Stereoselective Formation of Platinum−Carbon Bonds from Imines

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The reaction of imines with hydridometal complexes, especially with electropositive metals, can lead to formation of amidometal complexes. For example, the catalytic hydrogenation of imines is thought to involve amido intermediates [**A**, Scheme 1, X = H] formed by migratory insertion of imines into metal−hydrogen bonds.[1] More recently, new M−C bonds have been formed by the insertion of imines into palladium−acyl bonds.[2] The present article reports that, if the imine is a ligand substituent, combination of a proton, an imine, and a metal complex can lead to formation of an aminoalkylmetal complex [**B**, Scheme 1, X = Cl or CF_3CO_2] and that, if the ligand contains a chiral center, the aminoalkyl group is formed with >99% stereoselectivity. Mechanistically, the reaction is suggested to involve protonation at the nitrogen atom of the imine group, followed by oxidative addition of the resulting transient iminium ion to platinum(II) (Scheme 1). Preformed iminium salts, such as $Me_2NCH_2^+$, are already known to undergo oxidative addition to transition metal complexes, including platinum(0) complexes, and the aminoalkyl complexes formed have been shown to have interesting reactivity in insertion or reductive coupling reactions.[3] Hence, chiral aminoalkyl complexes of type **B** (Scheme 1) are potentially useful synthons, since chiral aminoalkyl groups are found in many natural products and pharmaceuticals.

The new chemistry is illustrated in Scheme 2. Reaction of excess of the bis(bidentate) ligand *cis*-1,2-C_6H_{10}(N=CH-2-$C_5H_4N)_2$ (**1**, C_5H_4N = pyridyl) with $[PtMe_2(\mu\text{-}SMe_2)]_2$ gave the platinum(II) complex **2**, which is asymmetric and is formed as a racemic mixture (the uptake of a single dimethylplatinum(II) unit breaks the mirror plane symmetry of the free ligand **1**). Complex **2** contains one free pyridyl/imine unit and was readily characterized by ^{1}H NMR spectroscopy.[4]

The reaction of **2** with HCl initially gave complex **3**, but this slowly isomerized to give complex **4** (Scheme 2). Complexes **3** and **4** were characterized by ^{1}H and ^{13}C NMR spectroscopy and by X-ray structure determinations (Figure 1).[4,5] In both complexes **3** and **4**, there is an octahedral platinum(IV) center, and compared to **2**, there are new bonds to a chloride ligand and to the aminoalkyl group that is formed by protonation/metalation of the imine substituent of **2**. The aminoalkyl group is part of a meridional *N,N,C*-tridentate ligand and contains a new asymmetric carbon atom (C16 in Figure 1). Comparison of parts a and b of

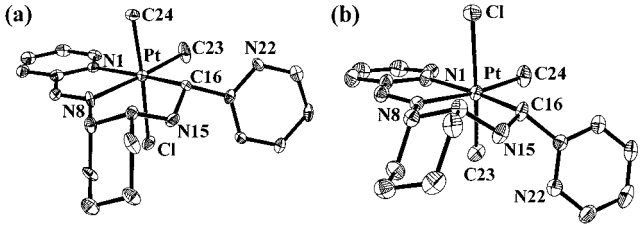
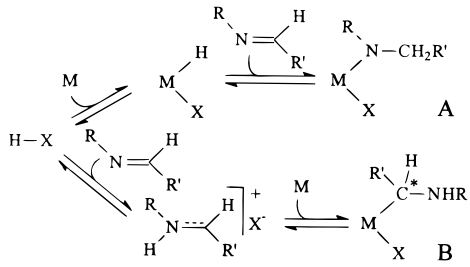


Figure 1. Structures of (a) complex **3** (*S,R-R-C* enantiomer) and (b) complex **4** (*S,R-R-A* enantiomer).

Scheme 1[a]



[a] M = transition metal complex.

Scheme 2

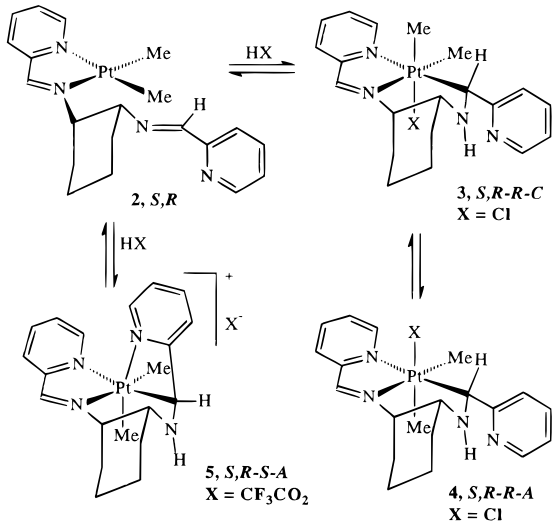


Figure 1 shows that the isomerization of **3** to **4** leads to a change in the absolute configuration (*C* to *A*)[6] at the asymmetric platinum(IV) center, while the chirality at the aminoalkyl carbon atom is maintained (Scheme 2). Based on literature precedent, this equilibration is expected to occur easily by dissociation of the chloride ligand, migration of the methylplatinum groups, and recoordination of chloride, but the successful isolation and

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(4) NMR in CD_2Cl_2: **2**, $\delta(^1H)$ = 1.05 [s, 3H, ^2J(Pt−H) = 86 Hz, PtMe], 1.08 [s, 3H, ^2J(Pt−H) = 84 Hz, PtMe], 8.18 [s, 1H, N=CH], 8.91 [s, 1H, ^3J(Pt−H) = 38 Hz, N=CH]; $\delta(^{13}C$, acetone-d_6) = −16.5 [^1J(Pt−C) = 834 Hz, PtMe], −14.6 [^1J(Pt−C) = 810 Hz, PtMe], 162.5 [N=CH], 163.7 [^2J(Pt−C) = 5 Hz, N=CH]. **3**, $\delta(^1H)$ = 0.55 [s, 3H, ^2J(Pt−H) = 71 Hz, PtMe], 0.65 [s, 3H, ^2J(Pt−H) = 76 Hz, PtMe], 4.87 [s, ^2J(Pt−H) = 66 Hz, PtCHR−NH], 9.13 [s, 1H, ^3J(Pt−H) = 32 Hz, N=CH]. **4**, $\delta(^1H)$ = 0.37 [s, 3H, ^2J(Pt−H) = 79 Hz, PtMe], 0.71 [s, 3H, ^2J(Pt−H) = 72 Hz, PtMe], 5.92 [s, ^2J(Pt−H) = 140 Hz, PtCHR−NH], 9.17 [s, 1H, ^3J(Pt−H) = 36 Hz, N=CH]; $\delta(^{13}C)$ = −2.5 [^1J(Pt−C) = 757 Hz, PtMe], 0.2 [^1J(Pt−C) = 745 Hz, PtMe], 47.8 [s, ^1J(Pt−C) = 611 Hz, PtCHR−NH], 164.6 [^2J(Pt−C) = 9 Hz, N=CH]. **5**, $\delta(^1H)$ = 0.58 [s, 3H, ^2J(Pt−H) = 76 Hz, PtMe], 0.94 [s, 3H, ^2J(Pt−H) = 72 Hz, PtMe], 4.59 [s, ^2J(Pt−H) = 40 Hz, PtCHR−NH], 9.97 [s, 1H, ^3J(Pt−H) = 37 Hz, N=CH]; $\delta(^{13}C)$ = −10.7 [^1J(Pt−C) = 738 Hz, PtMe], −3.7 [^1J(Pt−C) = 722 Hz, PtMe], 34.2 [s, ^1J(Pt−C) = 533 Hz, PtCHR−NH], 168.7 [^2J(Pt−C) = 13 Hz, N=CH].

