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^{31}P NMR Spectroscopy as a Powerful Tool for the Determination of Enantiomeric Excess and Absolute Configurations of α-Amino Acids

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An easy method for the determination of the enantiomeric excess (ee) of mixtures of α-amino acids, and also for the elucidation of the absolute configuration of each component of the mixture, is reported. The method is based on the formation of diastereoisomers by reaction of the enantiomerically pure acetylacetonate derivative [Pd(acac-*O*,*O*′)(P$_2$-dach)]ClO$_4$ (**4**) [P$_2$-dach = (1*R*,2*R*)-C$_6$H$_{10}$(NHPPh$_2$)$_2$] with D,L-mixtures of α-amino acids AaH (Pd:AaH = 1:1 molar ratio, refluxing MeOH). The reaction occurs with protonation of the acac ligand and N,O-coordination of the amino acidate group, giving the corresponding [Pd(Aa-*N*,*O*)(P$_2$-dach)]ClO$_4$ complexes L-**5** and D-**6**. The composition of these mixtures of amino acidate complexes was analyzed by integration of the corresponding peaks (four doublets, two for each diastereomer) in their ^{31}P{^{1}H} NMR spectra. A series of 14 α-amino acids was studied (**a**, alanine; **b**, 2-aminobutyric acid; **c**, valine; **d**, phenylalanine; **e**, proline; **f**, leucine; **g**, isoleucine; **h**, norleucine; **i**, serine; **j**, threonine; **k**, methionine; **l**, aspartic acid; **m**, glutamine; **n**, cysteine), and excellent agreement between the expected values of ee and those obtained from integration of the ^{31}P{^{1}H} NMR spectra was obtained. Moreover, the position of the signals of each isomer is diagnostic, in such a way that the outer doublets are always due to the L-derivatives **5a**–**l**, while the inner ones are due to the D-derivatives **6a**–**l**, allowing the assignation of absolute configurations to each isomer in the mixture.

Introduction

One of the most important problems in enantioselective processes is the accurate and reliable determination of the enantiomeric excess (ee) of a given reaction and the correct assignment of the respective absolute configurations to each isomer. The chromatographic methods (chiral GC, HPLC on chiral solid phases)[1] have undergone an impressive growth in recent years and are quite adequate for a large number of substances. NMR analysis has also proved to be a powerful, accessible[2] technique mainly through the use of chiral derivatizing or shift agents (CDAs/CSAs).[3] ^{1}H NMR spectra are the most widely used,[2−4] due to the ubiquity of the protons, but this latter fact can sometimes engender serious problems (e.g., overlapped signals and the absence of baseline resolution to perform a proper integration). The measurement of other nuclei is still rare,[5] despite very relevant advances.[5d,e]

Previous NMR work on the estimation of the ee of α-amino acids or esters using metal complexes as CDAs was based on the use of chiral diamines,[4a] most of them expensive or tedious to prepare, or chiral macrocycles derived from porphyrins[4b] or dach.[4c] In the published description of the latter the signal splitting is described, but no details of the ee measurements are given. Several β- and γ-amino acids have been complexed to Pd(II) derivatives containing the

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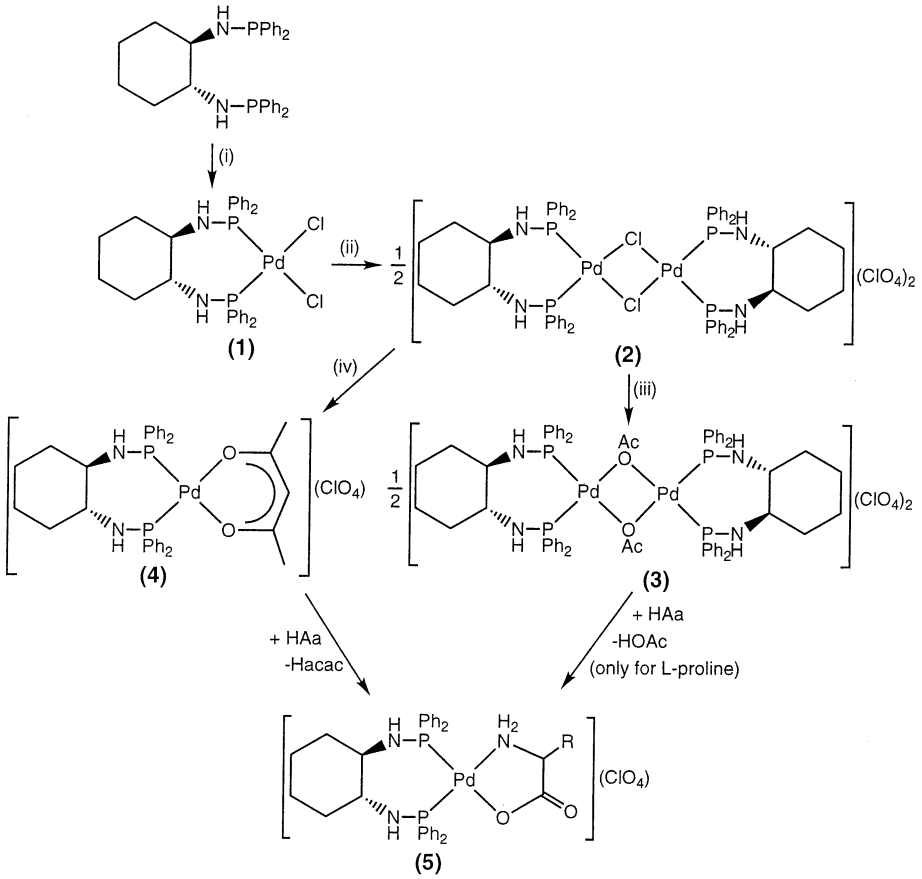
Scheme 1 [a]



[a] Reagents: (i) $PdCl_2(NCPh)_2$, − 2NCPh; (ii) + $AgClO_4$, − AgCl; (iii) + AgOAc, − AgCl; (iv) + Tl(acac), − TlCl.

chiral ligand *R*-(or *S*-)-$C_6H_4C(H)MeNMe_2$.[4d] By this means, ee can be determined and, moreover, absolute configurations can be assigned to β^2-amino acids. However, the complexity of the ^{1}H NMR spectra precludes the use of a unique resonance, and a search for a proper resonance is mandatory in each case. Moreover, in some cases the ^{1}H NMR spectra are not useful due to peak overlap, and $^{13}C\{^1H\}$ NMR spectra must be used instead.

In the course of our research work on α-amino acids,[6] we have reported a facile method for the assignment of absolute configurations of α-amino acids, based on the circular dichroism spectra of Pd−amino acidate complexes.[7] We propose here a new useful method for the determination of the ee of a given mixture of α-amino acids, and also for the elucidation of the absolute configuration of each component, based on $^{31}P\{^1H\}$ NMR data. This method uses a Pd(II) complex of the diphosphine (1*R*,2*R*)-$C_6H_{10}(NHPPh_2)_2$ (P_2-dach), which is easily prepared[8] from the cheap, commercial (1*R*,2*R*)-diaminocyclohexane [(1*R*,2*R*)-$C_6H_{10}(NH_2)_2$] and used as a CDA.

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Results and Discussion

1. Synthesis of the Precursors 1−4. The synthesis of the diphosphine P_2-dach has been carried out by reaction of commercially available (1*R*,2*R*)-diaminocyclohexane with stoichiometric amounts of Ph_2PCl and NEt_3 (1:2:2 molar ratios), following published procedures.[8] The reaction of $PdCl_2(NCPh)_2$ with P_2-dach (1:1 molar ratio, CH_2Cl_2) results in the formation of the corresponding dichloride derivative *cis*-$Cl_2Pd(P_2$-dach) (**1**) (see the Experimental Section and Scheme 1), which in turns reacts with $AgClO_4$ (1:1 molar ratio) to give the dinuclear chloride bridge derivative [Pd(μ-Cl)(P_2-dach)]$_2(ClO_4)_2$ (**2**). Complex **2** reacts with silver(I) acetate (AgOAc; 1:2 molar ratio), affording the acetate bridge derivative [Pd(μ-OAc)(P_2-dach)]$_2(ClO_4)_2$ (**3**), while **2** reacts with Tl(acac) (1:2 molar ratio; acac = acetylacetonate), giving the mononuclear species [Pd(acac-*O*,*O*′)(P_2-dach)](ClO_4) (**4**) with the acac ligand coordinated as an O,O′-chelate. Complexes **1**−**4** are yellow or orange crystalline solids, quite stable to exposure to the air and moisture at room temperature for an indefinite time without noticeable signs of decomposition. Analytic and spectroscopic data are in good agreement with the structures proposed in Scheme 1 for **1**−**4**. The spectroscopic characterization of **1**−**4** (see the Experimental Section and Supporting Information) shows also that the C_2-symmetry of the starting ligand is preserved in all these molecules, since only one signal is observed in the $^{31}P\{^1H\}$ NMR spectra [δ_P = 68.54 ppm (**1**), 68.75 ppm

(**2**), 68.53 ppm (**3**), and 63.33 ppm (**4**)]. The reactivity of the precursors **3** and **4** with several α-amino acids has been examined. Keeping in mind that our final goal is the characterization of mixtures of amino acids through $^{31}P\{^1H\}$ NMR measurements, the first logical step seems to be the study of the reactivity of the suitable precursors **3** and **4** toward enantiomerically pure α-amino acids.

2. Characterization of L-Complexes 5a−5n. Parallel reactions were performed between complexes **3** and **4** and α-amino acids [refluxing MeOH, 3 h; complex **3**, 1:2 molar ratio; complex **4**, 1:1 molar ratio]. The acetylacetonate **4** was chosen as the best precursor due to its cleaner reactivity compared with **3**, which only gave the expected amino acidate derivative with L-proline (**5e**). In this first step, a series of 14 enantiomerically pure L-α-amino acids have been complexed to Pd(II) as chelating *N,O*-amino acidate ligands (**5a**−**5l**) through reaction of **4** with the stoichiometric amount of the free, unprotected α-amino acid (see Scheme 1). The N,O-bonding of the amino acidate ligand is observed regardless of the presence of other functional groups at the C_α of the amino acids **5i**−**5m**, except for **5n**. The behavior of the L-cysteine is quite different, since the spectroscopic data of **5n** show unambiguously that L-cysteinate bonds as a N,S-chelate.

Complexes **5a**−**5n** were obtained as air-stable solids in good yields and were fully characterized according to their analytic and spectroscopic data (see the Supporting Information). The IR spectra of complexes **5a**−**5m** show characteristic absorptions corresponding to the presence of the coordinated NH_2 groups (3200 cm^{-1} region) and the carboxylate moiety (about 1630 cm^{-1}).[6,7] In addition, the IR spectra of **5i** and **5j** show absorptions corresponding to the presence of the OH group (3500−3600 cm^{-1}), and the IR spectrum of **5l** shows a strong absorption at 1723 cm^{-1} and a weak band at 3604 cm^{-1}, indicating the presence of the free COOH unit. In the case of complex **5n** the N,S-coordination mode is clearly inferred by the presence of absorptions at about 3300 cm^{-1} (N−H stretch) and 1732 cm^{-1} (free COOH group), and by the disappearance of the S−H stretch observed in the free ligand.

As expected, the ^1H and $^{13}C\{^1H\}$ NMR spectra of **5a**−**5n** show a complex set of signals. Full assignment of all resonances in the ^1H NMR spectra was not trivial, and it was performed with the help of the two-dimensional $^1H-^1H$ COSY and $^1H-^1H$ NOESY correlation spectra measured in complexes **5a**, **5c**, and **5f**. However, the $^{31}P\{^1H\}$ NMR spectra show only two well-separated doublets (see Figure 2). The signal at about 66 ppm is attributed to the P atom *trans* to the oxygen and that at about 50 ppm to the P *trans* to the N atom. As expected, for **5n** the signal at lowest field appears at 58 ppm, due to the P *trans* to the S atom of the cysteinate ligand. The large difference observed between the chemical shifts of the two P atoms [$\Delta(\delta(P_O) - \delta(P_N))$; see the Supporting Information] is not unusual, and reflects the different nature of the atoms *trans* to the P nuclei.

Moreover, the molecular structure of complex **5i**·$3H_2O$ has been determined by X-ray diffraction methods. A drawing of the cationic metallic complex is shown in Figure

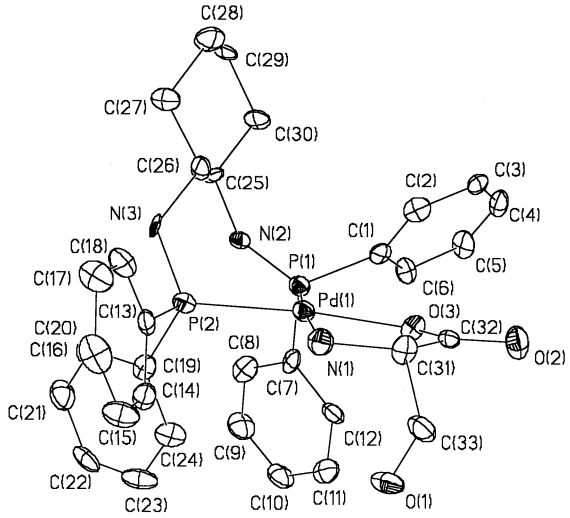

Figure 1. Thermal ellipsoid plot of the cationic fragment of complex **5i**·$3H_2O$. Non-hydrogen atoms are drawn at the 50% probability level. H atoms are omitted for clarity.

1, relevant parameters concerning the data acquisition and structure solution and refinement are collected in Table 1 and the Experimental Section, and selected bond distances and angles are given in Table 2. The palladium atom is located in a distorted square planar environment, surrounded by the two P atoms of the P_2-dach ligand, and by the aminic N atom and the carboxylic O atom of the L-serinate ligand. The structural parameters of the two ligands are similar to those found in the literature,[9,10] and do not merit further comments. The most remarkable structural feature is the relative arrangement of the cyclohexyl fragment of the diphosphine and the CH_2OH group of the serinate ligand, which are located on opposites sides of the molecular plane, minimizing steric interactions. This structural conformation of the diphosphine moiety seems to be characteristic of the P,P′-bonded P_2-dach ligand, since in the only P_2-dach-containing complex structurally characterized to date,[9] [Rh(P_2-dach)(1,5-COD)](ClO_4) (1,5-COD = 1,5-cyclooctadiene), the arrangement found for the diphosphine ligand is virtually the same as that found in **5i**. Thus, the structure adopted by the diphosphine is the same, regardless the presence of an achiral ligand such as 1,5-cyclooctadiene or a chiral ligand such as L-serinate. This fact is worthy of note, taking into account the usual conformational flexibility of the seven-membered chelating ligands.

3. Characterization of the Racemic Mixtures 5/6. In the second step, and once the N,O-coordination of the pure L-α-amino acids to the Pd(II) center was clearly established, racemic mixtures of α-amino acids were reacted with **4** under the same conditions as those described above (1:1 molar ratio, refluxing MeOH). These reactions afford the corresponding mixtures of diastereoisomers (L-amino acidate, **5a**−**5n**; D-amino acidate, **6a**−**6n**, except for complex **6m**, since only L-glutamine is available) in yields similar to those

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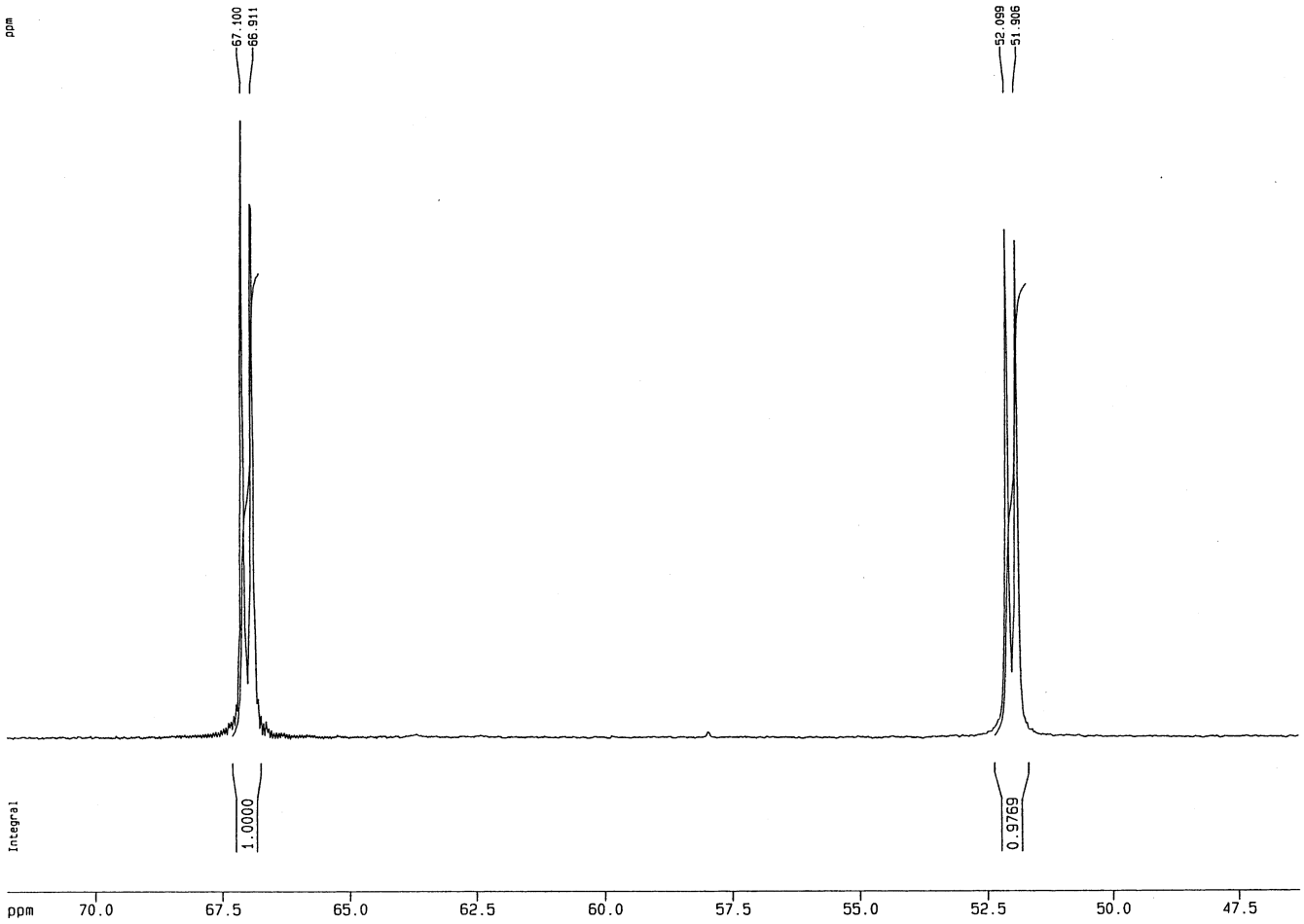

Figure 2. $^{31}P\{^{1}H\}$ NMR spectrum of complex **5e**.

Table 1. Crystal Data and Structure Refinement for **5i**·$3H_2O$

empirical formula	$C_{33}H_{38}ClN_3O_{10}P_2Pd$	D_{calcd} (Mg/m^3)	1.503
Fw	840.45	μ (mm^{-1})	0.716
temp (K)	100(2)	cryst size (mm^3)	0.22 × 0.13 × 0.11
radiation (***λ*, Å**)	Mo K**α** (0.71073)	no. of reflns collected	17447
cryst syst	orthorhombic	no. of independent reflns	5348 [R_{int} = 0.0832]
space group	$P2_12_12_1$	no. of data/restraints/params	5348/0/452
a (Å)	9.7196(10)	goodness-of-fit on F^2	0.896
b (Å)	18.6420(19)	final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0491, wR2 = 0.0754
c (Å)	20.499(2)	*R* indices (all data)	R1 = 0.0682, wR2 = 0.0797
V (Å^3)	3714.3(7)	absolute structure param	0.01(4)
Z	4	largest diff peak and hole (e·Å^{-3})	0.719 and −0.562

described for the pure L-derivatives **5a**−**5n**. The attempted characterization of the mixtures **5**/**6** by analysis of the ^{1}H NMR spectra proved to be very difficult, due to extensive overlapping of the resonances. This fact avoids a proper integration of the peaks and the determination of the diastereomeric molar ratios, making the ^{1}H NMR spectra unusable for ee determination.

In contrast, very simple $^{31}P\{^{1}H\}$ NMR spectra were obtained, since for each couple of compounds (**5a/6a**, etc.) four doublet signals were observed (see Figure 3 and the Supporting Information). The simplicity of the $^{31}P\{^{1}H\}$ NMR spectra and the differences between the chemical shifts of the same P atom in the two diastereosiomers [$\Delta(\delta_{PO(L)} - \delta_{PO(D)})$] allow a proper integration of the corresponding peaks. Although the ^{31}P nucleus could be somewhat less sensitive than, for instance, the ^{1}H or the ^{19}F nuclei, the $^{31}P\{^{1}H\}$ NMR spectra of the mixtures **5**/**6** here reported show a very good signal/noise ratio within a few minutes of accumulation using routine experiments. The same values of the integrals were obtained using delays of $d_1 = 1$ s or $d_1 = 20$ s, and due to this fact all measurements have been carried out using the shortest delay. The values of integration presented in Table 3 have always been obtained from the signals at about 64−66 ppm (P-*trans*-O nuclei), since this region shows enough difference between peaks to perform a correct integration, while the signals at about 50 ppm (P-*trans*-N nuclei) sometimes show partial ovelapping. As can be seen from Table 3, excellent agreement was found in all studied cases between the expected values for the racemic D,L-mixtures and those measured experimentally (±3%).

It is worthy of note that, even if the syntheses are performed in the presence of an excess of D,L-amino acids

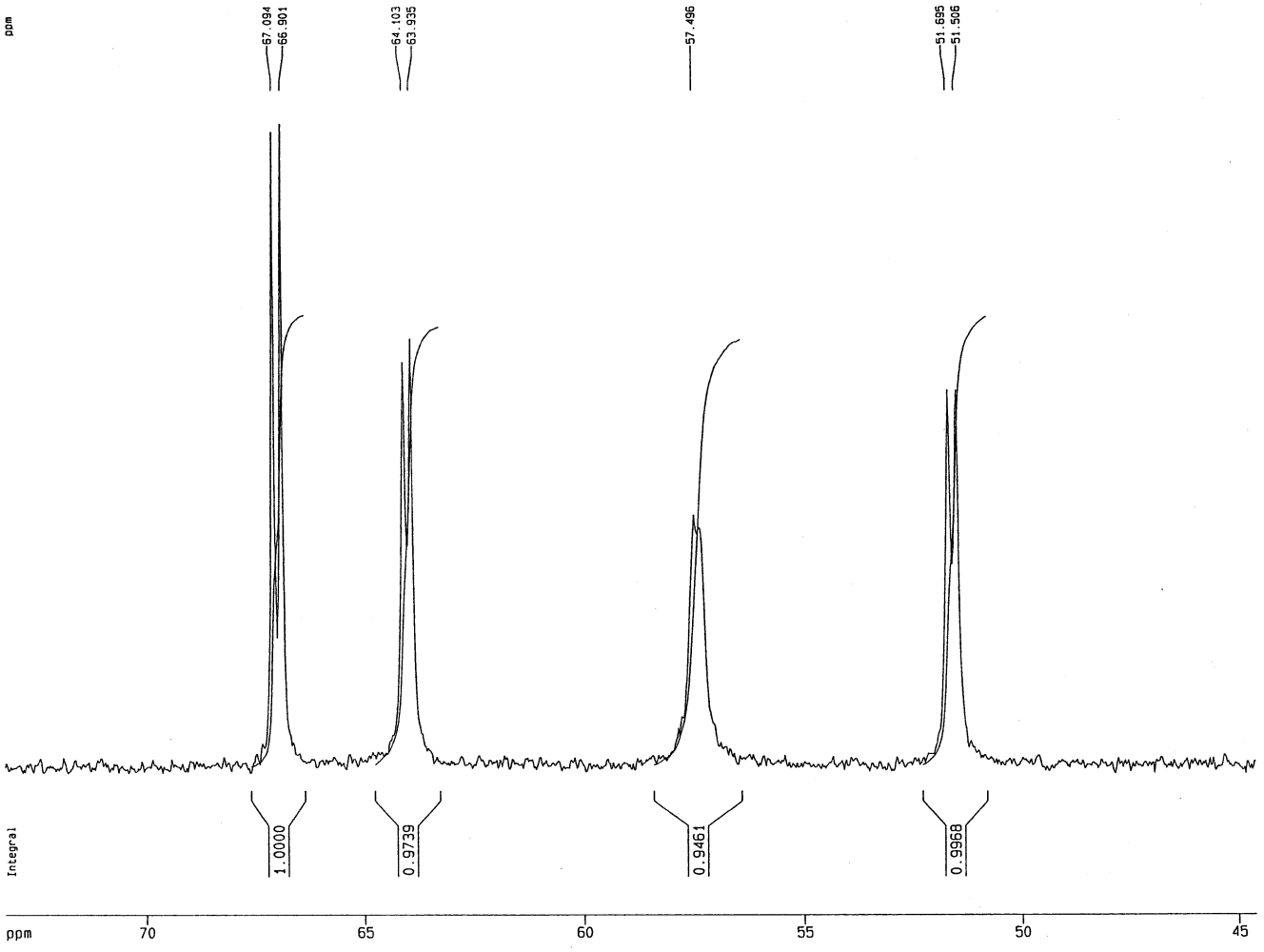

Figure 3. $^{31}P\{^{1}H\}$ NMR spectrum of the racemic mixture of complexes **5e**/**6e**.

(Pd:amino acids = 1:2 molar ratio), the integration of the corresponding signals in the $^{31}P\{^{1}H\}$ NMR spectra of the crude material shows almost the same values as those obtained from the 1:1 reactions, and 1:1 molar ratios of the two diastereoisomers were measured. That is, the differences between the expected and the obtained values are not larger in all cases than 3%, which is within the accepted experimental error in ^{31}P measurements (2−5%).[11] However, this value could also imply that a slight diastereoselective induction cannot be ruled out completely. This virtual absence of stereoselective induction is, obviously, a prerequisite for the establishment of a method of ee determination.

Moreover, the relative position of the $^{31}P\{^{1}H\}$ NMR signals due to each component of the mixture **5**/**6** could be diagnostic for the elucidation of its absolute configuration. In fact, the comparison of the chemical shifts in the mixtures **5/6** with those obtained for the pure L-derivatives **5** allows the unambiguous attribution of each signal, since very small differences can be detected in the position of a given resonance in pure **5** and in the mixtures **5/6**. As a general pattern, we have observed that the *outer* doublets always correspond to the L-isomer **5** while the *inner* signals are due to the D-isomer **6**. The only exception we have found is the mixture **5n**/**6n**, since the position of the signals does not follow the general trends described for the mixtures of complexes **5a**/**6a** to **5l**/**6l**, this fact probably being due to the different coordination mode of the cysteinate ligand (N,S- versus N,O-bonding).

4. Characterization of Nonracemic Mixtures 5/6. Further extension of the work described in the preceding sections comes from the study of a more realistic situation, that is, the presence of a nonracemic mixture of α-amino acids. Thus, mixtures of L- and D-amino acids with known compositions were reacted with **4**, under the same experimental conditions. Following isolation, the $^{31}P\{^{1}H\}$ NMR spectra of the resulting crude **5**/**6** complexes have been measured as routine experiments. The results are collected in Table 3. As expected, the resulting mixtures **5**/**6** show $^{31}P\{^{1}H\}$ NMR spectra with the *outer* signals (L-**5**) always more intense than the *inner* ones (D-**6**), and the agreement between the expected and found values for ee was excellent, even in 95:5 mixtures (see in Figure 4 the series for mixtures **5d**/**6d**). Thus, not only can the enantiomeric excess of a given

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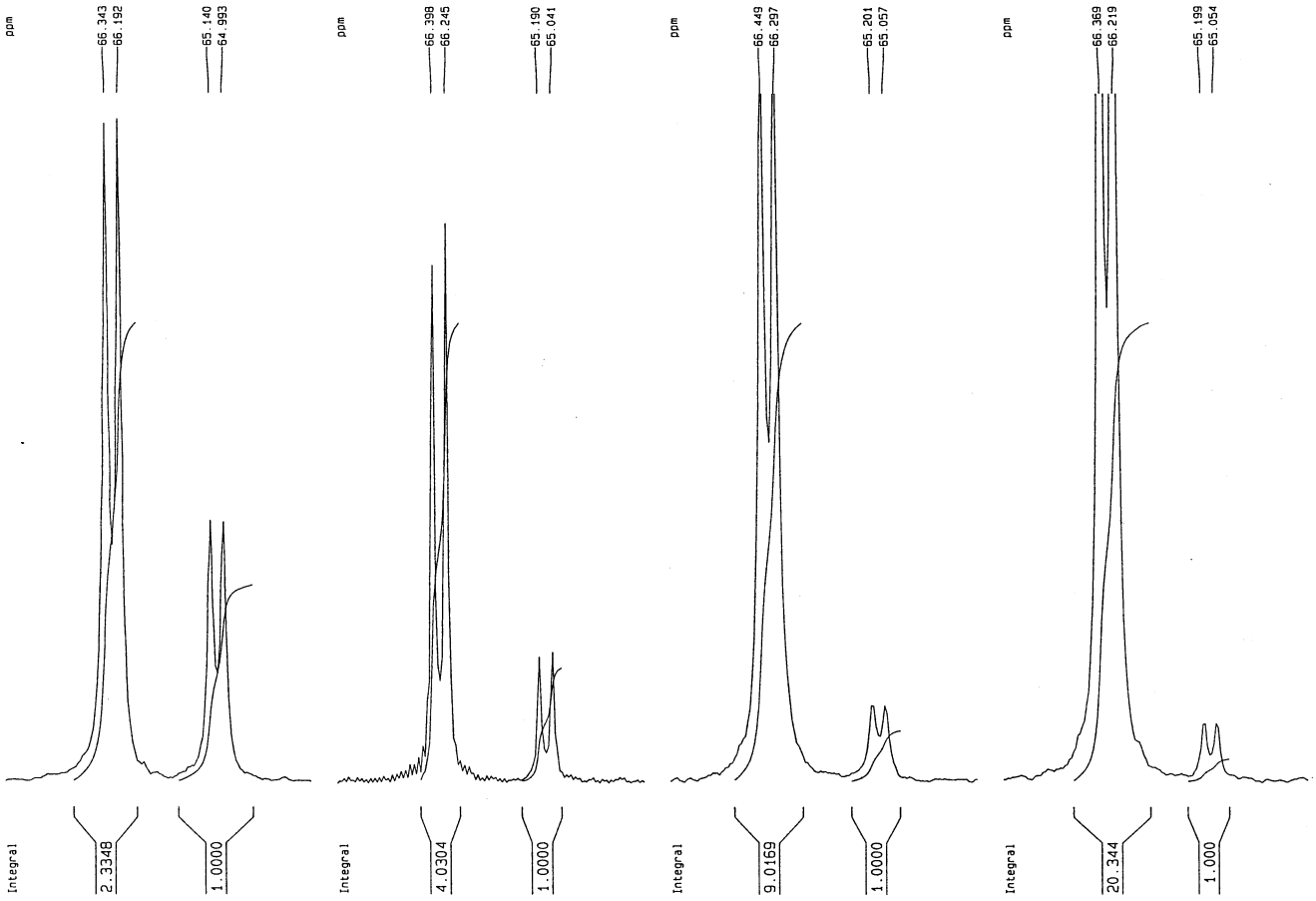

Figure 4. $^{31}P\{^{1}H\}$ NMR spectrum (P-*trans*-O signal) of mixtures of **5d**/**6d** in different ratios: 70:30, 80:20, 90:10, and 95:5, from left to right.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for **5i**·$3H_2O$

Pd(1)−O(3)	2.061(5)	Pd(1)−N(1)	2.085(5)
Pd(1)−P(2)	2.226(2)	Pd(1)−P(1)	2.244(2)
P(1)−N(2)	1.634(6)	P(1)−C(7)	1.803(8)
P(1)−C(1)	1.809(8)	P(2)−N(3)	1.627(6)
P(2)−C(13)	1.795(8)	P(2)−C(19)	1.823(8)
N(1)−C(31)	1.496(8)	N(2)−C(25)	1.474(8)
N(3)−C(26)	1.479(9)	O(1)−C(33)	1.413(8)
O(2)−C(32)	1.232(8)	O(3)−C(32)	1.275(8)
C(25)−C(30)	1.512(10)	C(25)−C(26)	1.549(10)
C(26)−C(27)	1.497(9)	C(27)−C(28)	1.517(10)
C(28)−C(29)	1.535(9)	C(29)−C(30)	1.527(9)
C(31)−C(33)	1.515(10)	C(31)−C(32)	1.524(10)
O(3)−Pd(1)−N(1)	80.0(2)	O(3)−Pd(1)−P(2)	174.60(16)
N(1)−Pd(1)−P(2)	96.74(16)	O(3)−Pd(1)−P(1)	93.83(15)
N(1)−Pd(1)−P(1)	173.63(16)	P(2)−Pd(1)−P(1)	89.36(8)
N(2)−P(1)−C(7)	104.3(3)	N(2)−P(1)−C(1)	110.6(3)
C(7)−P(1)−C(1)	105.4(3)	N(2)−P(1)−Pd(1)	119.9(2)
C(7)−P(1)−Pd(1)	108.1(3)	C(1)−P(1)−Pd(1)	107.5(3)
N(3)−P(2)−C(13)	106.5(3)	N(3)−P(2)−C(19)	109.5(3)
C(13)−P(2)−C(19)	104.5(3)	N(3)−P(2)−Pd(1)	113.8(2)
C(13)−P(2)−Pd(1)	109.5(2)	C(19)−P(2)−Pd(1)	112.5(3)
C(31)−N(1)−Pd(1)	112.6(4)	C(25)−N(2)−P(1)	130.1(5)
C(26)−N(3)−P(2)	124.7(5)	C(32)−O(3)−Pd(1)	117.9(5)
N(2)−C(25)−C(30)	112.7(6)	N(2)−C(25)−C(26)	112.6(6)
C(30)−C(25)−C(26)	109.5(6)	N(3)−C(26)−C(27)	109.1(6)
N(3)−C(26)−C(25)	110.3(6)	C(27)−C(26)−C(25)	110.4(6)
C(26)−C(27)−C(28)	111.7(7)	C(27)−C(28)−C(29)	110.6(7)
C(30)−C(29)−C(28)	112.0(6)	C(25)−C(30)−C(29)	110.5(6)
N(1)−C(31)−C(33)	110.2(6)	N(1)−C(31)−C(32)	110.8(6)
C(33)−C(31)−C(32)	110.8(6)	O(2)−C(32)−O(3)	124.7(7)
O(2)−C(32)−C(31)	117.5(7)	O(3)−C(32)−C(31)	117.8(7)
O(1)−C(33)−C(31)	107.4(6)		

mixture of α-amino acids be determined by routine integration, regardless of the coordination mode of the amino acidate ligand to the Pd(II) center, but also the absolute configuration can be attributed to each component of the mixture, proving that the amino acidate ligand is N,O-coordinated.

Table 3. Calculated and Experimental Values of ee for Different α-Amino Acids

entry	amino acid	% L:% D	int (calcd)	int (exptl)	ee(calcd) (%)	ee(exptl) (%)
1	alanine	50:50	1:1	1.06:1	0	2.9
2	alanine	60:40	1.5:1	1.72:1	20	26.5
3	alanine	40:60	1:1.5	1:1.43	20	17.7
4	alanine	80:20	4:1	4.8:1	60	65.4
5	aminobutiric acid	50:50	1:1	1.01:1	0	0.5
6	valine	50:50	1:1	1.04:1	0	1.96
7	valine	60:40	1.5:1	1.58:1	20	22.48
8	valine	70:30	2.33:1	2.37:1	40	40.66
9	phenylalanine	50:50	1:1	1.02:1	0	0.98
10	phenylalanine	60:40	1.5:1	1.57:1	20	22.18
11	phenylalanine	70:30	2.33:1	2.335:1	40	40.03
12	phenylalanine	80:20	4:1	4.03:1	60	60.24
13	phenylalanine	90:10	9:1	9.02:1	80	80.03
14	phenylalanine	95:5	19:1	20.34:1	90	90.63
15	proline	50:50	1:1	1.01:1	0	0.5
16	proline	60:40	1.5:1	1.80:1	20	28.6
17	proline	70:30	2.33:1	2.58:1	40	44.1
18	leucine	50:50	1:1	1.04:1	0	1.96
19	isoleucine	50:50	1:1	1.04:1	0	1.96
20	norleucine	50:50	1:1	1.02:1	0	0.99
21	serine	50:50	1:1	1.01:1	0	0.5
22	threonine	50:50	1:1	1.01:1	0	0.5
23	methionine	50:50	1:1	1.01:1	0	0.5
24	aspartic acid	50:50	1:1	1.03:1	0	1.47
25	cysteine	50:50	1:1	1.01:1	0	0.5

The advantages of this method merit some comments: (i) the complexes **5**/**6** are stable to the air and moisture, avoiding

special cautions to perform the reactions or handle the compounds (except those derived from the use of perchlorate salts); (ii) all starting materials are cheap and commercially available or easy to synthesize in a few steps; (iii) the amount of amino acid required for complex formation is very small (typically 10−20 mg) and can be recovered from the metallic complexes after NMR measurements by protonation with HCl; (iv) the reactions are really reproducible; (v) complexes are adequately soluble in the usual NMR solvents, and no special techniques are required, allowing a fast and accurate determination of the ee by routine measurements.

The application of this method to other nonproteinogenic amino acids and the elucidation of the structural changes promoted by the coordination of the different enantiomers of the amino acids are currently under study.

Conclusion

The ee of a mixture of α-amino acids can be measured accurately, and absolute configurations of each component can be assigned, in most cases, using this method.

Experimental Section

Safety Note. *Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of these materials should be prepared, and they should be handled with great caution.* See *J. Chem. Educ.* **1973**, *50*, A335−A337.

General Methods. Elemental analyses were carried out on a Perkin-Elmer 2400-B microanalyzer. Infrared spectra (4000−200 cm^{-1}) were recorded on a Perkin-Elmer Spectrum One FT-infrared spectrophotometer from Nujol mulls between polyethylene sheets. ^1H (300.13 MHz), $^{13}C\{^1H\}$ (75.47 MHz), and $^{31}P\{^1H\}$ (121.49 MHz) NMR spectra were recorded in $CDCl_3$, CD_2Cl_2, and DMSO-d_6 solutions at 25 °C on a Bruker ARX-300 spectrometer; ^1H and $^{13}C\{^1H\}$ NMR spectra were referenced using the residual solvent signal as internal standard, while $^{31}P\{^1H\}$ NMR spectra were externally referenced to H_3PO_4 (85%). The two-dimensional $^1H-^1H$ COSY and $^1H-^1H$ NOESY spectra of complexes **5a**, **5c**, and **5f** were performed at a measuring frequency of 300.13 MHz. The data were acquired in a 512 × 1024 matrix, and then transformed into 1024 × 1024 points using a sine window in each dimension. The mixing time was 400 ms for the NOESY experiments. Mass spectra (positive ion FAB) were recorded from CH_2Cl_2 solutions on a VG Autospec spectrometer.

Synthesis of *cis*-Cl_2Pd[(1R,2R)-$(PPh_2NH)_2C_6H_{10}$] (1). To a solution of $PdCl_2(NCMe)_2$ (0.270 g, 1.04 mmol) in CH_2Cl_2 (30 mL) was added the bisphosphine (1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}$ (0.502 g, 1.04 mmol). This mixture was stirred at room temperature for 2 h. During this time a white solid precipitated, which was filtered, washed with CH_2Cl_2 (10 mL) and Et_2O (20 mL), air-dried, and characterized as **1**. Obtained: 0.506 g (74% yield). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, rt): δ (ppm) 68.54.

Synthesis of [Pd(*μ*-Cl)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}]_2(ClO_4)_2$ (2). To a suspension of **1** (0.300 g, 0.45 mmol) in a mixture of CH_2Cl_2 (30 mL)/acetone (10 mL) was added $AgClO_4$ (0.094 g, 0.45 mmol). This mixture was stirred at room temperature with exclusion of light for 1 h, and then filtered over Celite to remove the precipitated AgCl. The resulting deep yellow solution was evaporated to dryness, and the residue was treated with Et_2O (30 mL). The yellow solid obtained (**2**) was filtered, washed with Et_2O (20 mL), and air-dried. Obtained: 0.259 g (79% yield). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, rt): δ (ppm) 68.75.

Synthesis of [Pd((*μ*-OAc)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}]_2(ClO_4)_2$ (3). To a solution of **2** (0.200 g, 0.14 mmol) in CH_2Cl_2 (30 mL) was added AgOAc (0.047 g, 0.28 mmol). This mixture was stirred at room temperature with exclusion of light for 30 min, and then filtered over Celite. The resulting yellow solution was evaporated to dryness, and the residue was treated with Et_2O (30 mL). The yellow solid obtained (**3**) was filtered, washed with Et_2O (20 mL), and air-dried. Obtained: 0.190 g (92% yield). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, rt): δ (ppm) 68.53.

Synthesis of [Pd(acac-*O*,*O*′)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (4). To a solution of **2** (0.4532 g, 0.313 mmol) in CH_2Cl_2 (30 mL) was added Tl(acac) (0.190 g, 0.626 mmol). This mixture was stirred at room temperature for 30 min, and then filtered over Celite to remove the precipitated TlCl. The resulting cream-colored solution was evaporated to dryness, and the residue was treated with Et_2O (30 mL). The cream solid was filtered, washed with Et_2O (20 mL), air-dried, and identified as **4**. Obtained: 0.428 g (87% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 63.33.

General Method for the Synthesis of Complexes [Pd(L-amino acidate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5a−5m). All complexes **5a**−**5m** were prepared in the same way. The synthesis of **[Pd(L-alaninate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5a)** is reported here as a representative example. To a solution of **4** (0.100 g, 0.127 mmol) in methanol (30 mL) was added L-alanine (0.0113 g, 0.13 mmol). This mixture was refluxed for 3 h. After cooling, the solvent was evaporated to dryness, and the residue was treated with Et_2O (30 mL). The white solid was filtered, washed with Et_2O (20 mL), air-dried, and identified as **5a**. Obtained: 0.0923 g (94% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.31 (d, P-*trans*-O, $^2J_{P-P}$ = 16.6 Hz), 54.69 (d, P-*trans*-N). $^{31}P\{^1H\}$ NMR (dmso-d_6, rt): δ (ppm) 64.06 (d, P-*trans*-O, $^2J_{P-P}$ = 18.9 Hz), 50.96 (d, P-*trans*-N).

[Pd(L-2-aminobutyrate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5b). Prepared from **4** (0.100 g, 0.127 mmol) and L-2-aminobutyric acid (0.0131 g, 0.13 mmol) as described for **5a**. Obtained: 0.087 g (86.5% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.49 (d, P-*trans*-O, $^2J_{P-P}$ = 17.5 Hz), 52.61 (d, P-*trans*-N).

[Pd(L-valinate-*κ*-*N*,*O*)(1*R*,2R)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5c). Prepared from **4** (0.100 g, 0.127 mmol) and L-valine (0.0149 g, 0.13 mmol) as described for **5a**. Obtained: 0.083 g (81% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.16 (d, P-*trans*-O, $^2J_{P-P}$ = 19.0 Hz), 51.35 (d, P-*trans*-N).

[Pd(L-phenylalaninate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5d). Prepared from **4** (0.100 g, 0.127 mmol) and L-phenylalanine (0.0210 g, 0.13 mmol) as described for **5a**. Obtained: 0.088 g (81% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.47 (d, P-*trans*-O, $^2J_{P-P}$ = 18.7 Hz), 52.16 (d, P-*trans*-N).

[Pd(L-prolinate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5e). Prepared from **4** (0.100 g, 0.127 mmol) and L-proline (0.015 g, 0.13 mmol) as described for **5a**. Obtained: 0.100 g (90% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 67.00 (d, P-*trans*-O, $^2J_{P-P}$ = 23.0 Hz), 52.00 (d, P-*trans*-N).

[Pd(L-leucinate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5f). Prepared from **4** (0.100 g, 0.127 mmol) and L-leucine (0.0166 g, 0.13 mmol) as described for **5a**. Obtained: 0.092 g (88% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.65 (d, P-*trans*-O, $^2J_{P-P}$ = 18.2 Hz), 54.11 (d, P-*trans*-N).

[Pd(L-isoleucinate-*κ*-*N*,*O*)(1*R*,2*R*)-$(PPh_2NH)_2C_6H_{10}](ClO_4)$ (5g). Prepared from **4** (0.100 g, 0.127 mmol) and L-isoleucine (0.0166 g, 0.13 mmol) as described for **5a**. Obtained: 0.097 g (93% yield). $^{31}P\{^1H\}$ NMR ($CDCl_3$, rt): δ (ppm) 66.29 (d, P-*trans*-O, $^2J_{P-P}$ = 18.8 Hz), 51.20 (d, P-*trans*-N).

[Pd(L-norleucinate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5h). Prepared from **4** (0.100 g, 0.127 mmol) and L-norleucine (0.0166 g, 0.13 mmol) as described for **5a**. Obtained: 0.088 g (84% yield). ^{31}P{^{1}H} NMR (CDCl$_3$, rt): δ (ppm) 66.64 (d, P-*trans*-O, $^2J_{P-P}$ = 16.9 Hz), 51.77 (d, P-*trans*-N).

[Pd(L-serinate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5i). Prepared from **4** (0.100 g, 0.127 mmol) and L-serine (0.0133 g, 0.13 mmol) as described for **5a**. Obtained: 0.092 g (91% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 67.76 (d, P-*trans*-O, $^2J_{P-P}$ = 15.0 Hz), 52.58 (d, P-*trans*-N).

[Pd(L-threoninate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5j). Prepared from **4** (0.100 g, 0.127 mmol) and L-threonine (0.0151 g, 0.13 mmol) as described for **5a**. Obtained: 0.087 g (85% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 65.72 (d, P-*trans*-O, $^2J_{P-P}$ = 17.6 Hz), 49.99 (d, P-*trans*-N).

[Pd(L-methioninate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5k). Prepared from **4** (0.100 g, 0.127 mmol) and L-methionine (0.0189 g, 0.13 mmol) as described for **5a**. Obtained: 0.103 g (97% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 64.88 (d, P-*trans*-O, $^2J_{P-P}$ = 18.2 Hz), 50.32 (d, P-*trans*-N).

[Pd(L-aspartate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5l). Prepared from **4** (0.100 g, 0.127 mmol) and L-aspartic acid (0.0169 g, 0.13 mmol) as described for **5a**. Obtained: 0.093 g (89% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 65.38 (d, P-*trans*-O, $^2J_{P-P}$ = 16.6 Hz), 50.09 (d, P-*trans*-N).

[Pd(L-glutaminate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5m). Prepared from **4** (0.100 g, 0.127 mmol) and L-glutamine (0.0190 g, 0.13 mmol) as described for **5a**. Obtained: 0.094 g (88.8% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 64.70 (d, P-*trans*-O, $^2J_{P-P}$ = 18.6 Hz), 50.33 (d, P-*trans*-N).

[Pd(L-cysteinate-κ-*N,O*)(1*R*,2*R*)-(PPh$_2$NH)$_2$C$_6$H$_{10}$](ClO$_4$) (5n). