Stereoselectivity in the Substitution Reaction of Square-planar Platinum(II) Complexes determined *in situ* by Nuclear Magnetic Resonance Spectroscopy using a Chiral Solvent

Sumio Shinoda,* Tadashi Nishikimi, Sho-ichi Uchino, Yasuyuki Koie, and Yasukazu Saito *
Institute of Industrial Science, University of Tokyo, 22-1, Roppongi 7 Chome, Minato-ku, Tokyo 106, Japan

By use of a chiral solvent [(*S*)-(+)-2,2,2-trifluoro-1-phenylethanol], the stereoselectivity in the associative ligand-substitution reaction of *trans*-[$PtCl_2(SR_2)$(*R*,*S*-Val-OMe)] (Val-OMe = *R*,*S*-valine methyl ester (R = Me, CH_2Ph, or Bu^t) with *R*- or *S*-1-phenylethylamine has been determined *in situ* by time-sequential ^1H n.m.r. As compared with the stereoselection in the formation of stable bis(amino acidate)–platinum(II) complexes without a third binding site in the amino acid, the observed kinetic stereoselectivity is substantial (6—10% excess), which suggests closer arrangement of chiral ligands in the trigonal-bipyramidal state. The importance of this reaction, which is close to an elementary process, is that it can give a detailed understanding of more complex asymmetric reactions.

While development of effective catalysts for various types of asymmetric syntheses is one of the remarkable achievements in the field of homogeneous catalysis,[1,2] it still lacks total rationalization. It was recently pointed out for asymmetric hydrogenation that the stereoselection was dictated not by the catalyst–substrate adduct formed in the pre-equilibrium step ('lock-and-key' model), but rather by the difference in the activation energy of the subsequent reaction.[3]

We have been interested in the stereoselection in stable platinum(II) complexes including a chiral amino-acid ligand.[4,5] In the present study, as an extension of these studies, stereoselection in the transition state is investigated. We chose the ligand-substitution reaction of square-planar platinum(II) complexes [equation (i)], because a trigonal-bipyramidal state

trans-[$PtCl_2(SR_2)$(Val-OMe)] + $PhCH(NH_2)CH_3$ ⟶
trans-[$PtCl_2(SR_2)${$PhCH(NH_2)CH_3$}] + Val-OMe (i)

is expected to be incorporated as a sole step for stereoselection, without the complexity of usual asymmetric reactions; R = Me, CH_2Ph, or Bu^t and Val-OMe † is *N*-co-ordinating *R*- or *S*-valine methyl ester.

When the racemic form of Val-OMe is taken for the platinum(II) complexes and a pure enantiomer is adopted for 1-phenylethylamine, inequivalent amounts of *R*- and *S*-Val-OMe would be liberated due to the stereoselection in the substitution reaction. It should be noted that there is virtually no energy difference between Val-OMe enantiomers both in the reactant (co-ordinated) and the product (liberated) states; this type of purely-kinetic diastereomeric differentiation has been rarely investigated for transition-metal amine or amino-acid complexes in comparison to a thermodynamic one.[6,7]

Relative amounts of liberated *R*- and *S*-Val-OMe in the course of the reaction were measured *in situ* by ^1H n.m.r., where a chiral n.m.r. solvent (*S*)-(+)-2,2,2-trifluoro-1-phenylethanol [(*S*)-(+)-tfpe][8] had been added to the solvent beforehand so as to separate the corresponding peaks throughout the reaction. As demonstrated here, this technique provides a facile method for an accurate determination of stereoselectivity even for the reactions of small differentiation, ensuring the identity of reaction conditions (concentrations, temperature, *etc.*).

† The abbreviations used for amino acids follow the IUPAC–IUB recommendations [see *Pure Appl. Chem.*, 1984, **56**(5), 595].

