Synthesis and Properties of Diammineplatinum(II) and Diammineplatinum(IV) Complexes Involving Cyclohexylidenemalonate Ligand

Chul Soo Jung, Sung Sil Lee, Kwan Mook Kim, Ok-Sang Jung, and Youn Soo Sohn*

Inorganic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea

Received July 19, 1995

New diammineplatinum(II) complexes of cyclohexylidenemalonate (chm) ligand, $A_2Pt(OOC)_2C=\overline{C(CH_2)_4CH_2}$ (**1**, A_2=ethylenediamine (en); **2**, A_2=propylenediamine (pn); **3**, A=NH_3; **4**, A=isopropylamine (ipa)) have been prepared. Their oxidation with H_2O_2 has led to the corresponding dihydroxoplatinum(IV) complexes: *cis, cis, trans*-$A_2Pt((OOC)_2C=\overline{C(CH_2)_4CH_2})(OH)_2$ (**5**, A_2=en; **6**, A_2=pn; **7**, A=NH_3; **8**, A=ipa). The title complexes have been characterized by means of various spectroscopies and X-ray crystallography. **5** crystallizes in the monoclinic space group $P2_1/a$ (Z=4) with a=12.098(7) Å, b=9.552(2) Å, c=16.258(4) Å, β=98.03(5)° and V=1860(1) Å^3. The structure was refined to R=0.074. The local geometry around platinum atom is approximately octahedral with each hydroxide group in trans position. These platinum complexes are stable in aqueous solution. Pt(IV) complexes are readily reduced to the corresponding Pt(II) complexes by ascorbic acid.

Introduction

Although cisplatin is a widely used antitumor agent, it has several problems such as severe nephrotoxicity, narrow range of activity, and acquired resistance.[1,2] In order to overcome these problems a great deal of efforts have been made to find new platinum complexes that not only have higher activity with lower toxicity than cisplatin, but also could be administered orally.[3~5] Platinum complexes suitable for oral administration have been known to be water-soluble, lipophilic, and robust enough to survive the gastric environment.[6,7] One of the most promising platinum complexes so far is *cis, trans, cis*-$Pt(NH_3)(C_6H_{11}NH_2)(OOCC_3H_7)_2Cl_2$, that contains a platinum(IV) metal center.[8] For the platinum(IV) complexes, ligand substitution reactions are slow compared with their platinum(II) analogues,[9,10] and Pt(IV) complexes may be required to be reduced to the kinetically more labile and reactive Pt(II) derivatives in vivo. Indeed previous studies have shown that platinum(IV) metal centers are readily reduced by cellular components such as glutathione and ascorbic acid to form the platinum(II) analogues that bind more rapidly to DNA.[7,11~13]

Thus, we have performed synthesis and characterization of new platinum(II) and platinum(IV) complexes involving more lipophilic cyclohexylidenemalonate ligand and herein report the results along with the reduction properties of the platinum(IV) complexes by ascorbic acid.

Experimental

Materials and Instrumentation. Potassium tetrachloroplatinate(II) (Kojima), ammonia, isopropylamine, ethylenediamine and propylenediamine (Aldrich) were used without further purification. Diethyl cyclohexylidenemalonate was prepared by the literature procedure,[14] and converted to barium salt by our method.[15] *cis*-Diaminediiodoplatinum(II) was also prepared by the known method.[16]

Elemental analysis was performed by the Advanced Analysis Center at KIST. The infrared spectra in the 4000-400 cm^{-1} region were measured as KBr pellets on a MIDAC model 101025 FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Varian Gemini-300 NMR spectrometer relative to $SiMe_4$ as an external standard.

Synthesis of $A_2Pt(chm)$ (A_2=en, pn; A=NH_3, ipa). To a suspension of 3.0 mmol of *cis*-A_2PtI_2 in 50 cm^3 of water was added 3.0 mmol of silver sulfate in 100 cm^3 of water. The reaction mixture was stirred for 6 h and then silver iodide formed was filtered off. An equimolar solution of $Ba(chm)\cdot 2H_2O$ in 50 cm^3 of water was dropped into the filtrate containing A_2PtSO_4, and the reaction mixture was stirred further for 3 h. After barium sulfate was filtered off, the filtrate was condensed to 5 cm^3, to which excess acetone was added to precipitate a solid product. The crude product was recrystallized from water to obtain a crystalline solid.