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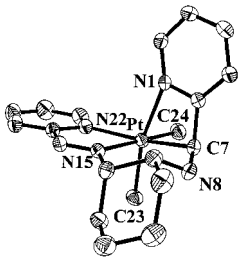


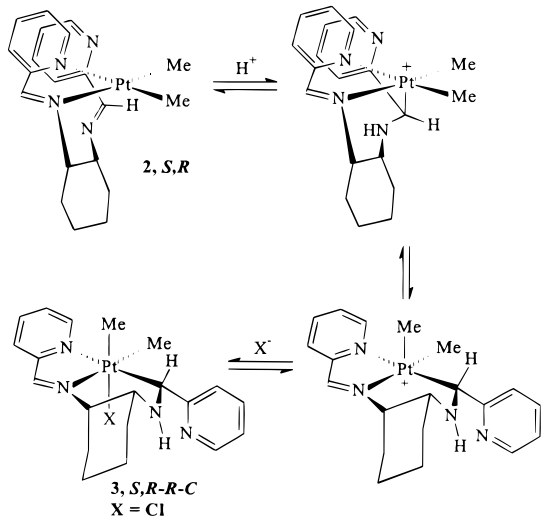
Figure 2. View of the structure of complex **5** (*S,R-S-A* enantiomer).

structure determination of both isomers is noteworthy.[7] The aminoalkylplatinum(IV) complexes form with >99% stereoselectivity at the aminoalkyl carbon position, as no other complexes were detected by ^{1}H NMR; the enantiomer **2** (*S,R*) gives only **3** (*S,R-R-C*) and **4** (*S,R-R-A*), as shown in Scheme 2.[6,8]

When the protonation of **2** was carried out using trifluoroacetic acid, the product was **5**, and it was formed with >99% stereoselectivity at both the platinum and aminoalkyl carbon centers.[4,8] The structure of **5** has been determined crystallographically and is shown in Figure 2.[5] The 2-pyridyl group, which is free in **3** and **4**, is coordinated in **5**, and so the complex ligand is now present as an *N,N,C,N*-tetradentate. Remarkably, the chirality at the aminoalkyl carbon atom (C7, Figure 2) is *opposite* to that found in complexes **3** and **4**, as is readily apparent by comparison of Figures 1 and 2. An interesting feature of the structure of **5** is the presence of a four-membered azametalacyclobutane ring.[9] This ring is strained, but the combination of the chelate effect and the weak competition from the trifluoroacetate anion is enough to compensate for this in forming **5**, in preference to **3** or **4**, when X = trifluoroacetate. The formation of the azametallacyclobutane ring, with constraints imposed by the tetradentate ligand, is only possible with the relative chiralities at the aminoalkyl and platinum centers observed in **5** (*S,R-S-A*).

Reaction of a mixture of isomers **3** and **4** (X = Cl) with silver trifluoroacetate gave a second route to complex **5** (X = CF_3CO_2). This reaction must occur with overall inversion at the aminoalkyl carbon atom. The mechanism presumably involves chloride abstraction from **3** or **4** to give a five-coordinate cation, reversible loss of a proton from the cationic intermediate to regenerate the free imine, and then protonation at the opposite face of the imine to give a second five-coordinate intermediate in which the free pyridyl group is in the axial position that allows coordination to platinum to give **5** (Scheme 2). The chirality at the aminoalkyl carbon center is thus determined by thermodynamic rather than kinetic factors and is not controlled by the primary protonation step. Consistent with this conclusion, reaction of **5** (*S,R-S-A*) with chloride regenerated a mixture of complexes **3** (*S,R-R-C)* and **4** (*S,R-R-A*) again with inversion at the aminoalkyl carbon center.