Table 1. Proton n.m.r. data * for *trans*-[$PtCl_2(SR_2)${NH_2CH(COOMe)$CHMe_2$}]

R	Chemical shift (δ)
Me	1.07 (Me_2C, $^3J_{HH}$ = 6.4), 3.79 (MeO), 2.40 (Me_2S, $^3J_{PtH}$ = 42.9)
CH_2Ph	1.00, 1.04 (Me_2C, $^3J_{HH}$ = 6.8), 3.71 (MeO), 4.0 (br, CH_2), 7.25 (br, Ph)
Bu^t	1.09 (Me_2C, $^3J_{HH}$ = 6.4), 3.75 (MeO), 1.67 (Me_3C)

* Measured in $CDCl_3$ at 35 °C. Chemical shifts (δ) in p.p.m. relative to $SiMe_4$, positive values representing shifts to high frequency. *J* Values are in Hz. CH protons positioned α and β to NH_2 commonly appear at δ 4.0 (br) and 2.5 (br) p.p.m., respectively.

Table 2. Carbon-13 n.m.r. data [a] for *trans*-[$PtCl_2(SR_2)${NH_2CH(COOMe)$CHMe_2$}]

	Chemical shift (δ) $NH_2CH(COOMe)CHMe_2$					
R	Me	$C_\alpha H$	$C_\beta H$	OMe	CO	SR_2
Me	17.53, 18.67	62.25 (8.3)	31.29 (18.6)	52.47	171.45	*b*
CH_2Ph	17.32, 18.83	62.21 (8.3)	31.04 (18.1)	52.43	171.33	*c*
Bu^t	17.86, 18.62	62.17 (8.3)	30.88 (16.6)	52.47	171.54	*d*

[a] Measured in $CDCl_3$ at 29 °C. Chemical shifts (δ) in p.p.m. relative to $SiMe_4$, positive values representing shifts to high frequency. Values in parentheses are ^nJ(PtC)/Hz. [b] Me, 22.72 (13.9). [c] CH_2, 40.33 (25.6); Ph, 127.99, 128.52, 129.90, 131.18. [d] CMe_3, 32.14 (17.7); CMe_3, 55.47.

Results and Discussion

Preparation and Structure of trans-[$PtCl_2(SR_2)$(Val-OMe)] (R = Me, CH_2Ph, *or* Bu^t).—This was prepared by the 1 : 1 molar reaction of *trans*-[$PtCl_2(\eta\text{-}C_2H_4)$(Val-OMe)] and SR_2 in dichloromethane, with evolved ethene removed under slightly reduced pressure. The *trans* disposition of the obtained complex is substantiated by the following facts. (*i*) The reaction of *trans*-[$PtCl_2(\eta\text{-}C_2H_4)$(py)] (py = pyridine) with Me_2SO under the same conditions leads to the exclusive formation of the well characterized *S*-co-ordinated complex *trans*-[$PtCl_2$-(Me_2SO)(py)].[9] (*ii*) The reaction of *trans*-[$PtCl_2(SR_2)$(Val-OMe)] with 1-phenylethylamine is exactly composed of the