(en)Pt(chm) (**1**). Yield 82%. Found (Calc. for $PtC_{11}H_{18}N_2O_4\cdot H_2O$) : C, 28.8 (29.0); H, 4.45 (4.43); N, 6.92 (6.15). IR (KBr, cm^{-1}) : ν $(C=O)_{asy}$, 1638, 1597; ν $(C=O)_{sy}$, 1365. ^1H NMR (D_2O, ppm) : 2.53 (s, 4H), 2.36 (t, 4H), 1.70 (br, 6H).

(pn)Pt(chm) (**2**). Yield 73%. Found (Calc. for $PtC_{12}H_{20}N_2O_4$) : C, 31.8 (31.9); H, 4.31 (4.47); N, 6.40 (6.21). IR (KBr, cm^{-1}) : ν $(C=O)_{asy}$, 1654; ν $(C=O)_{sy}$, 1366. ^1H NMR (D_2O, ppm) : 2.60 (t, 4H), 2.39 (br, 4H), 1.80 (br, 2H), 1.68 (br, 6H).

$(NH_3)_2Pt(chm)$ (**3**). Yield 79%. Found (Calc. for $PtC_9H_{16}N_2O_4\cdot H_2O$) : C, 25.8 (25.2); H, 4.31 (4.23); N, 6.70 (6.53). IR (KBr, cm^{-1}) : ν $(C=O)_{asy}$, 1624; ν $(C=O)_{sy}$, 1372. ^1H NMR (D_2O, ppm) : 2.38 (t, 4H), 1.76 (br, 4H), 1.66 (br, 2H).

$(ipa)_2Pt(chm)$ (**4**). Yield 79%. Found (Calc. for $PtC_{15}H_{28}N_2O_4\cdot H_2O$) : C, 34.8 (35.1); H, 5.81 (5.89); N, 5.70 (5.46). IR (KBr, cm^{-1}) : ν $(C=O)_{asy}$, 1634, 1576; ν $(C=O)_{sy}$, 1385. ^1H NMR (D_2O, ppm) : 2.93 (m, 2H), 2.40 (t, 4H), 1.76-1.61 (br, 6H), 1.33 (d, 12H).

Synthesis of $A_2Pt(chm)(OH)_2$ (A_2=en, pn; A=NH_3, ipa). To a suspension of 2 mmol of $A_2Pt(chm)$ in 20 cm^3 of water was added 20 cm^3 of H_2O_2 (30%), and the solution was stirred for 2 h. The resulting pale yellow solution was concentrated to 5 cm^3 on a rotavapor at 40 °C, to which 100 cm^3 of acetone was added. The light yellow precipitate was filtered and washed with ethyl ether. The crude product was recrystallized from water to obtain crystals suitable for X-ray crystallography.

Table 1. Details of crystallographic data for **5**

formula	$C_{13}H_{24}N_2O_6Pt \cdot 2H_2O$
fw	507.40
space group	$P2_1/a$ (No. 14)
a, Å	12.098(7)
b, Å	9.552(2)
c, Å	16.258(4)
β, deg	98.03(5)
v, Å^3	1860.3(12)
z	4
d_{calcd}, g cm^{-3}	1.812
crystal size, mm	0.24×0.28×0.36
μ, cm^{-1}	72.7
scan method	ω/2θ
data collected	± h, k, l, 6<2θ<50
no. total observation	1634
no. unique data (I>3σ(I))	1348
no. parameters refined	94
$R=(\sum\|\|F_o\|-\|F_c\|\|)/\sum\|F_o\|$	0.074
$wR=\{\sum[w(F_o^2-F_c^2)^2]/\sum[wF_o^4]\}^{1/2}$	0.190

$w=1/[\sigma^2(F_o^2)+(0.1695P)^2+6.88P]$ where $P=[Max(F_o^2, 0)+2F_c^2]/3$

(en)Pt(chm)(OH)$_2$ (**5**). Yield 54%. Found (Calc. for $PtC_{11}H_{20}N_2O_6 \cdot 2H_2O$) : C, 25.7 (26.0); H, 4.54 (4.77); N, 5.41 (5.52). IR (KBr, cm^{-1}) : ν (C=O)$_{asy}$, 1630; ν (C=O)$_{sy}$, 1358, 1330. ^{1}H NMR (D_2O, ppm) : 2.92 (s, 4H, $^3J_{Pt-H}$, 30.3 Hz), 2.50 (br, 4H), 1.69 (br, 6H).

