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Zn(II) and Pd(II) Complexes of Thiosemicarbazone-*S*-alkyl Esters Derived from 2/3-Formylpyridine

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ABSTRACT

Representative *S*-methyl/ethyl-4-H/phenylthiosemicarbazones and their Zn(II) and Pd(II) complexes were synthesized. Characterization of the 1 : 1 complexes, $[Zn(L)Cl_2]$, $[Pd(L)Cl_2]$, and $[Pd(L)Cl]Cl$, was accomplished by means of elemental analyses, IR and ^1H NMR spectra. The multidentate *S*-alkyl thiosemicarbazones coordinate as mono-, bi-, or tridentate ligands depending on the types of the alkyl moiety and metal ion.

Key Words: Polydentate thiosemicarbazones; Zn(II) and Pd(II) complexes.

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INTRODUCTION

Thiosemicarbazones and their derivatives have been of great importance because of their biological activities. In additon to the bacteriostatic and fungistatic activities of thiosemicarbazone derivatives, the antiviral and antitumor activities of this class of compounds have become very popular in recent years.[1–9] Thiosemicarbazones that have a nitrogen or another heteroatom at the α-position, along with *S*-alkyl esters of thiosemicarbazones, have outstanding selective biological activities when compared with others in the same class. In the last decade, when the antitumor activity of metal complexes of these compounds was discovered, the structural analysis of thiosemicarbazones in metal complexes has been an important topic.[10–12]

Thiosemicarbazones coordinate to metal ions through the azomethine nitrogen and sulfur atoms. In addition, the coordination behavior is enhanced by the presence of a heteropolar atom in the ring, which is also likely to be coordinated to the metal ion and, therefore, a tridentate function is generated.[13] Pd(II) and Zn(II) complexes of biologically active tridentate thiosemicarbazones, like the complexes of 2-acetylpyridine and 2-formylpyridine thiosemicarbazone derivatives, have been studied intensively.[14–20,22]

The thiosemicarbazone ligands outlined in Fig. 1 were synthesized and some of the structural properties of their Zn(II) and Pd(II) complexes were investigated. Characterization of the compounds was accomplished by melting points, molar conductivities, elemental analyses, IR and ^{1}H NMR spectra.

RESULTS AND DISCUSSION

Synthesis and Some Physical Properties of the Compounds

It can be said that because the isolation of pure formylpyridine-*S*-alkylthiosemicarbazones without the hydrohalide form is generally not possible, they are thought to be solids with low melting points (Table 1). These compounds could be obtained only as oily, viscous liquids in solution. The hydrohalide forms of the ligands are bright yellow in color, while they are pale yellow in the free ligand form. The melting points of the hydrohalides were found to be in the 160–170 °C range, whereas the unique ligand L^3, which we were able to isolate in the free ligand form, has a melting point of 62–63 °C. The zinc complexes are bright yellow while the palladium complexes are brown.

The interaction of the ligands L (L = L^{1-6}) with metal salts in 1 : 1 molar ratio in ethanol yielded stable solid complexes corresponding to the general formulae [M(L)Cl_2] and [M(L)Cl]Cl.

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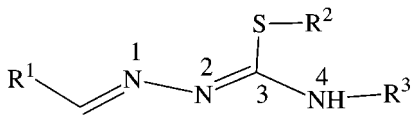

Ligand	R^1	R^2	R^3	Ligand	R^1	R^2	R^3
L^1	2-py	Me	H	L^4	2-py	Et	Ph
L^2	2-py	Et	H	L^5	3-py	Me	H
L^3	2-py	Me	Ph	L^6	3-py	Et	H

Figure 1. Structures of the ligands.

Typical complexation reactions are given below.

$$L \cdot HI + ZnCl_2 \longrightarrow [Zn(L)Cl_2] + HI$$

$$L \cdot HI + Li_2[PdCl_4] \longrightarrow [Pd(L)Cl_2] + 2LiCl + HI$$

$$L \cdot HI + Li_2[PdCl_4] \longrightarrow [Pd(L)Cl]Cl + 2LiCl + HI$$

Hydroiodide salts of the ligands have poor solubilities in chlorinated organic hydrocarbons such as dichloromethane, but are very soluble in polar solvents like DMF or DMSO. The solubilities of the free ligands in non-polar solvents are greater than their hydroiodide salts. The complexes are very easily soluble in DMF and DMSO while their solubilities in ethyl alcohol are negligible.

