NOVEL PALLADIUM CHIRAL PHOSPHINO-OXAZOLINE COMPLEXES: CRYSTAL STRUCTURE STUDIES AND APPLICATION TO ASYMMETRIC HECK REACTION†

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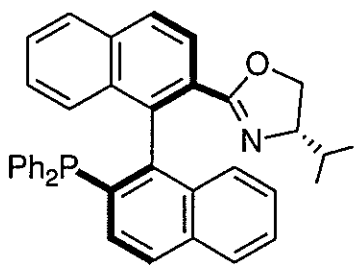
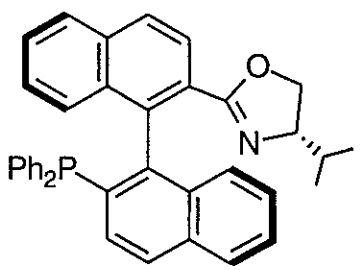
Abstract- The novel palladium(II) complexes coordinated with (*S,S*)- and (*S,R*)-2-[4-(isopropyl)oxazol-2-yl]-2'-diphenylphosphino-1,1'-binaphthyls (**1a** and **1b**) were prepared and their structures were determined by X-Ray crystallography. The X-Ray single crystal structure studies reveal that the axially chiral binaphthyl skeletons are more strongly regulating the chiral environment around the palladium centers than the chiral carbon centers in the oxazoline moieties. The results from application of **1a** and **1b** to the asymmetric Heck reaction also supported this conclusion. The highest enantioselectivity (88% ee) was observed in (*R*)-2-phenyl-2,5-dihydrofuran which was obtained from 2,3-dihydrofuran and phenyl triflate catalyzed by Pd/**1a**.

Recently, Ikeda[1] and we[2] independently reported a synthesis of a diastereomeric pair of new chiral phosphinooxazoline ligands, (*S,S*)- and (*S,R*)-2-[4-(isopropyl)oxazol-2-yl]-2'-diphenylphosphino-1,1'-binaphthyls (**1a** and **1b**). One of their structural characteristics is that the phosphinooxazolines (**1a**) and (**1b**) have two independent chiral elements, the binaphthyl axial chirality and the carbon central chirality on the oxazoline ring. Of the two chiral elements, the axial chirality plays more important role in the enantiocontrol at the palladium-catalyzed asymmetric allylic alkylation rather than the carbon central chirality on the oxazolines.[1,2] This observation prompted us to investigate the structural differences and/or similarities between the palladium complexes of **1a** and **1b**. The novel dichloro-palladium(II) complexes of



(*S,S*)-1a



(*S,R*)-1b

1a and **1b** were prepared and single crystal X-Ray crystallography determined their structures successfully. The ligand pair was also applied to the palladium-catalyzed asymmetric Heck reaction and it showed similar trend in the enantiocontrol to the palladium-catalyzed allylic alkylation. We report here our observations.

RESULTS AND DISCUSSION

Preparation of the Palladium Complexes. Stirring a dichloromethane solution of an equimolar mixture of $PdCl_2$(cod) and **1a** gives immediate conversion to $PdCl_2$[(*S,S*)-**1a**] (**2a**), quantitatively. A choice of the palladium precursor $PdCl_2$(cod) is important for clean conversion to and high yield of the product, since reaction of $PdCl_2(NCMe)_2$ with **1a** gives an impure product because of relative instability of the acetonitrile complex. Analytically pure complex (**2a**) was obtained in 89% isolated yield as a mono-CH_2Cl_2 adduct by slow diffusion of pentane into the concentrated dichloromethane solution at room temperature, though prolonged evacuation of the prismatic crystals of **2a**·CH_2Cl_2 at 100 °C gave a solvent-free complex in pure form. Only one signal is observed in a $^{31}P\{^1H\}$ NMR spectrum of the solvent-free product, and no significant trend is shown in its ^1H NMR spectrum.

The palladium complex $PdCl_2$[(*S,R*)-**1b**] (**2b**) was analogously prepared from $PdCl_2$(cod) and **1b** in 89% isolated yield and showed similar characteristics to those of **2a**.

$$PdCl_2(cod) + P\text{–}N \xrightarrow[25\ ^\circ C]{CH_2Cl_2} PdCl_2(P\text{–}N) + COD \qquad (1)$$

1a: (*S,S*)- **1b**: (*S,R*)- **2a**: (*S,S*)- **2b**: (*S,R*)-

X-Ray Crystal Structure Determination. Crystal structures of the both complexes are readily solved by X-Ray crystallography and shown in Figure 1. It reveals that each of the crystal contains one molecule of dichloromethane per palladium complex unit (co-crystallized dichloromethane molecules are omitted from the Figure for clarity). Selected crystallographic data of **2a** and **2b** are summarized in Table 1.

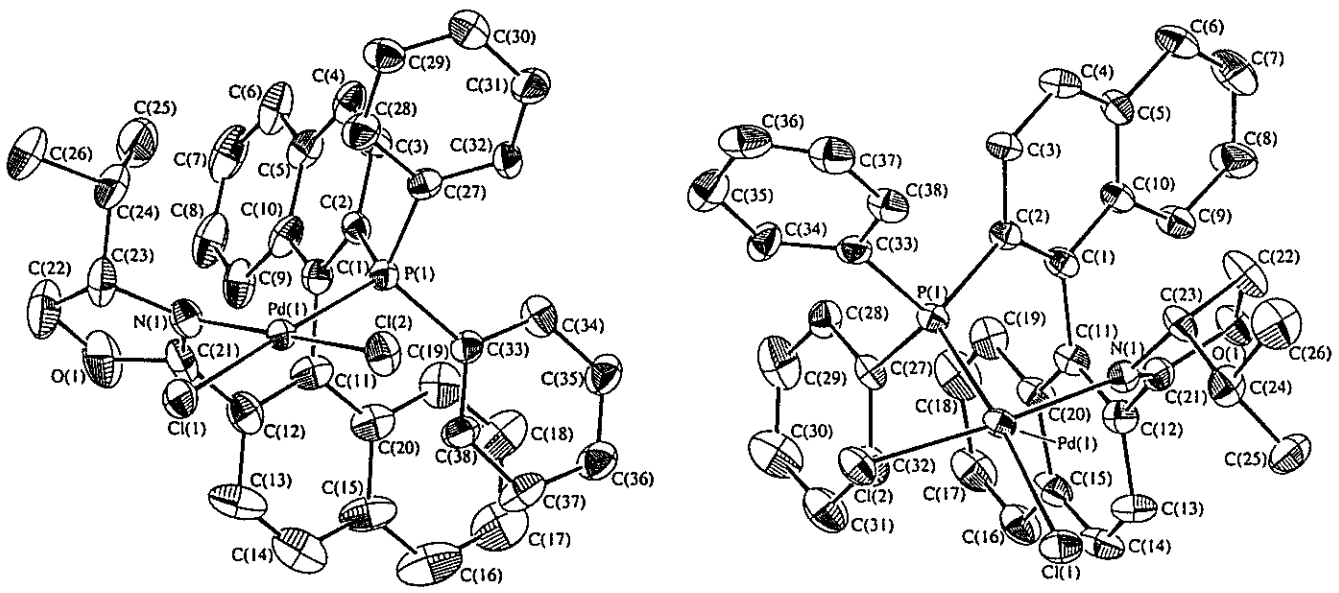


Figure 1. ORTEP drawings of the non-hydrogen atoms of **2a** (left) and **2b** (right) with atom numbering.

Table 1. Crystallographic data

	2a·CH_2Cl_2	**2b**·CH_2Cl_2
formula	$C_{39}H_{34}NOCl_4PPd$	$C_{39}H_{34}NOCl_4PPd$
crystal system	orthorhombic	orthorhombic
a (Å)	15.1 (1)	14.272 (4)
b (Å)	20.0 (1)	20.945 (4)
c (Å)	12.19 (9)	12.344 (5)
V (Å^3)	3676 (39)	3689 (1)
Z	4	4
fw (g/mol)	811.89	811.89
space group	$P2_12_12_1$	$P2_12_12_1$
T (°C)	23.0	23.0
λ (Å)[a]	0.71069	0.71069
D_{calc} (g/cm^3)	1.467	1.461
μ (cm^{-1})	8.71	8.68
$R(F_o)$[b]	0.056	0.051
$R_w(F_o)$[c]	0.052	0.051

[a] Graphite monochromator. [b] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [c] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$ where $w = 1/\sigma^2(|F_o|)$.

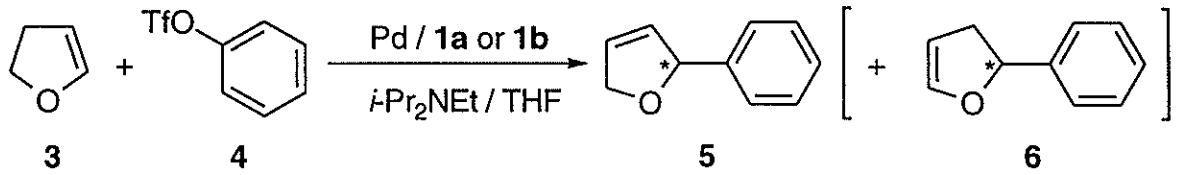
Table 2. Selected bond distances (Å) and angles (deg) for **2a**·CH_2Cl_2 and **2b**·CH_2Cl_2

2a·CH_2Cl_2		**2b**·CH_2Cl_2	
Pd(1)–Cl(1)	2.395 (3)	Pd(1)–Cl(1)	2.348 (3)
Pd(1)–Cl(2)	2.293 (3)	Pd(1)–Cl(2)	2.293 (3)
Pd(1)–P(1)	2.298 (3)	Pd(1)–P(1)	2.259 (3)
Pd(1)–N(1)	2.042 (9)	Pd(1)–N(1)	2.016 (8)
Cl(1)–Pd(1)–Cl(2)	91.32 (10)	Cl(1)–Pd(1)–Cl(2)	90.8 (1)
Cl(1)–Pd(1)–P(1)	175.7 (1)	Cl(1)–Pd(1)–P(1)	172.1 (1)
Cl(2)–Pd(1)–P(1)	84.37 (9)	Cl(2)–Pd(1)–P(1)	86.49 (10)
Cl(1)–Pd(1)–N(1)	86.6 (2)	Cl(1)–Pd(1)–N(1)	90.7 (2)
Cl(2)–Pd(1)–N(1)	177.7 (3)	Cl(2)–Pd(1)–N(1)	174.9 (2)
N(1)–Pd(1)–P(1)	97.6 (2)	N(1)–Pd(1)–P(1)	92.7 (2)

The angles of N(1)–Pd(1)–P(1) are larger than 90° (97.6° for **2a** and 92.7° for **2b**) due to the large bite angles of the chelating ligands.[3] In accordance with this, small distortion of the bond angles around the palladium centers is observed for both **2a** and **2b**. Though Pd(1), P(1), N(1), Cl(1), and Cl(2) are located on the same plane and sum of the angles between the adjacent coordination sites is nearly 360° (359.9° for **2a** and 360.7° for **2b**). The bond distances of Pd(1)-Cl(1), which are *trans* to the phosphine moieties, are longer than those of Pd(1)–Cl(2) indicating stronger *trans* influence of the phosphine ligands than the oxazoline moieties. The isopropyl groups in the oxazoline moieties are pointing away from the palladium centers in the structures of both **2a** and **2b**, indicating *less* importance of the carbon central chirality at C(23) for palladium-catalyzed asymmetric reactions, which is consistent with previous observations[1,2] and

studies on the asymmetric Heck reaction reported below. In the structure of **2a**, a π-stacking interaction can be seen between the C(11)-C(20) naphthylene and the C(33)-C(38) phenyl ring with the space of approximately 3.4 Å. A similar interaction is detected between the C(11)-C(20) naphthylene and the C(27)-C(32) phenyl in the structure of **2b** and the distance between the two parallel aryls is *ca.* 3.5 Å. These values are comparable to the distance between the stacking layers in graphite (3.35 Å).

Asymmetric Heck Reaction. Both of the diastereomeric ligands were examined in the asymmetric Heck reaction catalyzed by palladium complexes. It was found that a palladium complex generated *in situ* from $Pd_2(dba)_3$·(dba) and **1a** (2 equiv. to Pd) was an effective catalyst for the reaction of 2,3-dihydrofuran (**3**) with phenyl triflate (**4**). The Heck reaction proceeded smoothly at or above room temperature with high enantio- and regio-selectivity to afford the product (**5**) whose enantiomeric excess was 88% (entry 1 in Table 3). The purity of the product (**5**) was determined to be >99% by GC analysis and the regioisomer (**6**), which was a major product in the asymmetric Heck reaction catalyzed by $Pd(OAc)_2$/binap,[4] was not detected at all. The regioselectivity observed here is similar to that in a recent report by Pfaltz and co-workers where a phosphinooxazoline was used.[5] The absolute configuration (*R*) was determined by comparison of the specific rotation ($[\alpha]_D^{20}$ +210° (*c* 1.03, $CHCl_3$) for the product from entry 3) with that reported for (*S*)-**5**[4c] and the enantiomeric excess was determined by GC analysis using a chiral stationary phase column (CP-CHIRASIL-DEX-CB). The catalyst coordinated with **1b** showed better catalytic activity (i.e. a faster reaction) than with **1a**, but the enantioselectivity was slightly lower. As shown in the asymmetric allylic alkylation,[1,2] ligands (**1a**) and (**1b**), they have opposite configurations in respect to axial chirality on the binaphthyl backbones, induced opposite configurations in the product (**5**), respectively. This observation indicates that the axial chirality in ligands (**1a**) and (**1b**) is the more influential factor



3 **4** **5** **6** (2)

Table 3. Asymmetric Heck reaction of 2,3-dihydrofuran with phenyl triflate[a]

entry	ligand	temp/°C	time/h	conv./%[b]	yield/%[c]	% ee[d] (config[e])
1	**1a**	30	240	69	65	88 (*R*)
2	**1a**	50	48	100	87	85 (*R*)
3	**1a**	70	18	100	85	81 (*R*)
4	**1b**	30	168	100	84	80 (*S*)
5	**1b**	50	18	100	85	79 (*S*)
6	**1b**	70	3	100	85	74 (*S*)

[a] The reaction was carried out in THF in the presence of 3 mol % of the catalyst generated *in situ* from $Pd_2(dba)_3$·(dba) and the ligand. [b] Determined by GC analysis. [c] Isolated yield by preparative TLC on silica gel. [d] Determined by GC analysis with chiral stationary phase column, CP-CHIRASIL-DEX-CB. [e] Determined based on the sign of the specific rotation of the product (**5**).[4c]

determining the stereochemical outcome in the Heck reaction than the central chirality in the oxazoline unit, which has been supported by the X-Ray crystal structure studies described above.

EXPERIMENTAL SECTION

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk technique under predried nitrogen or with glovebox technique under prepurified argon. Tetrahydrofuran and Et_2O were distilled from benzophenone-ketyl under nitrogen prior to use. Dichloromethane was distilled from CaH_2 under nitrogen prior to use. (*S,S*)- And (*S,R*)-2-[4-(isopropyl)oxazol-2-yl]-2'-biphenylphosphino-1,1'-binaphthyls (**1a** and **1b**),[2] $PdCl_2$(cod),[6] $Pd_2(dba)_3$·(dba),[7] and phenyl triflate[8] were synthesized as reported. Tridecane was obtained from Wako Pure Chemical Industries. 2,3-Dihydrofuran was purchased from Tokyo Chemical Industry. Diisopropylethylamine was purchased from Aldrich Chemical Co. and used as received. Reaction progress was monitored by analytical TLC using 0.25 mm Merck F-254 silica gel glass plates. Visualization of the TLC plates was achieved by an UV illumination. NMR spectra were recorded on a JEOL JNM LA500 spectrometer (^{1}H, 500 MHz; ^{31}P, 202 MHz). ^{1}H NMR chemical shifts are reported in ppm downfield of internal tetramethylsilane. ^{31}P NMR chemical shifts are externally referenced to 85% H_3PO_4. Optical rotations were measured on a JASCO DIP-370 polarimeter. X-Ray crystallographic analyses were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Dichloro[(*S,S*)-2-[4-(isopropyl)oxazol-2-yl]-2'-diphenylphosphino-1,1'-binaphthyl]palladium (2a). A mixture of $PdCl_2$(cod) (25.7 mg, 0.090 mmol) and **1a** (50.6 mg, 0.092 mmol) in dichloromethane (2 mL) was stirred for 5 min at rt, then all the volatiles were removed under reduced pressure. The yellow residue was dissolved in a minimum amount of dichloromethane and recrystallized by slow diffusion of pentane into the concentrated dichloromethane solution at rt, yielding yellow prismatic crystals; yield 64.8 mg (89% as CH_2Cl_2 co-crystals). Although X-Ray crystallography showed co-crystallization with dichloromethane, prolonged evacuation of the crystals at 100 °C gave the solvent-free complex. mp 269-277 °C (decomp). ^{1}H NMR ($CDCl_3$, 25 °C): δ 0.09 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 7.1 Hz, 3H), 2.15-2.22 (m, 1H), 3.83 (t, J = 8.5 Hz, 1H), 4.47 (dd, J = 10.7 and 9.0 Hz, 1H), 5.10 (ddd, J = 12.5, 8.3, and 4.4 Hz, 1H), 6.26 (d, J = 8.3 Hz, 1H), 6.67-6.70 (m, 2H), 6.74-6.77 (m, 1H), 6.85-6.89 (m, 2H), 7.23 (ddd, J = 8.5, 6.8, and 1.2 Hz, 1H), 7.30 (ddd, J = 8.3, 6.8, and 1.0 Hz, 1H), 7.34 (t, J = 8.8 Hz, 1H), 7.49-7.55 (m, 6H), 7.69 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.94 (br, 2H), 8.02 (d, J = 8.5 Hz, 1H). ^{31}P{^{1}H} NMR ($CDCl_3$, 26 °C): δ 24.6 (s). $[\alpha]^{20}_D$ –416° (*c* 0.101, $CHCl_3$). Anal. Calcd for $C_{38}H_{32}NOCl_2PPd$: C, 62.78; H, 4.44; N, 1.93. Found: C, 62.60; H, 4.50; N, 1.82.

Dichloro[(*S,R*)-2-[4-(isopropyl)oxazol-2-yl]-2'-diphenylphosphino-1,1'-binaphthyl]palladium (2b). This complex was obtained as yellow prisms from $PdCl_2$(cod) (25.7 mg, 0.090 mmol) and **1b** (50.6 mg, 0.092 mmol) in dichloromethane (2 mL) and purified as described above; yield: 64.6 mg (89% as CH_2Cl_2 co-crystals). mp 281-287 °C (decomp). ^{1}H NMR ($CDCl_3$, 24 °C): δ 0.91 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.8 Hz, 3H), 2.98-3.05 (m, 1H), 3.50 (t, J = 9.5 Hz, 1H), 3.56-3.61 (m, 1H), 4.11 (t, J = 8.5 Hz, 1H), 6.24 (d, J = 8.3 Hz, 1H), 6.70 (td, J = 7.6 and 2.7 Hz, 2H), 6.79-

6.84 (m, 2H), 6.98 (d, J = 8.5 Hz, 1H), 7.25 (ddd, J = 8.5, 6.6, and 1.2 Hz, 1H), 7.32-7.37 (m, 3H), 7.45 (t, J = 8.8 Hz, 1H), 7.51-7.58 (m, 4H), 7.82 (d, J = 8.1 Hz, 1H), 7.85 (br, 2H), 7.92 (dd, J = 12.5 and 8.3 Hz, 2H), 8.03 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 25 °C): δ 24.8 (s). $[\alpha]^{20}_D$ +656° (*c* 0.10, $CHCl_3$). Anal. Calcd for $C_{38}H_{32}NOCl_2PPd$: C, 62.78; H, 4.44; N, 1.93. Found: C, 62.51; H, 4.45; N, 1.63.

X-Ray Structure Determination. ***(a) $PdCl_2$[(S,S)-1a].*** A crystal of suitable size was mounted on a glass fiber using an adhesive agent and it was then transferred to a goniostat for characterization and data collection. An automated search for peaks in the range $28.09° < 2\theta < 29.94°$ followed by analysis revealed a primitive orthorhombic cell. Following intensity data collection ($6° < 2\theta < 55°$), the additional conditions h ≠ 2n for h00, k ≠ 2n for 0k0, and l ≠ 2n for 00l, uniquely determined space group $P2_12_12_1$. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.67 to 1.00. The data were corrected for Lorentz and polarization effects.

The structure was solved by heavy-atom Patterson methods and expanded using Fourier techniques. The position of the palladium atom was obtained from an initial E-map. The positions of the remaining atoms, including hydrogens, were obtained from iterations of a least-squares refinement followed by a difference Fourier calculation. In the final cycles of refinement, the non-hydrogen atoms were varied with anisotropic thermal parameters and the hydrogen atoms were varied with isotropic thermal parameters. The final difference map was reasonably clean, the largest peak being 1.14 and the deepest hole –0.89 e/Å^3, respectively.

(b) $PdCl_2$[(S,R)-1b]. A small nearly equidimensional fragment was cleaved from a well-formed crystal affixed to the end of a glass fiber using an adhesive agent. The sample was then transferred to the goniostat for characterization and data collection ($6° < 2\theta < 55°$). A systematic search of a limited hemisphere of reciprocal space located a set of diffraction maxima with systematic orthorhombic space group $P2_12_12_1$. The data were collected using a standard moving crystal-moving detector technique with fixed backgrounds at each extreme of the scan. Data were corrected for Lorentz and polarization effects and equivalent reflections were averaged.

The structure was readily solved by a direct method (SIR92) and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropicaly in the full matrix least squares. A difference Fourier located the position of most hydrogen atoms, and all hydrogens were introduced as fixed atom contributors in the final cycles of refinement. A final difference Fourier was featureless, the largest peak being 0.87 and the deepest hole –0.60 e/Å^3, respectively.

Palladium-Catalyzed Asymmetric Heck Reaction of 2,3-Dihydrofuran with Phenyl Triflate: Typical Procedure (entry 4 in Table 3). A mixture of $Pd_2(dba)_3$·(dba) (6.9 mg, 6.0 μmol) and the phosphinooxazoline (**1b**) (13.2 mg, 24.0 μmol) in THF (1 mL) was stirred under N_2 at rt for 30 min. To this mixture, phenyl triflate (90.4 mg, 400 μmol), tridecane (36.9 mg, 200 μmol) which was an internal standard for GC analysis, additional THF (2 mL), and diisopropylethylamine (140 μL, 800 μmol) were added. The flask was then immersed in a bath maintained at 30 °C. Then 2,3-dihydrofuran (121 μL, 1.60 mmol) was added to the reaction mixture, and the homogeneous solution was stirred for 7

days. The conversion of **3** was determined by a GC analysis. The reaction mixture was diluted with pentane and the resulting suspension was filtered through a pad of silica gel. The reaction mixture was further eluted with Et_2O and the obtained solution was concentrated to give an oily residue. This crude product was purified by preparative TLC on silica gel (eluent: hexane/EtOAc = 10/1) to give 2-phenyl-2,5-dihydrofuran (**5**) in pure form; yield 49.0 mg (84%). The enantiomeric purity was determined to be 80% ee by GC analysis with chiral stationary phase column (CP-CHIRASIL-DEX-CB).

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REFERENCES AND NOTES

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