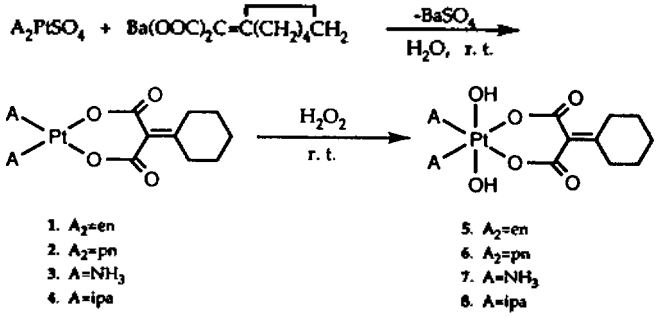
(pn)Pt(chm)(OH)$_2$ (**6**). Yield 49%. Found (Calc. for $PtC_{12}H_{22}N_2O_6$) : C, 29.9 (29.7); H, 4.59 (4.57); N, 5.35 (5.77). IR (KBr, cm^{-1}) : ν (C=O)$_{asy}$, 1672, 1648; ν (C=O)$_{sy}$, 1312. ^{1}H NMR (D_2O, ppm) : 2.61 (t, 4H, $^3J_{Pt-H}$, 32.5 Hz), 2.47 (br, 4H), 2.06 (br, 2H), 1.67 (br, 6H).

$(NH_3)_2$Pt(chm)(OH)$_2$ (**7**). Yield 60%. Found (Calc. for $PtC_9H_{18}N_2O_6$) : C, 24.7 (24.3); H, 3.94 (4.07); N, 6.41 (6.29). IR (KBr, cm^{-1}) : ν (C=O)$_{asy}$, 1636; ν (C=O)$_{sy}$, 1360, 1226. ^{1}H NMR (D_2O, ppm) : 2.51 (br, 4H), 1.80 (br, 6H).

(ipa)$_2$Pt(chm)(OH)$_2$ (**8**). Yield 49%. Found (Calc. for $PtC_{15}H_{30}N_2O_6$) : C, 23.7 (34.0); H, 5.54 (5.71); N, 5.41 (5.29). IR (KBr, cm^{-1}) : ν (C=O)$_{asy}$, 1646; ν (C=O)$_{sy}$, 1372, 1252. ^{1}H NMR (D_2O, ppm) : 3.20 (m, 2H), 2.50 (br, 4H), 1.68 (br, 6H), 1.32 (d, 12H).

Reduction of Pt(IV) Complexes with Ascorbic Acid. 6×10^{-2} mmol of a Pt(IV) complex and ascorbic acid were completely dissolved in 2 cm^3 of D_2O, and the progress of reaction was monitored at room temperature with ^{1}H NMR spectroscopy.

X-ray Crystallography. All the crystallographic data were obtained on an Enraf-Nonius CAD4 automatic diffractometer with graphite-monochromated Mo Kα radiation (λ= 0.71073 Å) at ambient temperature. Unit cell parameters and orientation matrix for the crystal were obtained from a least-squares procedure with the setting angles of 25 reflections. Three standard reflections measured every hour showed significant variation, probably due to desolvation. The part of intensity data which show severe changes in standard reflections were excluded and the rest were corrected for Lorentz and polarization effects. Decay corrections were applied to the data. The structure was solved by a conventional heavy atom method, followed by successive full-matrix least-squares refinement and different Fourier synthesis. Hydrogen atoms were placed in calculated positions and refined isotropically. All calculations were performed using SDP running on VAX/VMS V5.3 and SHELXS-86 and SHELXL-93 programs running on PC.[17] The details on the crystallographic data for **5** are summarized in Table 1.



Scheme 1.