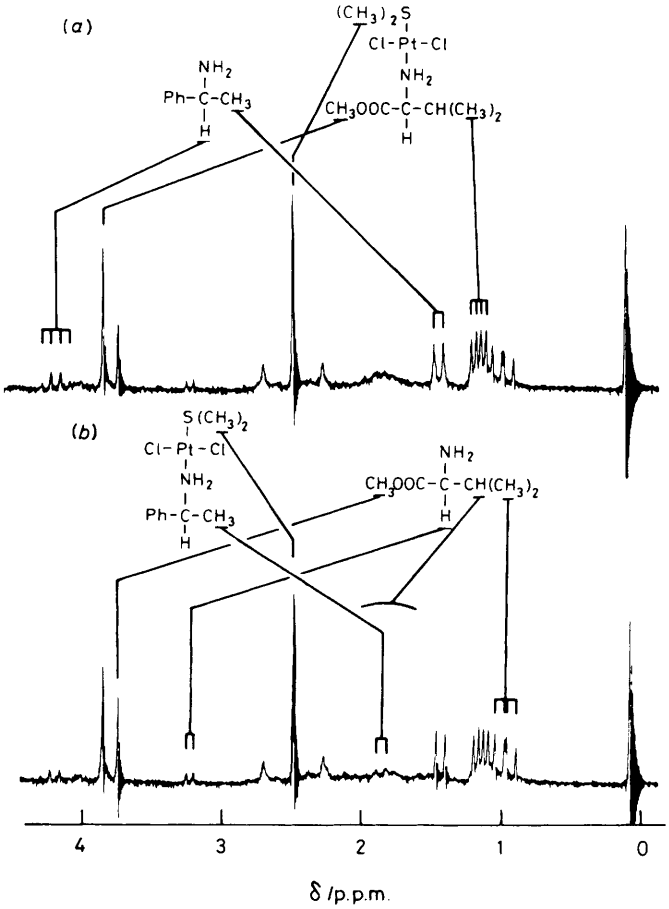


Figure 1. Time-sequential ^1H n.m.r. spectra obtained *in situ* for the substitution reaction of *trans*-[$PtCl_2(SMe_2)$(*R*,*S*-Val-OMe)] with 1-phenylethylamine (27 °C, CCl_4 solvent): after 70 (*a*) and 905 s (*b*) from the moment of setting the n.m.r. sample tube to the spectrometer. The peak near 0 p.p.m. is an external $SiMe_4$ reference employed to monitor the spectral resolution. Initial concentrations were 0.622 and 0.520 mol dm^{-3} for the complex and amine, respectively

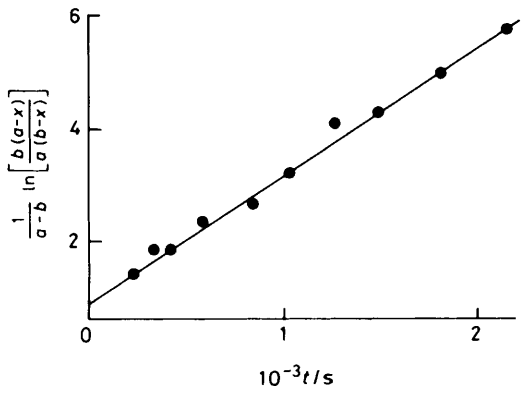


Figure 2. Second-order plot for the substitution reaction of *trans*-[$PtCl_2(SMe_2)$(*R*,*S*-Val-OMe)] with 1-phenylethylamine (35 °C, CCl_4 solvent). Initial concentrations were 0.100 and 0.138 mol dm^{-3} for the complex and amine, respectively

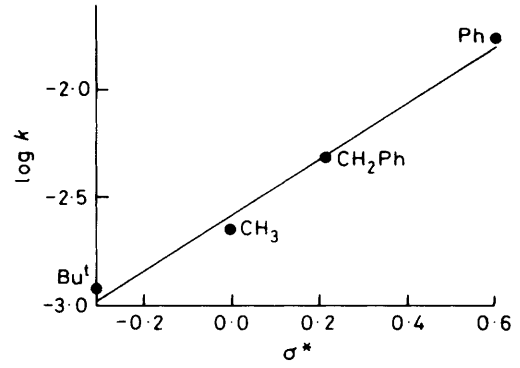


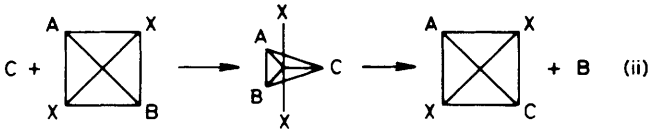
Figure 3. Rate constant (*k*) as a function of Taft parameter σ* of the sulphide substituent R for the substitution reaction of *trans*-[$PtCl_2(SR_2)$(*R*,*S*-Val-OMe)] with 1-phenylethylamine (0 °C). Solvent is CCl_4 except for R = CH_2Ph ($CDCl_3$). The SPh_2 derivative was also measured; since the rate was fast in comparison to the other three stereoselectivity was not determined in this case

substitution of the Val-OMe ligand with 1-phenylethylamine (see below), which is consistent with the highest *trans* effect of SR_2 [10] in this complex. The results of ^1H and ^{13}C n.m.r. characterization for *trans*-[$PtCl_2(SR_2)$(Val-OMe)] are given in Tables 1 and 2, respectively.

Reaction of trans-[$PtCl_2(SR_2)$(Val-OMe)] *with* 1-*Phenylethylamine*.—Figure 1 shows representative ^1H n.m.r. spectra, which were taken time-sequentially to follow the reaction of *trans*-[$PtCl_2(SMe_2)$(Val-OMe)] (1) with 1-phenylethylamine in CCl_4. It is apparent that the intensity of the methoxy protons of (1) (δ 3.79 p.p.m.) decreases with time while that of liberated Val-OMe (δ 3.61 p.p.m.) increases. Since the $(CH_3)_2S$ signal of (1) (δ 2.40 p.p.m. with ^{195}Pt satellites) is unchanged in the spectra, either the substitution of this ligand itself or a ligand-exchange reaction other than that between *N*-bonded ligands in the *trans*-position [11] can be excluded.

The behaviour of other peaks in the spectra is also consistent with the progress of the substitution of the Val-OMe ligand with 1-phenylethylamine. These features were confirmed to hold up to *ca.* 50% conversion for all the *trans*-[$PtCl_2(SR_2)$(Val-OMe)] complexes.

Associative Mechanism of the Substitution Reaction.—The ligand-substitution reactions of square-planar four-co-ordinate *trans*-[PtX_2AB] complexes occur *via* five-co-ordinate transition states (unstable intermediates) which have trigonal-bipyramidal structures; the exchange of ligand B for C occurs in the trigonal (equatorial) plane with retention of the *trans* arrangement of the X ligands [equation (ii)].[10]



The associative nature of the present substitution reaction was confirmed, because the reaction rate was analysed well by the second-order kinetics. A typical second-order plot is given in Figure 2. Notably the second-order rate constants correlate linearly with Taft σ* values [12] of the sulphide substituents R (Figure 3). It can be said that the more electron-withdrawing the substituent, the faster is the reaction rate.

The observed tendency is consistent with a theoretical analysis of Rossi and Hoffmann,[13] who showed that the square-pyramidal five-co-ordination is stabilized with increasing π-accepting ability of the equatorial ligand.[14] This may support

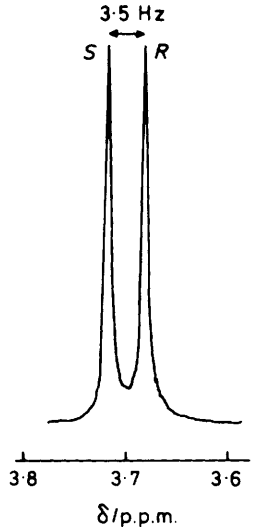


Figure 4. Proton n.m.r. spectrum (methoxy region) of *R,S*-valine methyl ester dissolved in (*S*)-(+)-2,2,2-trifluoro-1-phenylethanol–CCl_4 (12 : 88 w/w) mixed solvent (27 °C)

the residence of an SR_2 ligand at the equatorial site in the trigonal-bipyramidal state [equation (ii)].

Stereoselectivity in the Substitution Reaction of trans-[$PtCl_2(SR_2)$(*R,S*-Val-OMe)] *with* R- *or* S-1-*Phenylethylamine.*—The ^1H n.m.r. spectrum of racemic Val-OMe is shown in Figure 4; it was taken using the synthesized (*S*)-(+)-tfpe–CCl_4 (12 : 88 w/w) mixed solvent. The exact 1 : 1 peak ratio observed assures the validity of ^1H n.m.r. analysis for determining the relative abundance of Val-OMe enantiomers.

In determining the stereoselectivity of the corresponding substitution reaction, the ligand-exchange reaction between the reactant *trans*-[$PtCl_2(SR_2)$(*R,S*-Val-OMe)] and the product *R*- and *S*-Val-OMe can cause a problem: if the rate of the exchange reaction is much faster than the substitution reaction, determination of the stereoselectivity becomes uncertain. In order to clarify this uncertainty, we pursued the reaction of *trans*-[$PtCl_2(SMe_2)$(*S*-Val-OMe)] with *R,S*-Val-OMe in a chiral solvent [(*S*)-(+)-tfpe–CCl_4, 12 : 88 w/w]. Figure 5 shows time-sequential ^1H n.m.r. spectra taken *in situ* for this reaction.

