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SYNTHESIS OF CHIRAL 2,6-BIS[1-(*N*-PIPERIDINYL)ETHYL]-PYRIDINES AND CRYSTAL STRUCTURES OF THEIR METAL COMPLEXES

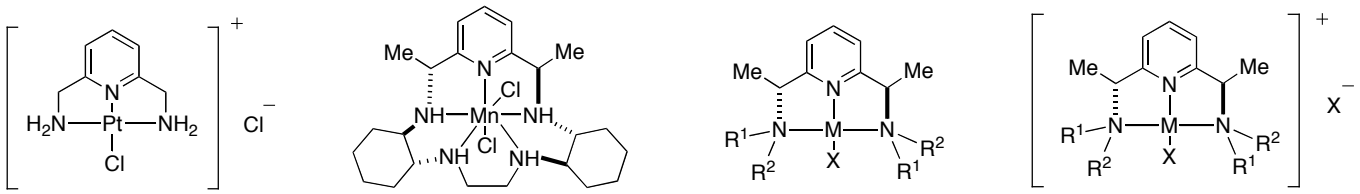
Jun'ichi Uenishi* and Taro Takami

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan
E-mail: juenishi@mb.kyoto-phu.ac.jp

Abstract – (*R,R*)- and (*S,S*)-2,6-bis[1-(*N*-cycloamino)ethyl]pyridines (**3**) were prepared from (*S,S*)- and (*R,R*)-pyridine-2,6-bis(1-hydroxyethyl) dimethane sulfonates (**2**) stereospecifically. Pd, Cu, and Zn complexes with **3** were synthesized, and their crystal structures were determined by X-ray analysis.

INTRODUCTION

Chiral ligands have been widely used in coordination chemistry and asymmetric organic synthesis.[1] Pincer-type ligand and metal complexes have been investigated in detail.[2] Metal *N,N,N*-pincer ligand complexes having a pyridine ring in the center of the molecule have been reported. Such complexes include Ru-complex,[3] Zn-complex,[4] Pd-complex,[5] Mn- and Cr-complexes,[6] Ln-complexes,[7] Ta-complex,[8] Fe- and Co-complexes,[9] Cu-complex,[10] Pt-complex,[11] Rh-complex.[12] Interesting feature has been shown not only in their structures[13,14] but also in their specific biological activities. Pt-2,6-bis(aminomethyl)-pyridine complex exhibits potent cytotoxic activity for breast cancer epithelial cells,[15] and chiral non-racemic Mn complexes has indicated a potent superoxide dismutase inhibitory activity.[16] Their structures are shown in Figure 1.



(ref. 15) (ref. 16) **3a-c** (***R,R***)**-4,5,7,8**

Figure 1

This paper is dedicated to Prof. Yoshito Kishi on the occasion of his 70th birthday.

We have developed an efficient method for the synthesis of chiral non-racemic heteroatom substituted 2-ethylpyridines[17] and recently have reported the synthesis of 2,6-bis(1-aminoethyl)pyridines.[18] Pincer-type chiral metal-pyridine complexes could be prepared from these chiral pyridines. We report here the preparation of enanitomerically pure chiral 2,6-bis[1-(*N*-cycloamino)ethyl]pyridines (**3**) and their Pd, Cu and Zn complexes (**4-8**).

RESULTS AND DISCUSSION

We have reported the stereospecific substitution of chiral 2-(1-hydroxyethy)pyridine with heteroatom nucleophiles via its methanesulfonate.[17] Chiral non-racemic 2,6-bis[1-(*N*-cycloamino)ethyl]pyridine ligands (**3**) can be derived from stereospecific substitution of chiral non-racemic 2,6-bis[(-hydroxyethyl)pyridines (**1**) and (**1'**) via their methanesulfonates (**2**) and (**2'**). Treatment of (*S,S*)-pyridine-2,6-bis(1-hydroxyethyl) dimethanesulfonates (**2a**) with an excess of piperidine in acetonitrile at 60 °C gave (*R,R*)- 2,6-bis[1-(*N*-piperidinyl)ethyl]pyridine (**3a**) in 94% yield. This reaction proceeded with inversion of the configuration. Reactions with morpholine and pyrrolidine also took place and gave the corresponding substituted pyridines (**3b**) and (**3c**) in 86% and 74% yields, respectively. On the other hand, the substitution of **2'** with piperidine gave **3a'** in 97% yield, of which specific degree indicated an opposite polarity to that of **3a**.

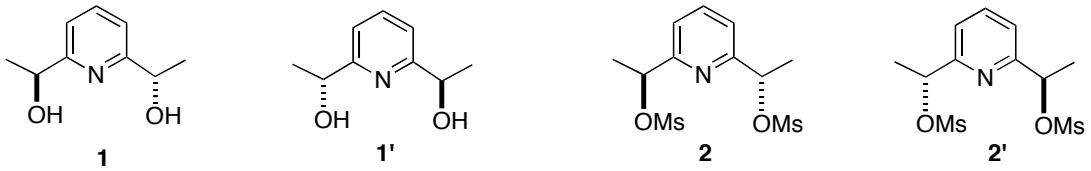
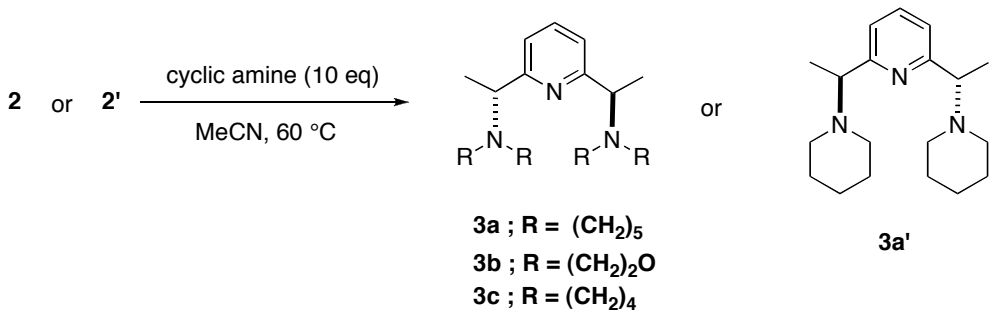


Figure 2. Structures of chiral pyridines 1 and 2

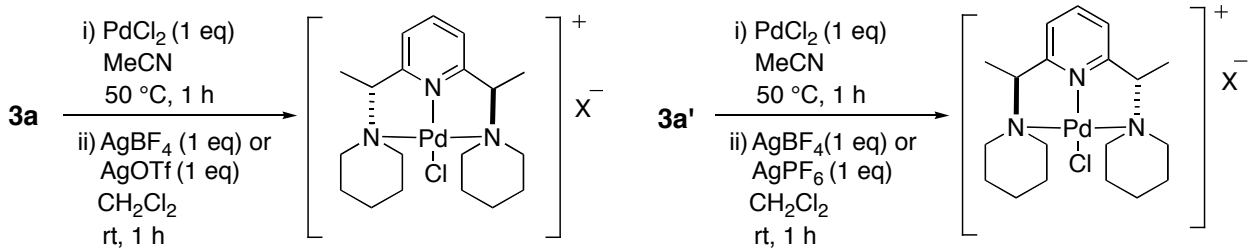


Scheme 1. Synthesis of compounds 3

Preparation of Pd complex

When $PdCl_2$ and **3a** were heated in CH_3CN, a Pd complex was formed. After a chloride anion was

replaced with tetrafluoroborate anion, the complex **(*R,R*)-4** was obtained in 97% yield as yellow crystals. **(*R,R*)-5** was also obtained with trifluoromethanesulfonate anion as yellow crystals in 49% yield. The corresponding enantiomer **(*S,S*)-4** was prepared in 90% yield from **3a'**, and hexafluorophosphate **(*S,S*)-6** was also prepared in 76% yield as yellow crystals.

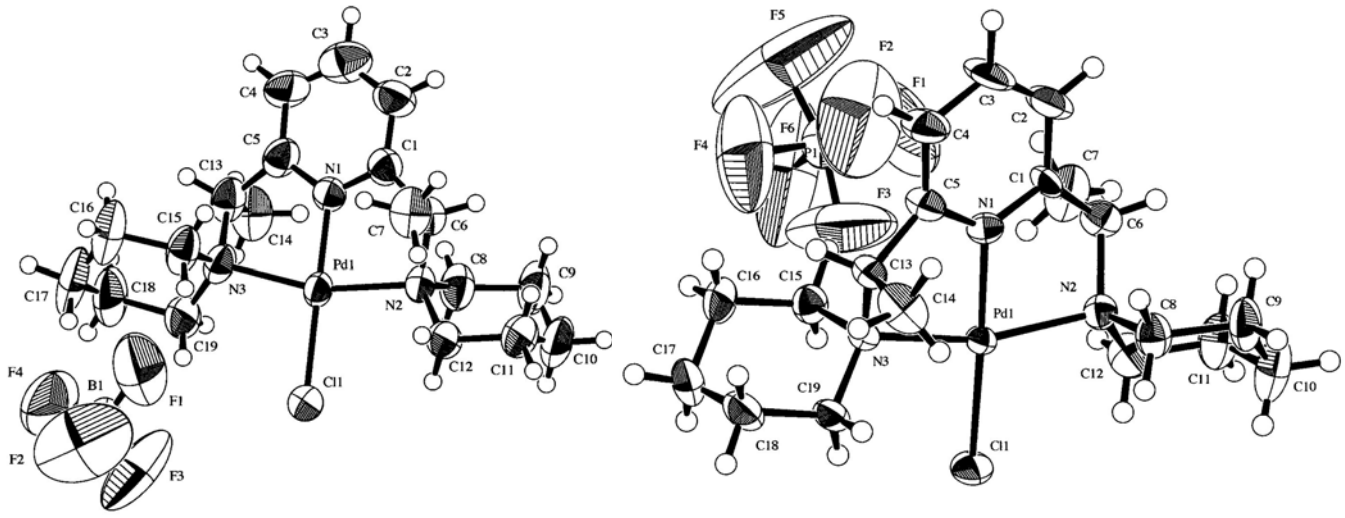


(*R,R*)-4 (X = BF_4)
(*R,R*)-5 (X = OTf)

(*S,S*)-4 (X = BF_4)
(*S,S*)-6 (X = PF_6)

Scheme 2

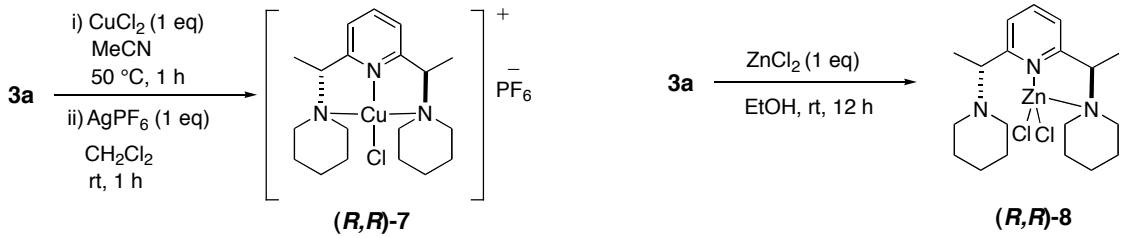
All of these single crystals can be subjected to X-ray crystallographic analysis. The ortep views of **(*R,R*)-4,** and **(*S,S*)-6** are shown in Figure 3. The bond distances of N1-Pd1, N2-Pd1, N3-Pd1 and Cl1-Pd1 for **(*R,R*)-4** are 1.920, 2.093, 2.098 and 2.304 Å, respectively. The bond angles of N2-Pd1-N1, N3-Pd1-N1, N1-Pd1-Cl1, N3-Pd1-N2, N2-Pd1-Cl1 and N3-Pd1-Cl1 are 81.2, 81.5, 177.2, 162.7, 99.0 and 98.2. Pd is located approximately in the center of the plane of three nitrogen and chlorine atoms. Other Pd complexes also possess very similar three-dimensional structures.



(*R,R*)-4 **(*S,S*)-6**

Figure 3. Ortep views of (*R,R*)-4 and (*S,S*)-6

Copper complex **(*R,R*)-7** was also synthesized from **3a** with $CuCl_2$ in 86% yield by a method similar to that used for the preparation of Pd complex **(*S,S*)-6**. On the other hand, a Zn complex was produced simply by stirring of **3a** with $ZnCl_2$ in ethanol overnight. Complex **(*R,R*)-8** was obtained in 57% yield.



Scheme 3

The structure of the blue crystals **(*R,R*)-7** is shown in Figure 4. The bond distances of N1-Cu1, N2-Cu1, N3-Cu1 and Cl1-Cu1 for **(*R,R*)-7** are 1.910, 2.102, 2.105 and 2.163 Å, respectively. The bond angles of N2-Cu1-N1, N3-Cu1-N1, N1-Cu1-Cl1, N3-Cu1-N2, N2-Cu1-Cl1 and N3-Cu1-Cl1 are 80.5, 79.8, 179.8, 160.3, 99.4 and 100.2, respectively. The Cu complex shows a planer structure, but the Cl1-Cu1 bond was shorter than the Cl1-Pd1 bond. On the other hand, Zn complex shows neutral unsymmetrical figure. Only two nitrogen atoms were coordinated on the Zn atom. The distance between Zn and one of the piperidine nitrogen atoms (N3-Zn1) was 2.529 Å, which is out of the general Zn-N coordination distance range, between 1.60-2.40 Å.

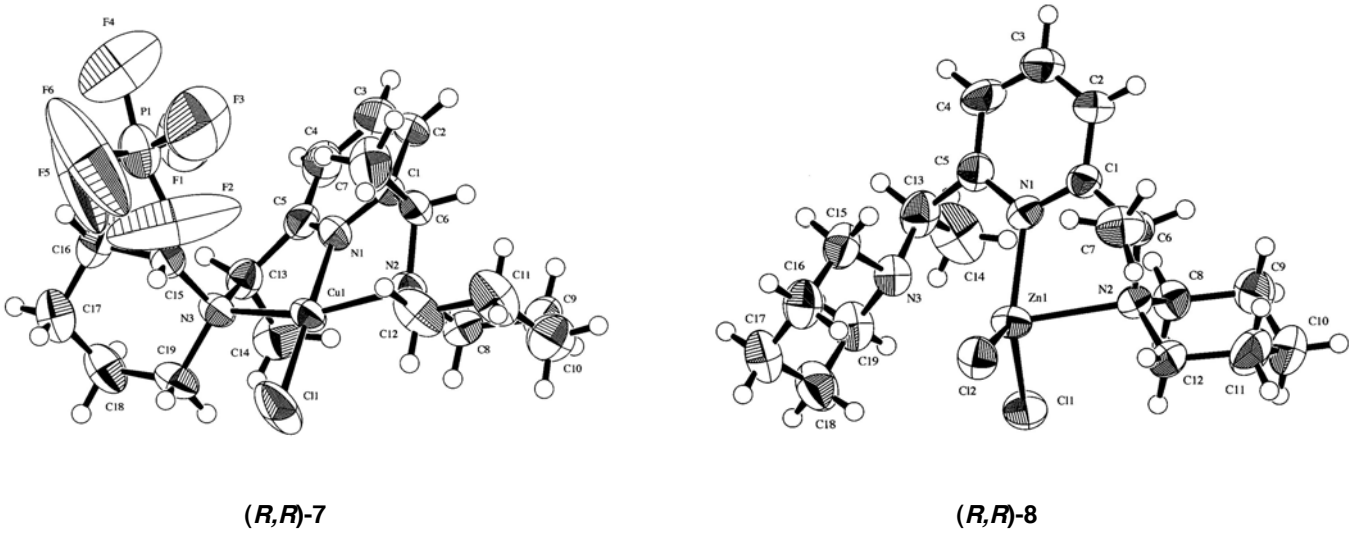


Figure 4. Ortep views of (*R,R*)-7 and (*R,R*)-8

In summary, we have synthesized optically pure (*R,R*)- and (*S,S*)-2,6-bis[1-(*N*-piperidinyl)ethyl] pyridines and have revealed the crystal structure of their Pd, Cu, and Zn complexes. The Pd and Cu complexes exhibit square planar structure, while the triamine ligand **3a'** is employed as a bidentate ligand in the

formation of a Zn complex.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL-300 (300 MHz and 75 MHz) spectrometer in $CDCl_3$ or CD_3COCD_3 with tetramethylsilane as an internal standard or $CDCl_3$. MS spectra were obtained on JMS-GC mate and JMS-SX 102A QQ instruments. IR spectra were recorded on JASCO FT/IR-410 instrument. Thin layer chromatography (TLC) was performed with Merck $60F_{245}$ precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh) for gravity column.

General procedure for the substitution reaction of 2 and 2' with piperidine, morpholine and pyrrolidine: A mixture of chiral dismesylate **2** or **2'** (1.5 g, 4.6 mmol) and cyclic amine (10 eq, 46 mmol) in MeCN (27 mL) was heated at 60 °C for 10-30 min. Aq. $NaHCO_3$ was added to the mixture and it was extracted with EtOAc. The extract was washed with water and brine, and dried over $MgSO_4$. The residue was purified by column chromatography on silica gel eluted with 5% Et_3N containing EtOAc to give **3**.

(*R,R*)-2,6-Bis[1-(*N*-piperidinyl)ethyl]pyridine (3a). 94% yield. Light yellow oil. *Rf* = 0.52 (5% Et_3N in EtOAc). $[\alpha]_D^{22}$ +62 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, t, *J* = 7.7 Hz), 7.19 (2H, d, *J* = 7.7 Hz), 3.56 (2H, q, *J* = 6.6 Hz), 2.53-2.32 (8H, m), 1.60-1.53 (8H, m), 1.50-1.36 (4H, m), 1.38 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (2C), 136.2, 119.7 (2C), 66.6 (2C), 51.6 (4C), 26.2 (4C), 24.6 (2C), 18.4 (2C). MS (FAB) *m/z*: 302 (M^++H). FAB-MS *m/z*: 302.2601 (Calcd for $C_{19}H_{32}N_3$: 302.2596).

(*S,S*)-2,6-Bis[1-(*N*-piperidinyl)ethyl]pyridine (3a'). 97% yield. Light yellow oil. $[\alpha]_D^{27}$ –62 (*c* 0.3, $CHCl_3$).

(*R,R*)-2,6-Bis[1-(*N*-morpholinyl)ethyl]pyridine (3b). 86% yield. Light yellow oil. *Rf* = 0.41 (EtOAc). $[\alpha]_D^{25}$ +78 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, t, *J* = 7.7 Hz), 7.24 (2H, d, *J* = 7.7 Hz), 3.70 (8H, t, *J* = 4.7 Hz), 3.54 (2H, q, *J* = 6.6 Hz), 2.60-2.36 (8H, m), 1.37 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (2C), 136.7, 120.0 (2C), 67.1 (4C), 66.6 (2C), 51.1 (4C), 18.5 (2C). MS (FAB) *m/z*: 306 (M^++H). FAB-MS *m/z*: 306.2175 (Calcd for $C_{17}H_{28}N_3O_2$: 306.2182).

(*R,R*)-2,6-Bis[1-(*N*-pyrrolidinyl)ethyl]pyridine (3c). 74% yield. Light yellow oil. *Rf* = 0.41 (5% Et_3N in EtOAc). $[\alpha]_D^{25}$ +104 (*c* 0.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, t, *J* = 7.7 Hz), 7.24 (2H, d, *J* = 7.7 Hz), 3.43 (2H, q, *J* = 6.6 Hz), 2.64-2.61 (4H, m), 2.42-2.39 (4H, m), 1.77 (8H, t, *J* = 6.6 Hz), 1.41 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (2C), 136.9, 119.4 (2C), 67.2 (2C), 52.6 (4C), 23.4 (4C), 22.1 (2C). MS (EI) *m/z*: 274 (M^+). EI-MS *m/z*: 274.2279 (Calcd for $C_{17}H_{27}N_3$: 274.2283).

Preparation of metal-triamine complex. $PdCl_2$ (68 mg, 0.381 mmol) was heated in MeCN (4 mL) at 50 °C for 20 min. An CH_3CN (1 mL) solution of **3a** or **3a'** (115 mg, 0.381 mmol) was added to the $PdCl_2$ solution, and the mixture was heated at 50 °C for 1 h with stirring. Solvent was removed under reduced pressure and a CH_2Cl_2 (5 mL) solution of $AgBF_4$ (74 mg, 0.381 mmol) was added at rt. The mixture was stirred for 1 h and the precipitates were collected. Yellow crystals were recrystallized from a mixture of ether and CH_2Cl_2.

Chloro{(1'*R*,1''*R*)-2,6-bis[1-(1-piperidinyl-κ*N*)ethyl]pyridine-κ*N*}palladium(II) tetrafluoroborate ((*R*,*R*)-4). 97% yield. Yellow crystals. mp 218-220 °C (decomp.). $[\alpha]_D^{28}$ -59 (*c* 0.25, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, t, *J* = 7.7 Hz), 7.79 (2H, d, *J* = 7.7 Hz), 4.90 (2H, q, *J* = 6.4 Hz), 3.66-3.50 (4H, m), 3.16-3.08 (4H, m), 2.09-1.50 (12H, m), 1.82 (6H, d, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (2C), 142.7, 122.2 (2C), 69.1 (2C), 59.7 (2C), 55.6 (2C), 22.9 (2C), 22.5 (2C), 21.4 (2C), 20.4 (2C). *Anal*. Calcd for $C_{19}H_{31}N_3BClF_4Pd$: C, 43.05; H, 5.89; N, 7.93. Found: C, 42.89; H, 5.99; N, 7.72. Crystal Data. Empirical Formula : $C_{19}H_{31}N_3BClF_4Pd$, Crystal System : monoclinic, Space Group : $P2_1$ (#4), Lattice Parameters : a = 12.146(1)*Å* , b = 7.340(1)*Å* , c =13.7057(8)*Å* , β = 112.522(5)°, V = 1128.6(2)*Å*^{3}, Z value : 2, D_{calc} : 1.560 g/cm^3, μ (Cu Kα) : 80.95 cm^{-1}, Residuals : R = 0.051 ; Rw = 0.108.

Chloro{(1'*R*,1''*R*)-2,6-bis[1-(1-piperidinyl-κ*N*)ethyl]pyridine-κ*N*}palladium(II) trifluoromethanesulfonate ((*R*,*R*)-5). 49% yield. Yellow crystals. mp 221-223 °C (decomp.). $[\alpha]_D^{26}$ -47 (*c* 0.25, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, t, *J* = 7.7 Hz), 7.84 (2H, d, *J* = 7.7 Hz), 4.92 (2H, q, *J* = 6.6 Hz), 3.68-3.51 (4H, m), 3.16-3.12 (4H, m), 2.15-1.55 (12H, m), 1.83 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (2C), 142.7, 122.3 (2C), 69.2 (2C), 59.7 (2C), 55.7 (2C), 22.9 (2C), 22.5 (2C), 21.5 (2C), 20.5 (2C). *Anal*. Calcd for $C_{20}H_{31}N_3ClF_3PdS$: C, 40.55; H, 5.27; N, 7.09. Found: C, 40.59; H, 5.41; N, 7.01. Crystal Data. Empirical Formula: $C_{20}H_{31}N_3O_3ClF_3PdS$, Crystal System: orthorhombic, Space Group: $P2_12_12_1$ (#19), Lattice Parameters: a = 10.198(9)*Å*, b = 712.187(9)*Å* , c =19.80(1)*Å*, V = 2460(3)*Å*^{3}, Z value : 4, D_{calc} : 1.599 g/cm^3, μ (Mo Kα) : 9.97 cm^{-1}, Residuals : R = 0.071 ; Rw = 0.122.

Chloro{(1'*S*,1''*S*)-2,6-bis[1-(1-piperidinyl-κ*N*)ethyl]pyridine-κ*N*}palladium(II) tetrafluoroborate ((*S*,*S*)-4). 90% yield. Yellow crystals. mp 218-220 °C (decomp.). $[\alpha]_D^{24}$ +53 (*c* 0.3, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, t, *J* = 7.7 Hz), 7.79 (2H, d, *J* = 7.7 Hz), 4.91 (2H, q, *J* = 6.6 Hz), 3.66-3.49 (4H, m), 3.15-3.08 (4H, m), 2.10-1.53 (12H, m), 1.82 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (2C), 142.7, 122.2 (2C), 69.2 (2C), 59.7 (2C), 55.6 (2C), 23.0 (2C), 22.5 (2C), 21.4 (2C), 20.4 (2C). Crystal Data. Empirical Formula : $C_{19}H_{31}N_3BClF_4Pd$, Crystal System : monoclinic, Space Group : $P2_1$ (#4), Lattice Parameters : a = 12.1550(7)*Å* , b = 7.330(7)*Å* , c =13.6815(5)*Å* , β = 112.598(3)°, V =

1125.4(1)Å^3, Z value : 2, D_{calc} : 1.564 g/cm^3, μ (Cu Kα) : 81.18 cm^{-1}, Residuals : R = 0.032 ; Rw = 0.089.

Chloro{(1'*S*,1''*S*)-2,6-bis[1-(1-piperidinyl-κ*N*)ethyl]pyridine-κ*N*}palladium(II) hexafluorophosphate ((*S,S*)-6). 76% yield. Yellow crystals. mp 223-226 °C (decomp.). $[\alpha]_D^{28}$ +52 (*c* 0.25, acetone). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.53 (1H, t, *J* = 8.1 Hz), 7.05 (2H, d, *J* = 8.1 Hz), 4.28 (2H, q, *J* = 7.0 Hz), 2.94-2.75 (4H, m), 2.56-2.39 (4H, m), 1.29-0.85 (12H, m), 1.16 (6H, d, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, CD_3COCD_3) δ 164.3 (2C), 143.4, 122.6 (2C), 70.4 (2C), 60.3 (2C), 56.3 (2C), 23.7 (2C), 22.7 (2C), 22.3 (2C), 21.3 (2C). *Anal.* Calcd for $C_{19}H_{31}N_3ClF_6PPd$: C, 38.79; H, 5.31; N, 7.14. Found: C, 38.71; H, 5.42; N, 7.06. Crystal Data. Empirical Formula: $C_{19}H_{31}N_3ClF_6PPd$, Crystal System : orthorhombic, Space Group : $P2_12_12_1$ (#19), Lattice Parameters: a = 12.242(3)Å, b = 19.700(3)Å, c =10.083(8)Å, V = 2431.7(8)Å^3, Z value: 4, D_{calc} : 1.607 g/cm^3, μ (Cu Kα) : 83.10 cm^{-1}, Residuals: R = 0.077 ; Rw = 0.183.

Chloro{(1'*R*,1''*R*)-2,6-bis[1-(1-piperidinyl-κ*N*)ethyl]pyridine-κ*N*}copper(II) hexafluorophosphate ((*R,R*)-7). $CuCl_2$ (45 mg, 0.332 mmol) was heated in MeCN at 50 °C for 20 min. Then, a solution of **3a** (100 mg, 0.332 mmol) in MeCN (1 mL) was added and the mixture was heated at 50 °C for 1 h. MeCN was removed and the residue was dissolved in CH_2Cl_2. $AgPF_6$ was added and the mixture was stirred for 1 h. The precipitates were collected and recrystallized from a mixture of MeOH and Et_2O gave **(*R,R*)-7** (156 mg) in 86% yield. Blue crystals. mp 221-223 °C (decomp.). *Anal.* Calcd for $C_{19}H_{31}N_3ClCuF_6P$: C, 41.84; H, 5.73; N, 7.70. Found: C, 41.93; H, 5.80; N, 7.67. Crystal Data. Empirical Formula: $C_{19}H_{31}N_3ClCuF_6P$, Crystal System: monoclinic, Space Group : $P2_1$ (#4), Lattice Parameters: a = 9.0578(8)Å, b = 15.1274(6)Å, c = 9.1162(7)Å, β = 108.233(6)°, V = 1186.4(1)Å^3, Z value: 2, D_{calc} : 1.527 g/cm^3, μ (Cu Kα): 35.11 cm^{-1}, Residuals: R = 0.057 ; Rw = 0.138.

{(1'*R*,1''*R*)-2-[1-(1-piperidinyl-κ*N*)ethyl]-6-[1-(1-piperidinyl)ethyl]pyridine-κ*N*}zinc(II) chloride ((*R,R*)-8). A mixture of **3a** (235 mg, 0.78 mmol) and $ZnCl_2$ (22 mg, 0.16 mmol) in EtOH (4.3 mL) was stirred for 12 h at rt. The precipitates were collected and dissolved in CH_2Cl_2. Pentane was added and white precipitates was collected. Recrystallization from a mixture of EtOH and CH_2Cl_2 gave **(*R,R*)-8** (40 mg) in 57% yield. mp 252-253 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, t, *J* = 7.7 Hz), 7.35 (2H, t, *J* = 7.7 Hz), 4.30 (2H, q, *J* = 6.8 Hz), 3.28-3.11 (4H, m), 1.56 (4H, s), 1.92-1.50 (12H, m), 1.57 (6H, d, *J* = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (2C), 141.2, 122.2 (2C), 60.1 (2C), 50.6 (4C), 24.0 (4C), 21.7 (2C), 17.6 (2C). MS (FAB) *m/z*: 436 (M^++H). FAB-MS *m/z*: 436.1265 (Calcd for $C_{19}H_{31}N_3Cl_2Zn$: 436.1262). *Anal.* Calcd for $C_{19}H_{31}N_3Cl_2Zn$: C, 52.13; H, 7.14; N, 9.60. Found: C, 52.25; H, 7.18; N, 9.55.

Crystal Data. Empirical Formula: $C_{19}H_{31}N_3Cl_2Zn$, Crystal System : orthorhombic, Space Group : $P2_12_12_1$ (#19), Lattice Parameters: a = 13.639(1)*Å*, b = 16.430(1)*Å*, c =9.5190(9)*Å* , V = 2133.2(3)$Å^3$, Z value: 4, D_{calc} : 1.363 g/cm^3, μ (Cu Kα) : 39.40 cm^{-1}, Residuals: R = 0.059 ; Rw = 0.088.

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