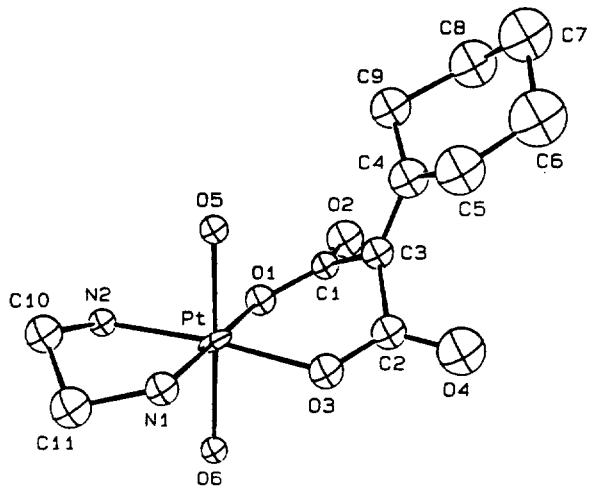


Figure 1. ORTEP drawing of the complex **5**.

Results and Discussion

Synthesis and Physical Properties. All the platinum (II) complexes of cyclohexylidenemalonate, $A_2Pt(OOC)_2C=C(CH_2)_4CH_2$ (A_2=en, pn; A=NH_3, ipa) were prepared by the reation of the corresponding diamineplatinum(II) sulfate with barium cyclohexylidenemalonate in water. Oxidation of the platinum(II) complexes with hydrogen peroxide yielded octahedral platinum(IV) complexes. As the reaction progressed, suspension of the platinum(II) complexes in H_2O_2 became clear. After filtering off unreacted reactants and evaporating the solvent, pure platinum(IV) complexes, $A_2Pt((OOC)_2C=C(CH_2)_4CH_2)(OH)_2$ (A_2=en, pn; A=NH_3, ipa), were obtained. The whole synthetic route is represented in Scheme 1. All these platinum complexes were characterized by means of chemical analyses and spectroscopic data along with X-ray crystallography for the representative complex **5**. All the complexes are air-stable white or yellow crystals. The complexes are soluble and stable in water at room temperature.

Table 2. Selected bond distances and angles for **5**

	bond distances		
Pt-N1	1.98(3)	Pt-N2	2.05(2)
Pt-O1	2.02(2)	Pt-O3	1.99(2)
Pt-O5	2.00(1)	Pt-O6	2.01(1)
C1-O1	1.29(4)	C1-O2	1.24(4)
C2-O3	1.24(4)	C2-O4	1.23(3)
C1-C3	1.53(2)	C2-C3	1.55(4)
C3-C4	1.37(4)	N1-C11	1.52(4)
N2-C10	1.49(4)		
	bond angles		
N1-Pt-N2	84.8(8)	O1-Pt-O3	90.2(7)
O5-Pt-O6	179(1)	C1-O1-Pt	121(1)
C2-O3-Pt	125(2)	C11-N1-Pt	110(2)
C10-N2-Pt	107(1)		

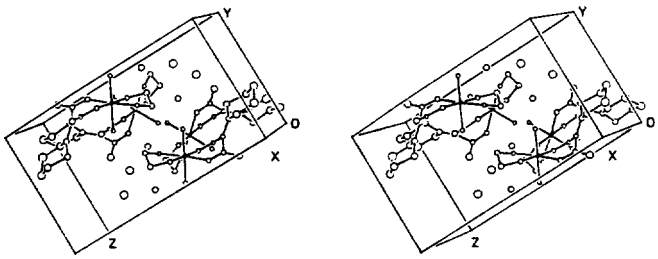


Figure 2. Stereoview of four molecules in a unit cell of the complex **5**.

The water-solubility of Pt(IV) complexes (>50 mg/cm^3 H_2O) is much greater than that of cisplatin (1 mg/cm^3 H_2O), and they seem to be suitable for oral administration.

Crystal Structure for 5. The molecular structure and labeling scheme for **5** are shown in Figure 1. Selected bond distances and angles are listed in Table 2. The local geometry around the platinum atom approximates to an octahedral arrangement with each hydroxide in trans position. The bond distances of Pt(IV)-O and Pt(IV)-N are in the range of 1.98-2.05 Å which are almost same as those of the similar Pt(IV) complexes[18,19] within the estimated standard deviation values. The bond distances of Pt(IV)-O show no significant differences between carboxylate oxygens and hydroxide oxygens. The bond angles around platinum(IV) slightly deviate from 90°, owing to the typical bite angle of en ligand. Both nitrogens in amine ligand are bonded to platinum atom in *cis* position providing a bite angle of 84.8(8)°, which is in part responsible for the distortion. The chm ligand chelates to the platinum atom *via* two carboxylate oxygens whose bite angle is 90.2(7)°. The ring conformation of the chm ligand adopts a boat form. The dihedral angle between the Pt(IV) coordinated plane and the plane of O1, O3, C1, and C2 is 26.0(1.4)°.

The five atoms (Pt, O1, O3, N1, N2) in Pt(IV) coordination sphere define a least-squares plane whose maximum deviation is 0.032(1) Å at Pt(IV) atom. The six atoms, C1, C2, C3, C4, C5 and C9, on sp^2 plane also consist of a least-squares plane whose maximum deviation is 0.043(24) Å at C3 atom. The dihedral angle between the two planes is 73.2(1.5)° which makes the whole molecule look largely bent, though not severe than that (86.6(2)°) of the Pt(II) complex with chm ligand.[15]

Table 3. Close intermolecular distances showing possible hydrogen bonding interactions for **5**

A	B	A---B, Å	A	B	A---B, Å
O2	O5^{i}	2.81	O4	Ow2^{ii}	2.79
O5	Ow1^{iii}	2.72	O6	N1^{iv}	2.79
O6	N2^{iv}	2.82	O6	Ow1	2.75
N2	Ow1	2.90	Ow1	Ow2	2.74

symmetry codes: i=0.5+x, 0.5−y, z; ii=1−x, −y, 1−z; iii=0.5−x, −0.5+y, 1−z; iv=0.5−x, 0.5+y, 1−z.

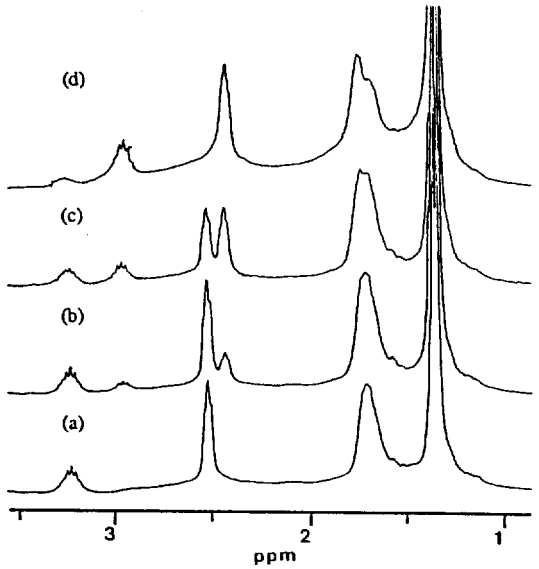


Figure 3. ^{1}H NMR spectra of **8** depending on the progress of reduction by ascorbic acid. (a) fresh, (b) after 1 h, (c) after 3 h, (d) after 30 h.

Figure 2 shows a stereoview of four molecules in a unit cell including water molecules. The molecules seem to be interacting with each other through hydrogen bondings. Close interatomic distances showing possible hydrogen bonding interactions are listed in Table 3. The water molecules, Ow1 and Ow2, have close interactions with each other and also with Pt(IV) complex molecules in the unit cell. These interactions are dispersed through all the molecules in the crystal.

Spectroscopic and Reduction Properties. In the IR spectra of the title complexes, the difference ($\Delta\nu$) between the asymmetric and symmetric carbonyl stretching frequences is larger than 200 cm^{-1}, suggesting that the both carboxylate groups in the cyclohexylidenemalonate ligand act as monodentate. ^{1}H NMR spectral data of the complexes in D_2O were consistent with the structure in solid state, and the spectra were unchanged for more than 30 days at room temperature, indicating that they are stable in solution.

