes lower in energy. The topology thereby changes to the situation represented by A (Figure 7), with the hydroxy group serving as the bulky substituent. This conformational change accounts well for the experimental results, explaining the different behavior of the two types of ligands.

Conclusion

The conformations of Pd(II) complexes of (hydroxyalkyl)pyridinooxazolines and (methoxyalkyl)pyridinooxazolines have been deduced by X-ray crystallography, DFT calculations, and NMR measurements. The study showed that in palladium-catalyzed allylations using the former type of ligand, a conformational change takes place which explains the different behavior of the two types of ligands in the catalytic process.

Experimental Section

All NMR spectra were recorded in $CDCl_3$; ^1H NMR spectra were obtained at 500 MHz and ^{13}C NMR spectra at 125 MHz. (4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)-pyridine (**1a**) and (4′*R*)-2-(3′,4′-dihydro-4′-phenyl-2′-oxazolyl)-6-(methoxymethyl)pyridine (**1b**) were prepared as previously described.[4b]

[(4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine]palladium(II) Chloride (3). A solution of $PdCl_2(PhCN)_2$ (75 mg, 0.197 mmol) in benzene (16 mL) was added to **1a** (50 mg, 0.197 mmol) under nitrogen. After the solution was stirred at room temperature for 16 h, it was centrifuged. The solvent was removed, and the remaining solid was washed twice with dry benzene and then dried under vacuum, resulting in **3** as a yellow solid, which was used without further purification for the NMR experiments. ^{13}C NMR (at 25 °C): δ 145.2, 140.9, 138.7, 132.0, 129.6, 129.4, 127.4, 125.3, 79.7, 66.1, 64.7. Not all quaternary carbons were observed. Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_2Pd$: C, 41.74; H, 3.27; Cl, 16.43; N, 6.49. Found: C, 41.88; H, 3.42; Cl, 16.19, N, 6.37.

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[(4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(methoxymethyl)pyridine]palladium(II) Chloride (10). A solution of $PdCl_2(PhCN)_2$ (8.4 mg, 0.022 mmol) in benzene (2 mL) was added to **2a** (6.0 mg, 0.022 mmol) under nitrogen. After it was stirred at room temperature for 2 h, the reaction mixture was worked up in the same way as for **3**. The yellow solid obtained was used without further purification for the NMR experiments. ^{13}C NMR (at −15 °C): δ 169.9, 168.2, 144.2, 140.5, 138.9, 129.6, 129.4, 129.1, 127.5, 125.0, 79.7, 74.7, 65.9, 59.7.

[(4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine](η^3-propenyl)palladium Hexafluorophosphate (11). (4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(hydroxymethyl)pyridine (**1a**; 50.0 mg, 197 μmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (36.0 mg, 99 μmol), and $AgPF_6$ (49.7 mg, 197 μmol) were mixed with CH_2Cl_2 (7.5 mL), and the resulting suspension was degassed at −78 °C for 15 min. The vessel was sealed under nitrogen and heated to 50 °C for 2 h. After it was cooled to room temperature, the suspension was filtered through Celite under dry conditions. Evaporation of the solvent yielded a solid (slightly yellow foam) which was used without further purification for the NMR experiments. The compound existed in solution as a mixture of two rapidly interconverting complexes in the ratio 1:0.7. ^{13}C NMR (at −15 °C): δ 170.7, 170.6, 164.6, 143.5, 141.7, 138.8, 130.0, 128.3, 128.0, 127.8, 124.6, 115.9, 115.7, 112.1, 79.9, 69.5, 67.4, 64.5, 64.1, 63.5, 61.5, 61.2. Anal. Calcd for $C_{18}H_{19}F_6N_2O_2PPd$: C, 39.54; H, 3.50; N, 5.12. Found: C, 39.31; H, 3.40; N, 4.96.

[(4′*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(methoxymethyl)pyridine](η^3-propenyl)palladium Hexafluorophosphate (12). This compound was prepared from (4′*R*)-2-(3′,4′-dihydro-4′-phenyl-2′-oxazolyl)-6-(methoxymethyl)pyridine (**2a**; 8.7 mg, 32 μmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (5.9 mg, 16 μmol), and $AgPF_6$ (16 mg, 64 μmol) as described for **11**. The product (a colorless oil) existed in solution as a mixture of two rapidly interconverting complexes in the ratio 1:0.7. ^{13}C NMR (at −33 °C): δ 170.5, 170.3, 161.4, 161.3, 144.2, 141.9, 139.1, 130.0, 129.9, 129.3, 128.7, 128.3, 128.2, 128.0, 127.7, 125.1, 116.2, 116.0, 80.1, 76.3, 69.4, 63.9, 63.3, 62.1, 61.8, 59.9, 59.8. Anal. Calcd for $C_{19}H_{21}F_6N_2O_2PPd$: C, 40.69; H, 3.77; N 5,00. Found: C, 40.57; H, 3.77; N, 4.88.

X-ray Crystallographic Analysis of 3. Yellow, needle-shaped crystals of **3** were grown from acetonitrile (mp 232 °C). X-ray intensity data were collected at room temperature using a STOE imaging plate diffraction system[17] equipped with a high-intensity rotating molybdenum anode. The derived F^2 values were corrected for background, Lorentz, polarization, and absorption effects. The numerical absorption correction was carried out using the STOE X-shape and X-red programs,[18] with the transmission factors varying between 0.86 and 0.93. The unit cell dimensions were refined against the calculated setting angles of 5000 selected reflections.[17] The structure was solved by application of the Patterson method and was completed and refined using the SHELXL-93 program package.[19]

There are two crystallographically independent molecules in the asymmetric unit (molecules A and B). Difference electron density ($\Delta\rho$) calculations showed that the alcoholic O(2″)−H(2″) groups are disordered in both complexes (Figure 1, A and B), occupying two possible positions with different probabilities. The hydrogen atoms were assumed to be in ideal positions, calculated using geometric evidence. In the final stage of the refinement the positions of the non-hydrogen atoms were refined together with their anisotropic displacement parameters, and isotropic vibration parameters were refined for the H atoms. Furthermore, the disordered alcoholic O(2″)−H(2″) groups were held riding on their C(1″) atoms, and the sum of the site occupation factors (sof) of each pair of disorder sites was made equal to 1. Anisotropic displacement parameters were refined for the major oxygen positions (isotropic for the minor ones), and fixed isotropic vibration parameters (1.2/1.5 times of that of the parent non-hydrogen atoms for the major/minor H disorder sites, respectively) were given for the partially occupied H positions. The sof of the major/minor disorder sites were refined to 0.915(14)/0.085(14) and 0.794(13)/0.206(13) for molecules A and B, respectively. Crystal data and further details of the data reduction and structure refinement calculations are shown in Table 1. The relatively low value of the refined Flack asymmetry parameter[19] (−0.07(3)) indicates that the crystal contains the compound **3** in optically pure form, and the final coordinates in Table 2 refer to the right enantiomer. Hence, the chiral C(4′) atom has the *R* absolute configuration in both molecules, as shown in Figure 1. The SHELXL-93[19] and PARST[20] programs were used for the geometrical calculations, and the illustrations were drawn using the XP routine of the SHELXTL/PC[21] software package.

DFT Calculations. Geometries and energies of all intermediates were calculated using the gradient-corrected hybrid density functional method B3LYP.[22] This popular and computationally relatively cheap method has been shown to predict reliable geometries and energetics.[23] We used a basis set of double-ζ valence quality labeled LANL2DZ in the Gaussian98 program.[24] For Pd the core electrons were replaced by the relativistic electron core potential (ECP) developed by Hay and Wadt.[25] For nonmetal atoms the double-ζ basis sets of Huzinaga and Dunning were assigned.[26] We recalculated structures C and D using the 6-311G(d,p) basis set,[27] but only small geometrical differences were observed and the relative differences in energy did not change by more than 0.4 kJ/mol. In addition, the effect of solvent (dichloromethane) was calculated using the DPCM method[28] as implemented in Gaussian98 for structures F and G (Figure 4), but this did not effect the structures or their relative stabilities.

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^{1}H NOE Measurements. Complexes **3** and **10**−**12** were investigated using standard 2D-NOESY and 2D-ROESY pulse programs. The mixing times were varied for **10**−**12** to ensure that the NOE buildup was in the linear regime. For **3** a mixing time close to T_1 was selected in order to maximize correlation signals. To rule out the possibility for correlations being null due to crossover effects on the NOE signals, NOESY measurements were made at different temperatures on complexes **3** and **11** as well as ROESY measurements on **11**.

Measurement of Rotational Barriers. The signals from the $H^{5'}$ proton in the two interconverting complexes were chosen for measuring the coalescence temperature. The two signals from **12** were 31.8 Hz apart, and those from **11** were 28.8 Hz apart. The optimized coalescence temperature was measured to 254 K for **12** and 287 K for **11**. Formulas[29] applied to these values gave $k_c^{254\ K}$(**12**) = 70.7 s^{-1}, $k_c^{287\ K}$(**11**) = 64.0 s^{-1}, $\Delta G^{\ddagger}{}_c$(**12**) = 52.9 kJ/mol, and $\Delta G^{\ddagger}{}_c$(**11**) = 60.3 kJ/mol. No line shape analysis was performed.

Acknowledgment. This work was supported by the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Sciences. We gratefully acknowledge Parallelldatorcentrum (PDC) at the Royal Institute of Technology for providing computer facilities.

Supporting Information Available: Tables of fractional atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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