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Convenient Resolution of (±)-Piperidine-2-carboxylic Acid ((±)-Pipecolic Acid) by Separation of Palladium(II) Diastereomers Containing Orthometallated (*S*)-(−)-1-[1-(Dimethylamino)ethyl]naphthalene

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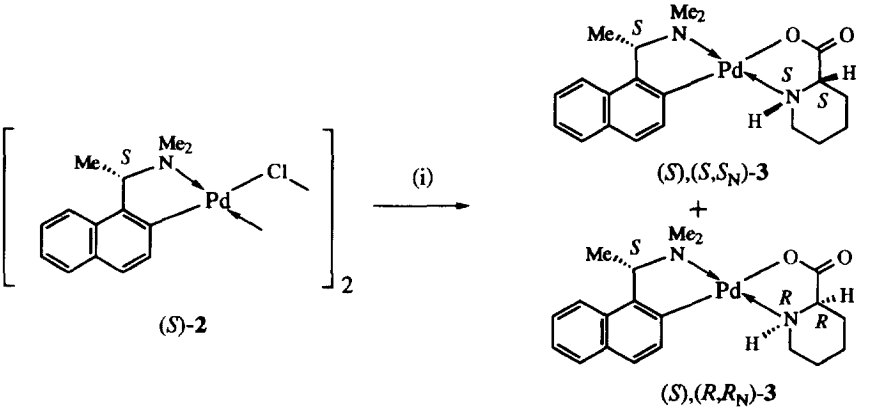
Abstract: (±)-Piperidine-2-carboxylic acid ((±)-pipecolic acid) has been resolved by the fractional crystallisation of diastereomeric palladium(II) complexes containing orthometallated (*S*)-(−)-1-[1-dimethylamino)ethyl]naphthalene. The enantiomers of the acid were liberated from the individual configurationally homogeneous diastereomers of the complex in high yield with $[\alpha]_D \pm 26.0$ (*c* 1.00, H_2O). The crystal and molecular structures of both diastereomers of the complex have been determined.

(*S*)-(−)-Piperidine-2-carboxylic acid ((*S*)-(−)-pipecolic acid) **1** is a naturally occurring non-proteinogenic amino acid of interest as a starting material for synthetic peptides,[1] local anaesthetics,[2] potential enzyme inhibitors,[3] and as a constituent of the potent immunosuppresant FK-506.[4] The (*S*)-acid can be obtained by the resolution of the racemate with (*L*)-tartaric acid[5] or by synthesis from (*L*)-lysine.[6,7] Several asymmetric syntheses of the (*S*)-acid have also been devised, the latest being a four-step synthesis from 2-cyano-6-phenyloxazolopiperidine in 47% overall yield.[8] Here we report that the sodium salt of (±)-**1** reacts with the readily prepared resolving complex di-μ-chlorobis[(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthalenyl-C^2,*N*]dipalladium(II)−1-dichloromethane, (*S*)-**2**·CH_2Cl_2,[9] to give the diastereomers (*S*),(*S*,S_N)- and (*S*),(*R*,R_N)-**3**, which can be separated by fractional crystallisation and individually treated with hydrochloric acid to give the respective hydrochlorides of the enantiomerically pure enantiomers of (±)-**1** and regeneration of (*S*)-**2**.

Results and Discussion

A suspension of (*S*)-**2**·CH_2Cl_2 in methanol reacts with sodium (±)-pipecolate (2 equiv.) at room temperature to give an almost colourless solution of an equimolar mixture of (*S*),(*S*,S_N)- and (*S*),(*R*,R_N)-**3** (Scheme 1). After concentration to ca. half-volume, the solution yields the (*S*),(*S*,S_N) diastereomer in 80% yield. Additional crystalline less-soluble diastereomer was obtained from the mother liquor by removal of solvent and re-dissolution of the residue in a small quantity of methanol. A single recrystallisation of the less soluble fraction from methanol afforded configurationally homogeneous (*S*),(*S*,S_N)-**3** in 80% yield as almost colourless prisms having $[\alpha]_D$ +161.3 (*c* 1.01, $CHCl_3$). The more soluble diastereomer was recovered from the combined mother liquors by removal of solvent and recrystallisation of the residue from chloroform–diethyl ether: pure (*S*),(*R*,R_N)-**3** formed almost colourless efflorescent needles and was isolated in 73% yield with $[\alpha]_D$ −32.3 (*c* 1.01, $CHCl_3$) after drying in vacuo. The ^1H NMR spectra of the (*S*),(*S*,S_N) and (*S*),(*R*,R_N)

diastereomers of **3** in chloroform-d_1 contain characteristic doublets centred at δ 7.04 ($^3J_{HH}$ = 8.31 Hz) and δ 6.92 ($^3J_{HH}$ = 8.31 Hz), respectively, for the γ naphthalene ring proton adjacent to the metallated carbon in each case. The NMR spectra also contain characteristic doublets for the CH*Me* and NMe_2 groups of each diastereomer, but the base-line separation of the upfield resonances for the γ-naphthalene-ring protons provides the most useful means of monitoring diastereomeric purity.

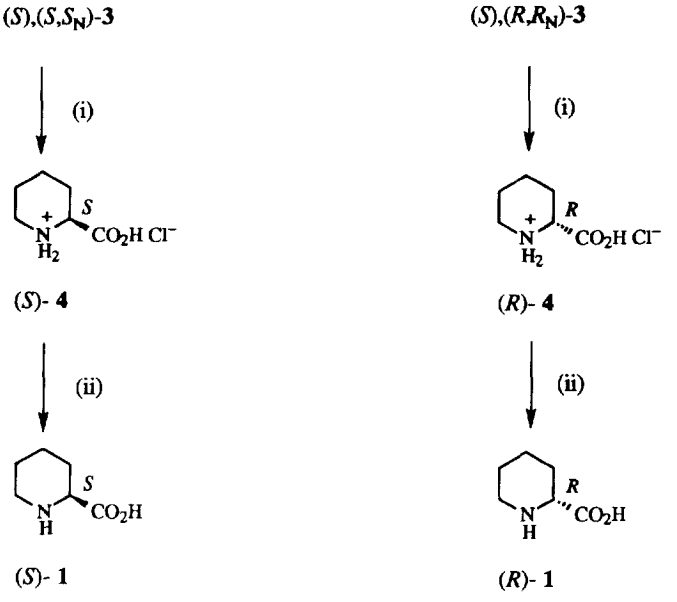


Scheme 1. *Reagents and conditions*: (i) Sodium (±)-pipecolate in methanol.

The crystal and molecular structures of $(S),(S,S_N)$-**3**·0.5Et_2O and $(S),(R,R_N)$-**3**·1.33$CHCl_3$ have been determined. Suitable crystals in each case were obtained from chloroform–diethyl ether. Crystal data for the complexes are listed in Table 1 and ORTEP plots of the molecules are given in Figures 1 and 2. In each of the structures, the coordination geometry around the palladium is slightly distorted from square-planar with the softer donor (pipecolate-*N* in this case) being situated trans to the dimethylamino group, which is typical for such complexes.[10] The five-membered metallacyclic ring in each diastereomer adopts the δ-envelope conformation in conjunction with an axial benzylic methyl group because of the unfavourable interaction between this methyl group and H4 of the naphthalene ring when it has the equatorial disposition in a ring of λ conformation.[11] The six-membered piperidine ring in each diastereomer of **3** has the chair conformation with the palladium and carboxylate substituents having equatorial and axial dispositions, respectively. The *R*,R** geometry of the two substituents in the ring is also found in the structure of the centrosymmetrical complex diaquabis(2-piperidinecarboxylato) copper(II),[12] but in the three other crystal structures of complexes of this amino acid reported the *R*,S** geometry having the diequatorial arrangement of the substituents was observed.[13] Indeed, it was concluded in an earlier work concerning the stereoselectivity of coordination of the *L*-acid that the trans-diequatorially substituted diastereomer was the only derivative possible on stereoelectronic grounds.[14]

The enantiomers of (±)-**1** were displaced from the respective diastereomers of **3** by treatment with 2 equiv. concentrated hydrochloric acid in methanol. The reaction with the acid led to the immediate precipitation of (*S*)-**2**, which was filtered off, dried, and recrystallised from dichloromethane for re-use as (*S*)-**2**·CH_2Cl_2. The *hydrochlorides* (±)-**4** were recovered from the respective mother liquors in high yields and subsequently converted into the parent *acids* with triethylamine in chloroform. Thus, enantiomerically pure (*S*)-**1** having $[\alpha]_D$ −25.9 (*c* 1.00, H_2O) was obtained from $(S),(S,S_N)$-**3**; (*R*)-**1** having $[\alpha]_D$ +25.5 (*c* 1.00, H_2O) was

similarly obtained from (*S*),(*R*,R_N)-**3**. The enantiomeric purities of the enantiomers of (±)-**1** were confirmed in each case by the quantitative re-preparation of the diastereomer from which it was derived by treatment with 1 equiv. aqueous sodium hydroxide followed by (*S*)-**2**·CH_2Cl_2 in chloroform-d_1, as determined by high resolution ^{1}H NMR spectroscopy.



Scheme 2. *Reagents and conditions*: (i) aq. HCl in methanol; (ii) triethylamine in chloroform.

Experimental

^{1}H NMR spectra were recorded at 34 °C on a Varian Gemini 300 spectrometer operating at 300.075 MHz. Optical rotations were measured at 20 °C on the specified solutions in a 1-dm cell with a Perkin Elmer Model 241 polarimeter. Specific rotations were estimated to be within ±0.5 10^{-1} deg cm^2 g^{-1}. Elemental analysis were determined by staff within the Research School of Chemistry.

(±)-Pipecolic acid was purchased from the Aldrich Chemical Company, Inc. Di-μ-chlorobis[(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthalenyl-C^2,*N*]dipalladium(II)–1-dichloromethane, (*S*)-**2**·CH_2Cl_2, was prepared and isolated in 92% yield as previously described.[9]

[SP-4-4]-[(S)-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C^2,N][(S,S_N)-2-piperidinecarboxylato-N,O] palladium(II) ((*S*),(*S*,S_N)-**3**). A suspension of (*S*)-**2**·CH_2Cl_2 (9.08 g, 11.9 mmol) in methanol (200 mL) was treated with sodium (±)-pipecolate (prepared from the acid (3.07 g, 23.8 mmol) and sodium hydroxide (0.96 g, 24.0 mmol)) and the mixture was stirred for 2 h. The almost colourless solution was then concentrated to ca. 100 mL, whereupon the almost colourless less-soluble diastereomer (*S*),(*S*,S_N)-**3** separated as a microcrystalline solid (4.2 g). An additional 0.7 g of the material was obtained by removal of the solvent from the mother liquor and redissolution of the residue in methanol (10 mL). A single recrystallisation of the combined less-soluble fraction from warm methanol afforded pure (*S*),(*S*,S_N)-**3** as almost colourless prisms

(4.1 g, 80%): mp 238–240 °C; $[\alpha]_D$ +161.3 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_2Pd$: C, 55.5; H, 6.1; N, 6.5. Found: C, 55.0; H, 6.6; N, 6.2. ^1H NMR ($CDCl_3$): δ 1.51 (m, 1 H, $C_{14}H$), 1.69 (m, 3 H, $C_{14}H$ and $2C_{13}H$), 1.84 (d, 3 H, ^3J = 6.41 Hz, $C_{17}Me$), 2.47 (m, 2 H, $C_{12}H$), 2.83 (s, 3 H, NMe), 2.84 (s, 3 H, NMe), 2.99 (m, 1 H, NH), 3.18 (m, 1 H, $C_{15}H$), 3.39 (m, 1 H, $C_{15}H$), 4.09 (m, 1 H, $C_{11}H$), 4.23 (q, 1 H, ^3J = 6.41 Hz, $C_{17}H$), 7.04 (d, 1 H, ^3J = 8.31 Hz, $C_{10}H$), 7.40 (m, 2 H, C_6H and C_5H), 7.51 (d, 1 H, ^3J = 8.31 Hz, C_9H), 7.61 (d, 1 H, ^3J = 8.25 Hz, C_4H), 7.81 (m, 1 H, C_7H). ^{13}C NMR ($CDCl_3$): δ 23.07 (C_{20}), 21.04 (C_{13}), 26.79 (C_{14}), 28.82 (C_{12}), 49.45 (C_{15}), 47.40 (C_{18}), 53.56 (C_{19}), 63.00 (C_{11}), 72.86 (C_{17}), 122.89 (C_{10}), 123.95 (C_7), 125.08 (C_6), 126.01 (C_9), 128.87 (C_5), 129.73 (C_4) 128.62, 131.63, 143.88, 148.76 (C_1, C_2, C_3 and C_8), 177.15 (C_{16}).