According to molar conductivities of the metal complexes of 2- and 3-pyridyl-derived ligands, it can be said that they fall into two groups. Molar conductivities in DMSO of the Pd(II) complexes of L^1, L^2, L^3, and L^4 range from 20 to 35 $\Omega^{-1}\,cm^2\,mol^{-1}$, in contrast, the Zn complexes have relatively low conductivities of about 7 $\Omega^{-1}\,cm^2\,mol^{-1}$. The complexes $[Pd(L^5)Cl_2]$ and $[Pd(L^6)Cl_2]$ have very low molar conductivities of about 1–3 $\Omega^{-1}\,cm^2\,mol^{-1}$.

IR Spectra

IR spectra were obtained on KBr disks in the 4000–400 cm^{-1} range. In the IR spectra of the HI salts of the ligands (except L^3), the bands in the 3350–3180 cm^{-1} region are assigned to $\nu(NH_2)$ vibrations. The 4-phenyl derivatives (L^3 and L^4) have only one band at *ca.* 3180–3210 cm^{-1}, as expected. There are complicated bands in the IR spectra of the ligands in the 1660–1550 cm^{-1} range, which may be attributed to δ(NH) deformation

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Table 1. Analytical data and physical properties of the ligands and their metal complexes.

Compound	M.p. (°C)	FW (yield, %)	Elemental analysis, % found (calculated)				
			C	H	N	M	Cl
$L^1 \cdot HI$ ($C_8H_{11}IN_4S$)	172 dec.	322.2 (52)	29.50 (29.82)	3.88 (3.44)	17.88 (17.39)	—	—
$[Zn(L^1)Cl_2]$ ($C_8H_{10}Cl_2N_4SZn$)	227 dec.	330.5 (48)	29.55 (29.07)	3.55 (3.05)	16.45 (16.95)	20.21 (20.01)	21.16 (21.45)
$[Pd(L^1)Cl]Cl$ ($C_8H_{10}Cl_2N_4PdS$)	345 dec.	371.6 (85)	25.50 (25.86)	2.87 (2.71)	15.44 (15.08)	28.21 (28.64)	18.78 (19.08)
$L^2 \cdot HI$ ($C_9H_{13}IN_4S$)	170 dec.	336.2 (25)	31.99 (32.15)	4.12 (3.90)	16.95 (16.66)	—	—
$[Pd(L^2)Cl]Cl$ ($C_9H_{12}Cl_2N_4PdS$)	186 dec.	385.6 (60)	27.76 (28.03)	3.19 (3.04)	14.71 (14.53)	27.94 (27.60)	18.00 (18.39)
L^3 ($C_{14}H_{14}N_4S$)	62–63	270.3 (92)	61.70 (62.20)	5.25 (5.22)	20.36 (20.72)	—	—
$[Zn(L^3)Cl_2]$ ($C_{14}H_{14}Cl_2N_4SZn$)	235 dec.	406.6 (47)	41.45 (41.35)	3.90 (3.47)	13.45 (13.78)	16.42 (16.08)	17.09 (17.44)
$[Pd(L^3)Cl_2]$ ($C_{14}H_{14}Cl_2N_4PdS$)	215 dec.	447.7 (54)	38.05 (37.56)	3.15 (3.15)	12.48 (12.51)	24.15 (23.77)	15.52 (15.84)
$L^4 \cdot HI$ ($C_{15}H_{17}IN_4S$)	165 dec.	412.3 (41)	43.45 (43.70)	4.55 (4.16)	13.65 (13.59)	—	—
$[Pd(L^4)Cl_2]$ ($C_{15}H_{16}Cl_2N_4PdS$)	156 dec.	461.7 (69)	39.25 (39.02)	4.05 (3.49)	12.75 (12.57)	23.20 (23.05)	15.08 (15.36)
$L^5 \cdot HI$ ($C_8H_{11}IN_4S$)	170–171	322.2 (90)	29.50 (29.82)	3.41 (3.44)	18.20 (18.03)	—	—
$[Zn(L^5)Cl_2]$ ($C_8H_{10}Cl_2N_4SZn$)	236–237	330.5 (60)	28.84 (29.07)	3.13 (3.05)	17.22 (16.95)	19.95 (19.78)	21.17 (21.45)
$[Pd(L^5)Cl_2]$ ($C_8H_{10}Cl_2N_4PdS$)	210 dec.	371.6 (57)	26.11 (25.86)	3.05 (2.71)	15.57 (15.08)	28.32 (28.64)	18.66 (19.08)
$L^6 \cdot HI$ ($C_9H_{13}IN_4S$)	166–167	336.2 (50)	31.98 (32.15)	3.98 (3.90)	16.78 (16.66)	—	—
$[Pd(L^6)Cl_2]$ ($C_9H_{12}Cl_2N_4PdS$)	211 dec.	385.6 (70)	27.74 (28.03)	3.30 (3.14)	15.02 (14.53)	27.25 (27.60)	18.12 (18.39)

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and ν(C═N) vibrations belonging to azomethine, thioamide, and the pyridine ring. In some spectra, it is also possible to observe those three bands separately. The stretching bands ν(C–H) at $2915 \pm 10\,cm^{-1}$ and ν(C–S) at $650–715\,cm^{-1}$ are present in the spectra.

The spectra of the Zn(II) complexes show some negligible shifts compared to the ligands. Besides, it is thought that both of the $\nu(NH_2)$ bands in $Zn(L^5)Cl_2$ at 3368 and $3268\,cm^{-1}$ are split into two bands.

In the spectra of the Pd(II) complexes of the ligands, one resonance was observed at either lower or higher frequency with respect to the ν(C═N) bands in the spectra. The spectra of the Pd(II) complexes with L^1 and L^2 do not contain the $\nu(NH_2)$ band system. However, the Pd(II) complexes of L^5 and L^6 give bands at $3425–3370\,cm^{-1}$, attributable to $\nu(NH_2)$ vibrations.

^{1}H NMR Spectra

The ^{1}H NMR spectra of HI salts of the ligands (except L^3) were found to be as expected (Table 2). The proton of HI in the ligands was observed at 12.0–14.0 ppm. The characteristic chemical shifts belong to the protons H_d (d, $J = 4.8–5.0$ Hz) for L^1, L^2, L^3, and L^4 and H_e for L^5 and L^6. These protons were observed at 8.50–9.12 ppm due to the effect of the pyridine nitrogen. The proton H_a of the pyridine ring in all of the ligands (d, $J = 4.6–4.8$) shows nearly the same chemical shift as the azomethine proton H_f. Both protons were observed either in a broad singlet or within a non-split peak since they are in the same system because of conjugation.

The *cis–trans* isomerism of methyl and ethyl groups as to the double bond in the N^2═C moiety can be clearly distinguished in the spectra of L^4 and L^5. From the integral values of the peaks belonging to the isomers, a 40 : 60 ratio of the *cis* and *trans* structures was determined. There are also *cis* and *trans* isomers of the alkyl moiety in $[Zn(L^1)Cl_2]$, $[Pd(L^1)Cl]Cl$, $[Pd(L^3)Cl_2]$, $[Pd(L^4)Cl_2]$, and $[Pd(L^6)Cl_2]$, with ratios between 40 : 60 and 30 : 70.

In the $ZnCl_2$ complexes of L^1 and L^3, the chemical shift of the proton H_d (d, $J = 4.2$ Hz) changes upfield by *ca.* 0.2 ppm. This might show that the pyridine nitrogen is coordinated to Zn(II) ion with a d^{10} system. The proton H_f in the azomethine group shifts in a similar manner and, therefore, it can be concluded that the Zn(II) ion coordinates through the pyridine and the azomethine nitrogens.

In the spectra of $[Zn(L^5)Cl_2]$, there is not a significant difference in the chemical shifts of the protons H_e and H_f compared with the free ligand. However, the amide protons in the complex $[Zn(L^5)Cl_2]$ were observed at 9.06 ppm by shifting *ca.* 0.45 ppm to lower frequency.