Scheme 3



Scheme 2 demonstrates the ease and very high stereoselectivity of formation of aminoalkylplatinum(IV) complexes by a new reaction. Mechanistically, this reaction is closely related to the known oxidative addition of iminium salts.[3] Nevertheless, within this context, it is the first method to yield aminoalkyl groups having both secondary nitrogen and carbon centers and the first to demonstrate stereoselectivity. In addition, with regard to the stereochemistry at platinum, the observation of both kinetic **3** and thermodynamic **4** products in the reaction of **2** with HCl gives an important clue to the mechanistic basis of the observed stereoselectivity. There are four possible stereoisomers from *S,R-***2**: *S,R-R-C* (observed in **3**, Figure 1), *S,R-R-A* (observed in **4**, Figure 1), *S,R-S-C* (not observed), and *S,R-S-A* (observed in **5**, Figure 2).[6] The new Pt−C bond should be formed above or below the square plane of the platinum atom in **2** to give a shortlived *fac*-N,N,C ligand, but it evidently migrates rapidly to give the observed *mer*-N,N,C stereochemistry; the chloride ligand then adds and so acts as a marker for the initial site of Pt−C bond formation (Scheme 3). Complex **3** is then formed by protonation/metalation of **2** in a conformation in which the free pyridylimine group lies below the plane of **2** with the imine face chosen to allow π-stacking of the two planar pyridylimine groups (Scheme 3). However, the initial protonation step of Scheme 3 is easily reversible, and protonation on the opposite face of the imine is required to give complex **5**. The reactions of Scheme 2 were monitored by low-temperature NMR methods, but no dimethyl(hydrido)platinum(IV) intermediates were detected. It is therefore clear that the imine nitrogen in **2** is more basic than the platinum(II) center (which is known to undergo oxidative addition of HX in several other dimethylplatinum(II) complexes[10]), and so the imine is the preferred site for electrophilic attack. There is no evidence for the hydride insertion mechanism of Scheme 1.

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Supporting Information Available: Tables of X-ray data for **3**−**5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) X-ray data: for **3**, $C_{20}H_{29}N_4ClOPt$, monoclinic, *P*2(1)/*n*, a = 9.6554(7), b = 13.7421(10), and c = 16.2126(9) Å, β = 101.382(4)°, V = 2108.9(2) Å^3, Z = 4, d_{calc} = 1.802 Mg/m^3, R_1 = 0.0373, wR_2 = 0.0494; for **4**, $C_{20}H_{33}N_4ClO_3Pt$, orthorhombic, *Pbca*, a = 10.4550(1), b = 17.3762(4), and c = 25.0232(6) Å, V = 4545.9(2) Å^3, Z = 8, d_{calc} = 1.759 Mg/m^{-3}, R_1 = 0.0409, wR_2 = 0.1091; for **5**, $C_{23}H_{29}N_4Cl_2F_3O_2Pt$, monoclinic, *P*2(1)/*c*, a = 12.1563(3), b = 17.2318(7), and c = 13.2224(4) Å, β = 106.158(2)°, V = 2660.35(15) Å^3, Z = 4, d_{calc} = 1.789 Mg/m^3, R_1 = 0.0322, wR_2 = 0.0555.

(6) In the descriptor *S,R-R-C*, the first two letters define chirality at the two cyclohexyl carbons, the third defines chirality at the aminoalkyl carbon, and the fourth defines the chirality at platinum (*A* = anticlockwise, *C* = clockwise). Because the complex **2** is actually racemic, each product is also racemic. Block, B. P.; Powell, W. H.; Fernelius, W. C. *Inorganic Chemical Nomenclature: Principles and Practice*; American Chemical Society: Washington, DC, 1990; Chapter 16.

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(8) The different stereochemistries at platinum(IV) of the products **3**−**5** are characterized by very different values of the coupling ^2J(PtH) for the aminoalkyl proton. The values in hertz are **5**, 40 < **3**, 66 ≪ **4**, 140. The low value for **5** is a result of the strained ring, but the basis for the large difference between **3** and **4** is less obvious.

(9) Aminoalkyl complexes containing MCCN rings, M = Pd or Pt, can be prepared by reaction of an amide with a metal−alkene complex. (a) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806. (b) Arnek, R.; Zetterberg, K. *Organometallics* **1987**, *6*, 1230. (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (d) Mitchenko, S. A.; Zamashchikov, V. V.; Slinkin, S. M. *Russ. J. Gen. Chem.* **1993**, *63*, 667. (e) Zamashchikov, V. V.; Mitchenko, S. A.; Slinkin, S. M. *Russ. Chem. Bull.* **1994**, *43*, 478.

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