It is apparent that while the enantiomer ratio of unco-ordinated Val-OMe is nearly unity at an early stage of the reaction, the relative abundance of *S*-Val-OMe to *R*-Val-OMe becomes gradually greater. The second-order rate constant k_E was determined from the rate expression (iii), where *a* and *b*

$$\frac{dx}{dt} = k_E(a - x)\left(\frac{b}{2} - x\right) - k_E x\left(\frac{b}{2} + x\right) \quad \text{(iii)}$$

are initial concentrations of the complex and *R,S*-Val-OMe, respectively, and *x* is the concentration of *trans*-[$PtCl_2(SMe_2)$-(*R*-Val-OMe)] at time *t*. Integration of equation (iii) with the limit of $x = 0$ at $t = 0$ yields equation (iv).

$$\frac{1}{a + b} \ln\left[\frac{ab}{ab - 2(a + b)x}\right] = k_E t \quad \text{(iv)}$$

The value of k_E was determined as 7.8×10^{-5} dm^3 mol^{-1} s^{-1} (0 °C), which is very close to the second-order rate constant of the substitution reaction (7.7×10^{-5} dm^3 mol^{-1} s^{-1}, 0 °C).

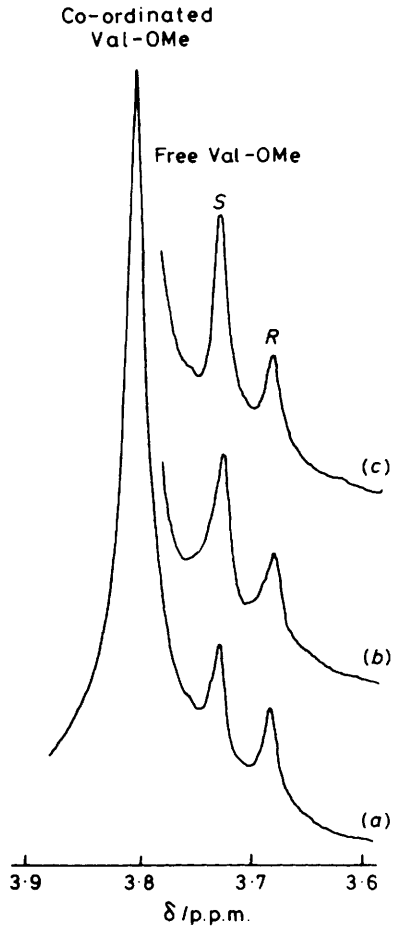


Figure 5. Time-sequential ^1H n.m.r. spectra obtained *in situ* for the exchange reaction of *trans*-[$PtCl_2(SMe_2)$(*S*-Val-OMe)] with *R,S*-Val-OMe [0 °C, (*S*)-(+)-tfpe–CCl_4 mixed solvent]: 68 (*a*), 215 (*b*), and 360 min (*c*). Initial concentrations were 0.330 and 0.086 mol dm^{-3} for the complex and amine, respectively

Comparable magnitudes of these rate constants was also found at 25 °C (8.8×10^{-4}, 9.0×10^{-4} dm^3 mol^{-1} s^{-1}). In view of the similarity of the two types of reactions (*N*-ligand/*N*-ligand substitution), the observed feature seems reasonable. Hence the stereoselectivity may be determined safely, if the conversion of the substitution reaction is limited below about 10%, because the interference from the exchange reaction would only cause an error of less than 10% in its accuracy.

Stereoselection in the substitution reaction of *trans*-[$PtCl_2(SR_2)$(*R,S*-Val-OMe)] with *R*- or *S*-1-phenylethylamine was pursued and analysed in the same manner, *i.e.* measuring the relative abundance of the liberated *R*- and *S*-Val-OMe. We formulate the stereoselectivity as the ratio of the rate constants k_{SR}/k_{RR} in equation (v), where [*R*], [*S*], and [A]

$$-\frac{d[R]}{dt} = k_{RR}[R][A], \quad -\frac{d[S]}{dt} = k_{SR}[S][A] \quad \text{(v)}$$

are respectively the concentrations of *trans*-[$PtCl_2(SR_2)$(*R*-Val-OMe)], *trans*-[$PtCl_2(SR_2)$(*S*-Val-OMe)], and unco-ordinated *R*-1-phenylethylamine at time *t*. Division and integration for equation (v) gives equation (vi), where $[S]_0$ and

$$\frac{k_{SR}}{k_{RR}} = \frac{\log([S]/[S]_0)}{\log([R]/[R]_0)} \quad \text{(vi)}$$

Table 3. Kinetic stereoselectivity in the substitution reaction of *trans*-[$PtCl_2(SR_2)$(*R*,*S*-Val-OMe)] with *R*- or *S*-1-phenylethylamine [a]

R	k_{SR}/k_{RR}	k_{RS}/k_{SS}	Solvent [b]
Me	1.13	1.06	CCl_4
CH_2Ph	1.08	1.13	$CDCl_3$
Bu^t	1.27	1.18	CCl_4

[a] Standard deviations are *ca.* 3%; reaction temperature 21 °C. [b] Each solvent contains (*S*)-(+)-2,2,2-trifluoro-1-phenylethanol (12% w/w).

$[R]_0$ are initial concentrations. If we define c and r as the conversion of the substitution reaction and the ratio of the liberated *R*- and *S*-Val-OMe, respectively [equation (vii)], this gives equation (viii). We can calculate k_{SR}/k_{RR} using equations (vi) and (viii).

$$c = \frac{([R]_0 - [R]) + ([S]_0 - [S])}{[R]_0 + [S]_0}, r = \frac{[R]_0 - [R]}{[S]_0 - [S]} \quad \text{(vii)}$$

$$\frac{[S]}{[S]_0} = 1 - \frac{2c}{1 + r}, \frac{[R]}{[R]_0} = 1 - \frac{2cr}{1 + r} \quad \text{(viii)}$$

Several sets of c and r values were obtained in the range below 10% conversion. The stereoselectivity data are summarized in Table 3. Since the differences between k_{SR}/k_{RR} and k_{RS}/k_{SS} are small, the possible effect of extra chirality due to the presence of chiral solvent molecules is probably negligible.

Consideration of the Stereoselection.—While metalloenzymes exhibit a high degree of stereospecificity, a model metal complex which bears a chiral amino-acidate ligand lacks stereoselectivity in binding to a second amino acidate, unless the amino acid has a third binding site as in histidine, penicillamine, *etc.*[15] This is apparently due to the large separation between the chiral centres,[16] even if the co-ordinated amino acidates form rigid five-membered chelate rings, which generally display higher asymmetric induction than more flexible seven- or higher-membered chelate rings.[1,2] The character of the chiral molecules adopted in the present kinetic stereoselection seems similar to the case of bis(amino acidate) complexes; they are *N*-co-ordinated with an asymmetric carbon at the α-position to the amino group. Moreover, the internal rotation of the chiral ligands may be a disadvantageous factor for effective inter-ligand chiral recognition.[17,18]

Since the stereoselectivity is determined in the trigonal-bipyramidal state, we ascribe the substantial stereoselectivity observed here (1.2 corresponds to 10% diastereomeric excess) to a closer arrangement of the two chiral molecules in the trigonal plane, compared with the above situation. The highest efficiency of the bulkiest auxiliary ligand SBu^t_2 may support this view.

One of the stable conformations assumed for the *SR* and *RR* diastereomers in the trigonal-bipyramidal state is depicted in Figure 6; asymmetric carbons are located opposite to each other with respect to the trigonal plane, and non-bonded repulsive interactions with chlorine ligands are minimized. With these conformations, the *SR* configuration seems more stable than the *RR* configuration from the viewpoint of a smaller repulsive interaction between the substituents ($CH_3 \cdots Pr^i < CH_3 \cdots COOMe$).