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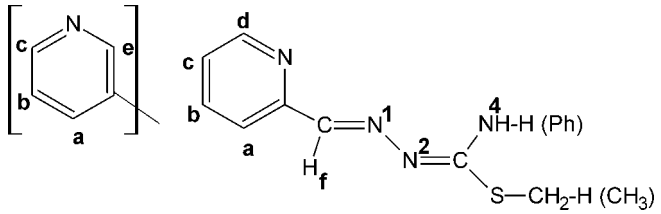
Table 2. ^{1}H NMR data of the ligands and their Zn(II) and Pd(II) complexes (δ, ppm and J value, Hz; in DMSO-d_6, TMS standard).



Compound	a	b	c	d	e	f	4
L^1	8.34 s[a]	8.00 t ($J = 7.32$)	7.53 t ($J = 6.71$)	8.68 d ($J = 4.63$)		8.34 s[a]	9.49 s, br
$[Zn(L^1)Cl_2$	8.18 s	7.39[a]	7.82 t ($J = 7.56$)	8.57 d ($J = 4.21$)		7.39[a]	—
$[Pd(L^1)Cl]Cl$	7.75 d ($J = 4.07$)	7.56 t ($J = 8.31$)	8.09 t ($J = 6.34$)	8.88 d ($J = 5.08$) 8.47 d[b] ($J = 4.98$)		7.93 s	—
L^2	8.47 d ($J = 4.55$)	7.72 t ($J = 7.50$)	8.20 t ($J = 7.47$)	8.80 d ($J = 4.84$)		8.40 s	9.81 s, br
$[Pd(L^2)Cl]Cl$	7.76 d ($J = 4.10$)	7.58 t ($J = 8.35$)	8.03 t ($J = 6.30$)	8.75 d ($J = 5.02$)		7.91 s	—

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				8.42 d[b] ($J = 4.95$)			
L^3	8.41[a]	7.83 t ($J = 7.30$)	8.41[a]	8.82 d ($J = 4.65$)		8.41[a]	—
$[Zn(L^3)Cl_2]$	7.62 d ($J = 6.72$)	7.89 t ($J = 6.65$)	8.24 t ($J = 6.75$)	8.59 d ($J = 4.21$)		7.86 s	—
$[Pd(L^3)Cl_2]$	7.78 d–d ($J = 8.69$) ($J = 7.70$)	7.63 d–d ($J = 8.07$) ($J = 7.75$)	8.16 t ($J = 6.66$) 8.02 t[b] ($J = 8.89$)	8.53 d ($J = 5.00$) 8.26 d[b] ($J = 6.57$)		8.23 s	10.27 s
L^4	8.39[a]	7.74 t ($J = 7.86$)	8.39[a]	8.77 d ($J = 4.80$)		8.29 s	—
$[Pd(L^4)Cl_2]$	7.74 d–d ($J = 9.42$) ($J = 4.36$)	7.63 d–d ($J = 7.88$) ($J = 9.13$)	8.02 t ($J = 3.10$) 7.86 t[b] ($J = 3.94$)	8.53 d ($J = 4.77$) 8.19 d[b] ($J = 7.53$)		8.35 s	10.27 s, br
L^5	8.44 d ($J = 7.81$)	7.58 t ($J = 5.03$)	8.69 d ($J = 4.44$)		9.11s	8.37 s	9.50 s
$[Zn(L^5)Cl_2]$	8.38[a] ($J = 4.93$)	7.59 t	8.68 d ($J = 4.0$)		9.06 s[a]	8.38[a]	9.06 s[a]
$Pd(L^5)Cl_2]$	8.78 d ($J = 4.35$)	7.63 t ($J = 5.6$)	9.37 d ($J = 8.16$)		8.67 s	8.22 s	9.92 s
L^6	8.45 d ($J = 7.3$)	7.60 t ($J = 5.55$)	8.70 d ($J = 4.90$)		9.12 s	8.38 s	9.55 s
$[Pd(L^6)Cl_2]$	8.82 d ($J = 9.41$)	7.64 t ($J = 7.29$)	9.38 d ($J = 5.83$)		8.67 s	8.23 s	9.94 s

Note: s, singlet; d, doublet; t, triplet; br, broad. The aromatic protons of phenyl ring were observed at 7.15–7.60 ppm (5H).
[a]In same peak.
[b]Isomer peak.

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An interesting result from the ^{1}H NMR spectra is that only the methyl esters form complexes with $ZnCl_2$. The unexpected degree of magnitude of steric hindrance from the ethyl group might have prevented the reaction of L^2, L^4, and L^6 with Zn(II) ion.

The split of $\nu(NH_2)$ bands in the IR spectra of $[Zn(L^5)Cl_2]$ confirms the structure. Taking the changeable character of amide protons into account, it was concluded that Zn(II) is coordinated only via the thioamide moiety of L^5 since the pyridine nitrogen is farther removed in the molecule.

A fundamental change appears for pyridine ring protons in the ^{1}H NMR spectra of the Pd(II) complexes with L^1, L^2, L^3, and L^4, especially the proton H_d (d, $J = 5.0–6.8$ Hz). For example, the proton H_d of L^1 at 8.34 ppm clearly splits into two doublets ($J = 5.1$ Hz) at 8.47 and 8.84 ppm with complexation. This splitting occurs in a similar manner for the spectra of the Pd(II) complexes with L^2, L^3, and L^4. In addition, the proton H_c (d, $J = 6.2–7.4$) in $[Pd(L^3)Cl_2]$ and $[Pd(L^4)Cl_2]$ also gives a similar splitting. The new doublets are due to *cis* and *trans* isomers of the protons H_c and H_d. Because the Pd(II) ion is coordinated through the pyridine nitrogen, Pd(II) and $(N{=}C)_{py}$ are in same coordination plane. The bonding can be compared with a π-acceptor ligand (ethylene derivatives, for example). Although the nitrogen atom of the 3-pyridine ring is more distant, the change of the chemical shift of the proton H_a by 0.35 ppm downfield indicates the coordination of the palladium ion with the ring nitrogen.

The resonances of the proton H_f in all of the Pd(II) complexes except for $[Pd(L^4)Cl_2]$ are shifted upfield when compared with the free ligand, indicating that this region (at least the azomethine nitrogen) is always involved in the coordination.

In the ^{1}H NMR spectra, the amide protons on N^4 of the Pd(II) complexes with L^1 and L^2 were not observed clearly, because of both the tautomerism on the thioamide groups and the proton N^4H, which may be more acidic due to the coordination of the N^4 atom. However, the amide protons of L^3, L^4, L^5, and L^6 in the complexes appear between 8.97 and 10.28 ppm. Therefore, the general formulae of the Pd(II) complexes with L^1 and L^2 should be written as [Pd(L)Cl)]Cl. This formulation is also confirmed by the relatively higher conductance values of these complexes. For the Pd(II) complexes of L^1 and L^2, the IR and ^{1}H NMR data suggest dual five-membered chelate rings (Fig. 2). The other Pd(II) complexes give a single five-membered chelate ring with the azomethine and the pyridine nitrogens (Fig. 3).

The broad proton N^4H signal of L^5 appears as three peaks at 10.15, 9.92, and 9.65 ppm in the spectra of $[Pd(L^5)Cl_2]$ and $[Pd(L^6)Cl_2]$ due to the *cis*/*trans* position of the amide protons relative to the double bonds ($CH{=}N^1$) and ($N^2{=}C$). In the complexes of L^5 and L^6, the Pd(II) ion comes close to the ring due to coordination with the N^3 nitrogen, and then the amide group rotates freely.

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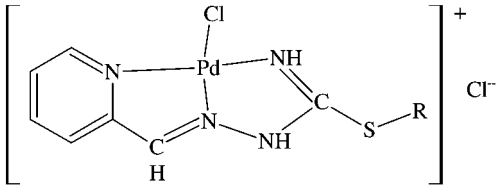

Figure 2. Tentative structures of [Pd(L^1)Cl)]Cl and [Pd(L^2)Cl)]Cl (R═CH_3, C_2H_5).

With these data in hand, we suggest the tentative structural formulae for these types of the complexes, as shown in Figs. 2 and 3. In the light of the above data, it was concluded that thiosemicarbazone-*S*-alkyl esters derived from some pyridine carboxaldehydes may exhibit mono-, di-, or tridentate functions depending on the types of alkyl moieties, the 2- or 3-position of the pyridine nitrogen, and the metal ion.

EXPERIMENTAL

Chemicals and Apparatus

All chemicals and solvents were reagent grade and purchased from Merck. IR spectra were recorded (KBr disks) on a Mattson 1000 FTIR spectrometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 NMR spectrometer (TUBITAK, Turkey). Chemical shifts were expressed in ppm relative to TMS. The residual DMSO-d_6 signal was also used as an internal reference. Analytical data were obtained with a Carlo Erba 1106 analyzer and Unicam Solar 929 atomic absorption spectrometer. The molar conductances of the compounds were measured in DMSO on a WPA CMD750 conductivity meter at $25 \pm 1\,^{\circ}C$. The chloride content was determined by a Jenway 3040 ion analyzer.

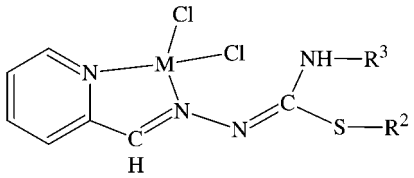

Figure 3. Tentative structures of [Zn(L^1)Cl_2], [Zn(L^3)Cl_2], [Pd(L^3)Cl_2], and [Pd(L^4)Cl_2] (M = Zn, Pd; R^2 = CH_3, C_2H_5; R^3 = H, Ph).

Synthesis of 2-Formylpyridine-*S*-methylthiosemicarbazone (L^1) Hydroiodide

Thiosemicarbazide (4.55 g, 50 mmol) and methyl iodide (6.5 mL, 100 mmol) were refluxed in 50 mL ethanol for 2 hr. After the reaction mixture was cooled to 50–60 °C, 2-formylpyridine (5 mL, 50 mmol) was added dropwise and stirred for 1 hr. The bright yellow precipitate was collected by filtration and washed with 5 mL portions of cold ethanol and diethyl ether, respectively. The final product was dried over $CaCl_2$ for 24 hr *in vacuo.*

The other ligands were prepared in a similar manner.[21] Melting points, yields, and some other properties of the ligands are included in Table 1.

Synthesis of Dichloro(2-formylpyridine-*S*-methylthiosemicarbazide)zinc(II)

The ligand $L^1 \cdot HI$ (100 mg, 0.31 mmol) was dissolved in 4 mL ethanol and neutralized with a sufficient amount of aqueous $NaHCO_3$ solution (10%, w/w). The ligand solution was added to a solution of $ZnCl_2$ (40 mg, 0.29 mmol) in 5 mL ethanol and the reaction mixture was stirred for 1 hr. The bright yellow precipitate was collected by filtration and washed with 2 mL portions of cold ethanol and diethyl ether, respectively. The final product was dried over $CaCl_2$ for 24 hr *in vacuo.*

The Zn(II) complexes with L^3 and L^5 were prepared in a similar manner (Table 1). The Zn(II) complexes of L^2, L^4, and L^6 could not be obtained in sufficient yield and purity. The beige-colored products obtained from the reaction mixtures do not yield reproducible elemental analysis results. Although the purity has been improved by recrystallization from various solvent mixtures, the analytical data are not acceptable values. TLC test indicates an impurity and the presence of free ligand in all cases.

Synthesis of Chloro(2-formylpyridine-*S*-methylthiosemicarbazonato)palladium(II) Chloride

The ligand $L^1 \cdot HI$ (100 mg, 0.31 mmol) was dissolved in 4 mL ethanol and neutralized with a sufficient amount of aqueous $NaHCO_3$ solution (10%, w/w). To the ligand solution was added 5 mL of a freshly prepared $Li_2[PdCl_4]$ solution (81 mg, 0.31 mmol) and the reaction mixture was stirred for 2 hr at 50 °C. The brown precipitate was collected by filtration and washed with 5 mL of cold ethanol. The product was dried over P_4O_{10} for 8 hr *in vacuo.*

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Reactions of the other ligands with $Li_2[PdCl_4]$ solution were accomplished as mentioned above. Only L^3 was obtained in the free ligand form.

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