Since previous studies[7,20] to date suggest that Pt(IV) complexes must be activated by reduction to Pt(II) complexes

Table 4. Reduction of platinum(IV) complexes by ascorbic acid

compound	% Pt(IV) complex remaining	
	after 3h	after 27 h
5	79	52
6	70	45
7	57	31
8	49	11

for antitumor activity, reduction properties of the present Pt(IV) complexes were examined. The reaction of compound **8** with 1 equivalent of ascorbic acid in D_2O at room temperature was monitored by ^1H NMR spectroscopy (Figure 3). As the reaction progressed, peaks corresponding to intact complex disappeared with increasing of resonances for Pt(II) complex **4**. The ratio of Pt(IV) and Pt(II) complexes is about one after 3 hours. This outcome is consistent with other group's study in which the isolated reduction product of *cis, trans, cis*-$Pt(ipa)_2(OH)_2Cl_2$ by ascorbic acid was identified to be *cis*-$Pt(ipa)_2Cl_2$,[7] but the rate of reduction has not been reported. As shown in Table 4, other title platinum(IV) complexes were also reduced to the corresponding platinum(II) complexes by ascorbic acid with variable rate. The reduction rate of the Pt(IV) complexes seems to be dependent on the type of the carrier amine ligands.

In conclusion, diamineplatinum(IV) complexes are easily prepared *via* diamineplatinum(II) complexes, and they are readily reduced by ascorbic acid. Such results indicate that the present Pt(IV) complexes can be reduced by cellular components for antitumor activity. Further investigations are underway to understand the relationship between reduction properties of the present platinum(IV) complexes and their oral antitumor activity.

Acknowledgment. This research was financially supported by the Ministry of Science and Technology.

References

1. Burchenal, J. H.; Kalaher, K.; O'Toole, T.; Chisholm, J. *Cancer Res.* **1977**, *37*, 2455.
2. Krakoff, I. H. *Cancer Treat. Rep.* **1979**, *63*, 1523.
3. Pasini, A. *Inorg. Chim. Acta* **1987**, *137*, 57.
4. Sherman, S. E.; Lippard, S. J. *Chem. Rev.* **1987**, *87*, 1153.
5. Bellon, S. F.; Coleman, J. H.; Lippard, S. J. *Biochemistry* **1991**, *30*, 8026.
6. Rahman, A.; Roh, J. K.; Wolpert-DeFilippes, M. K.; Goldin, A.; Venditti, J. M.; Woolley, P. V. *Cancer Res.* **1988**, *48*, 1745.
7. Pendyala, L.; Cowens, J. W.; Chheda, G. B.; Dutta, S. P.; Creaven, P. J. *Cancer Res.* **1988**, *48*, 3533.
8. Morgan, S. E.; Boxall, F. E.; Murrer, B. A.; Giandomenico, C. M.; Wyer, S. B.; Harrap, K. R. In *Proceedings of The Sixth International Symposisum on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Plenum Press: San Diego, U. S. A., 1992; p 277.
9. Hartley, F. R. *The Chemistry of Platinum and Palladium*; John Wiley and Sons: New York, U. S. A., 1973.
10. Giandomenico, C. M.; Abrams, M. J.; Murrer, B. A.; Vollano, J. F.; Rheinheimer, M. I.; Wyer, S. B.; Bossard, G. E.; Higgins III, J. D. *Inorg. Chem.* **1995**, *34*, 1015.
11. Blatter, E. E.; Vollano, J. E.; Krishnan, B. S.; Dabrowiak, J. C. *Biochemistry* **1984**, *23*, 4817.
12. Gibbons, G. R.; Wyrick, S.; Chaney, S. G. *Cancer Res.* **1989**, *49*, 1402.
13. van der Veer, J. L.; Peters, A. R.; Reedijk, J. *J. Inorg. Biochem.* **1986**, *26*, 137.
14. Holmberg, C. *Liebigs Ann. Chem.* **1981**, 748.
15. Lee, S. S.; Jun, M. J.; Kim, K. M.; Jung, O. S.; Sohn, Y. S. *Polyhedron* **1994**, *13*, 1397.
16. Johnson, G. L. *Inorganic Synthesis* **1966**, *8*, 242.
17. Sheldrick, G. M. *SHELXS-86 and SHELXL-93 : Program for Crystal Structure Determination and Refinement*; Universität Göttingen, 1986, 1993.
18. Kuroda, R.; Neidle, S.; Ismail, I. M.; Sadler, P. J. *Inorg. Chem.* **1983**, *22*, 3620.
19. Goto, M.; Hirose, J.; Noji, M.; Lee, K. I.; Saito, R.; Kidani, Y. *Chem. Phar. Bull.* **1992**, *40*, 1022.
20. Hartwig, J. F.; Lippard, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 5646.