As selected here, the reaction which is as close as possible to an elementary step may be a promising clue to a detailed understanding of more complex asymmetric reactions, generally composed of multiple steps, participating in stereoselection.

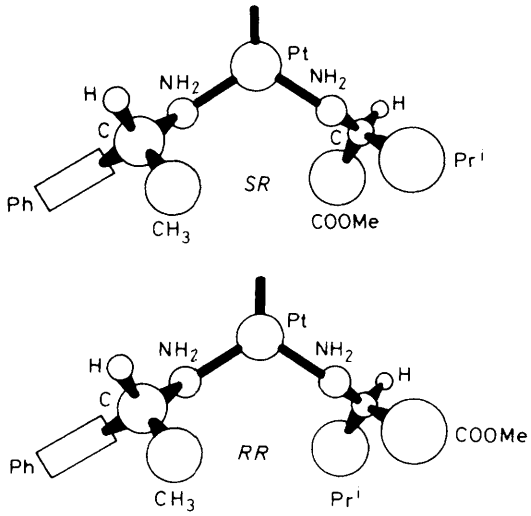


Figure 6. Conformation of the chiral amine ligands assumed stable in the trigonal-bipyramidal state (SR_2 and Cl ligands omitted). Configuration of 1-phenylethylamine is *R* with varying configuration of valine methyl ester

Experimental

Hydrogen-1 n.m.r. spectra were recorded on a JEOL PS-100 (100 MHz) spectrometer. Carbon-13 n.m.r. spectra were obtained with noise-modulated proton decoupling on a Fourier-transform pulsed n.m.r. spectrometer (JEOL FX-60, 15 MHz). Specific rotations were taken with a Jasco DIP-4 digital polarimeter.

(*S*)-(+)-2,2,2-Trifluoro-1-phenylethanol was synthesized following the procedure of Nasipuri and Bhattacharya [19] with 68% enantiomeric excess of the (*S*)-(+)-enantiomer. The hydrochloride salt of valine methyl ester, $Me_2CHCH(COOMe)NH_3^+Cl^-$, was prepared by the literature method.[20] The starting complex $K[PtCl_3(\eta\text{-}C_2H_4)]\cdot H_2O$ (Zeise's salt) was obtained by the method of Cramer *et al.*[21]

trans-[$PtCl_2(\eta\text{-}C_2H_4)$(Val-OMe)].—The hydrochloride salt of valine methyl ester (3.45 mmol) dissolved in water (5 cm^3) was added slowly to an aqueous solution (25 cm^3) of Zeise's salt (3.63 mmol) at 0 °C. Neutralization of the solution at 0 °C with aqueous $NaHCO_3$ to pH 7 gave a yellow oil, which was extracted with diethyl ether and then dried ($MgSO_4$). Crystallization from diethyl ether yielded yellow crystals (1.43 g, 97%) (Found: C, 22.1; H, 4.1; N, 3.4. $C_8H_{17}Cl_2NO_2Pt$ requires C, 22.6; H, 4.0; N, 3.3%).

trans-[$PtCl_2(SR_2)$(Val-OMe)].— Since the same route was used, only one example of each type of synthesis is given. $S(CH_2Ph)_2$(1.34 mmol) dissolved in CH_2Cl_2 (5 cm^3) was added slowly to a CH_2Cl_2 solution (50 cm^3) of *trans*-[$PtCl_2(\eta\text{-}C_2H_4)$-(Val-OMe)] (1.38 mmol) at 0 °C. The solution was allowed to stand at 0 °C with stirring under a slightly reduced pressure. Continued evacuation gave a yellow oil, which was purified by column chromatography (Florisil; 60—100 mesh, inside diameter 2 cm, length 35 cm) with CH_2Cl_2 as eluant. Crystallization from CH_2Cl_2–light petroleum (b.p. 30—60 °C) gave yellow crystals (0.59 g, 72%), m.p. 146—147 °C (Found: C, 38.9; H, 4.8; N, 2.6. $C_{20}H_{27}Cl_2NO_2PtS$ requires C, 39.3; H, 4.5; N, 2.3%).

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