[SP-4-4]-[(S)-1-[1-(Dimethylamino)ethyl]-2-naphthalenyl-C^2,N][(R,R_N)-2-piperidinecarboxylato-N,O] palladium(II) ((*S*),(*R*,R_N)-**3**). After separation of (*S*),(*S*,S_N)-**3** from the original crystallisation, the mother liquor was evaporated to dryness and the residue was dissolved in chloroform (50 mL) and the solution was diluted with diethyl ether. Pure (*S*),(*R*,R_N)-**3** crystallised from the solution as almost colourless needles that effloresced upon drying in vacuo (3.7 g, 73%): mp 200–202 °C; $[\alpha]_D$ −32.3 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_2Pd$: C, 55.5; H, 6.1; N, 6.5. Found: C, 55.3; H, 5.8; N, 6.1. ^1H NMR ($CDCl_3$): δ 1.56 (m, 1 H, $C_{14}H$), 1.77 (m, 3 H, $C_{14}H$ and $2C_{13}H$), 1.77 (d, 3 H, ^3J = 6.41 Hz, $C_{17}Me$), 2.38 (m, 2 H, $C_{12}H$), 2.78 (s, 3 H, NMe), 2.88 (s, 3 H, NMe), 3.09 (m, 1 H, NH), 3.38 (m, 1 H, $C_{15}H$), 3.53 (m, 1 H, C_6H), 4.07 (m, 1 H, $C_{11}H$), 4.21 (q, 1 H, ^3J = 6.41 Hz, $C_{17}H$), 6.92 (d, 1 H, ^3J = 8.31 Hz, $C_{10}H$), 7.39 (m, 2 H, C_6H and C_5H), 7.50 (d, 1 H, ^3J = 8.31 Hz, C_9H), 7.60 (d, 1 H, ^3J = 8.24 Hz, C_4H), 7.80 (m, 1 H, C_7H). ^{13}C NMR ($CDCl_3$): δ 22.81 (C_{20}), 20.70 (C_{13}), 27.29 (C_{14}), 28.44 (C_{12}), 49.09 (C_{15}), 47.48 (NMe), 53.51 (NMe), 62.70 (C_{11}), 72.84 (C_{17}), 122.86 (C_{10}), 123.96 (C_7), 125.08 (C_6), 126.05 (C_9), 128.92 (C_5), 129.49 (C_4), 128.70, 131.67, 143.12, 149.02 (C_1, C_2, C_3 and C_8), 176.46 (C_{16}).

(S)-(−)-Piperidine-2-carboxylic Acid Hydrochloride ((*S*)-**4**). Concentrated hydrochloric acid (10 M, 0.758 mL, 7.58 mmol) was added to a stirred suspension of (*S*),(*S*,S_N)-**3** (1.64 g, 3.79 mmol) in methanol (20 mL). A bright yellow precipitate of (*S*)-**2** separated. After ca. 30 min., the (*S*)-**2** was filtered off, washed with water, and dried (1.22 g, 94%). The mother liquor was evaporated to dryness and the pale yellow residue was extracted with water, the extract filtered, and the solvent removed. Recrystallisation of the residue from methanol–diethyl ether afforded colourless needles of the pure *hydrochloride* (0.50 g, 80%): mp 254–257 °C; $[\alpha]_D$ −11.5 (*c* 1.07, H_2O). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.5; H, 7.3; N, 8.5. Found: C, 43.2; H, 7.2; N, 8.2. ^1H NMR (D_2O): δ 1.69 (m, 3 H, C_3H, C_4H and C_5H), 1.89 (m, 2 H, C_4H and C_5H), 2.29 (m, 1 H, C_3H), 3.04 (m, 1 H, C_6H), 3.46 (m, 1 H, C_6H), 3.91 (m, 1 H, C_2H). ^{13}C NMR (D_2O): δ 24.05 (C_4 and C_5), 28.44 (C_3), 46.55 (C_6), 59.55 (C_2), 174.46 (COO).

(S)-(−)-Piperidine-2-carboxylic Acid ((*S*)-**1**). Freshly distilled triethylamine (0.257 mL, 1.84 mmol) was slowly added to a stirred suspension of (*S*)-**4** (0.303 g, 1.83 mmol) in dry chloroform (5 mL) at room temperature. After 2 h the precipitate of (*S*)-**1** was filtered off, washed with cold chloroform, and dried (0.23 g, 98%). Recrystallisation of the crude product from methanol–diethyl ether afforded pure (*S*)-**1** as colourless needles (0.19g, 79%): mp 256–261 °C; $[\alpha]_D$ −25.9 (*c* 1.00, H_2O). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.8. Found: C, 55.7; H, 8.8; N, 10.8. ^1H NMR (D_2O): δ 1.61 (m, 2 H, C_4H and C_5H), 1.67 (m, 1 H, C_3H) 1.86 (m, 2 H, C_4H and C_5H), 2.20 (m, 1 H, C_3H), 2.99 (m, 1 H, C_6H), 3.39 (m, 1 H, C_6H), 3.56 (m, 1 H, C_2H). ^{13}C NMR (D_2O): δ 24.24, 24.53 (C_4 and C_5), 29.22 (C_3), 46.33 (C_6), 61.69 (C_2), 177.29 (COO).

(R)-(+)-Piperidine-2-carboxylic Acid ((*R*)-**1**) was obtained from (*S*),(*R*,R_N)-**3** by an identical procedure to the above in similar yield: $[\alpha]_D$ +25.5 (*c* 1.00, H_2O).

The enantiomeric purities of (*S*)-(−)- and (*R*)-(+)-**1** were confirmed by the quantitative re-preparation of (*S*),(*S*,S_N)- and (*S*),(*R*,R_N)-**3** by treatment of the free ligands with 1 equiv. sodium hydroxide followed by 0.5 equiv. (*S*)-**2**·CH_2Cl_2. The ^1H NMR spectra in each case indicated ≥ 99% enantiomeric purities of the enantiomers of (±)-**1** based on the corresponding signal-to-noise ratios.

X-Ray Crystal Structure Determinations: Both diastereomers of **3** were obtained as fractional solvates by recrystallisation from chloroform–diethyl ether. Because of ready loss of solvent of crystallisation from both complexes, a crystal in each case was selected from beneath the mother liquor, mounted quickly and transferred to the diffractometer fitted with a dinitrogen cryostream cooling device. The structures were solved by heavy-atom and direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the calculations but were not refined. All calculations were performed using the teXsan structure analysis software.[15]. Atomic coordinates, bond lengths and angles, and thermal parameters for both complexes have been deposited at the Cambridge Data Centre.

Table 1. Crystal Data and Experimental Parameters for X-ray Structure Analyses

	(S),(S_N,S_N)-**3**·0.5Et_2O	(S),(R_N,R_N)-**3**·1.33$CHCl_3$
formula	$C_{20}H_{26}N_2O_2Pd·0.5C_4H_{10}O$	$C_{20}H_{26}N_2O_2Pd·1.33CHCl_3$
M_r	469.90	592.01
crystal system	othorhombic	trigonal
space group	$P2_12_12_1$(#19)	$R3$(#146)
a (Å)	10.015(3)	22.253(2)
b (Å)	14.500(8)	
c (Å)	29.221(5)	13.104(7)
cell vol. (Å^3)	4243(2)	5619(2)
Z	8	9
D_c (g cm^{-3})	1.47	1.574
F(000)	1944	2694
instrument	Rigaku AFC6R	Rigaku AFC6R
radiation	CuK_α	CuK_α
sean mode	ω–2θ	ω–2θ
θ range for data collection	60.2	60.2
scan angle	1.0 + 0.3tanθ	1.4 + 0.3tanθ
min, max *h*;*k*;*l*	0 to 11; 0 to 16; 0 to 33	−25 to 25; 0 to 25; −15 to 0
no. of rflns collected	3590	2040
no. observed $I>3\sigma(I)$	3234	1616
temperature (K)	213 ± 1	213 ± 1
crystal dim. (mm)	0.12 × 0.08 × 0.10	0.40 × 0.12 × 0.12
μ (cm^{-1})	72.14	100.91
min; max transmission (ψ)	0.8484, 1.000	0.7796, 1.000
residual electron density	min − 0.86; max 0.81	min − 0.57; max 0.63
final *R*, R_w	0.039, 0.049	0.045, 0.048

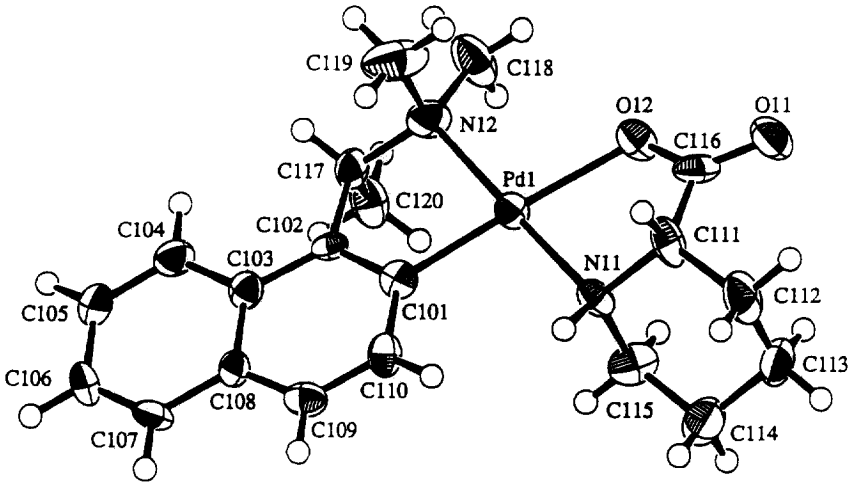


Fig. 1 ORTEP drawing of (*S*),(*S*,S_N)-**3**. Selected interatomic distances (Å) and angles (°) for one of the two independent molecules in the unit cell are as follows: Pd1–N11 2.050(8), Pd1–O12 2.149(7), Pd1–C101 2.00(1), Pd1–N12 2.076(8), Pd1–N11–C111 106.0(6), Pd1–O12–C116 112.8(6), N11–C111–C116 108.9(8), O11–C116–C111 116.8(10), O12–C116–C111 119.3(9), O11–C116–O12 123.8(9).

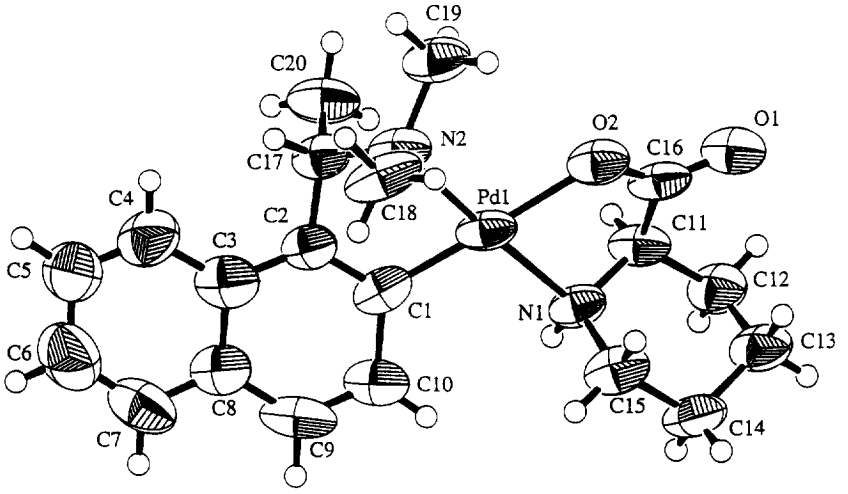


Fig. 2 ORTEP drawing of (*S*),(*R*,R_N)-**3**. Selected interatomic distances (Å) and angles (°) are as follows: Pd1–C1 1.94(1), Pd1–N1 2.062(9), Pd1–N2 2.049(9), Pd1–O2 2.114(9), Pd1–N1–C11 104.4(6), Pd1–O2–C16 113.2(8), N1–C11–C16 107.1(9), O1–C16–C11 119.(1), O2–C16–C11 115(1), O1–C16–O2 124(1).

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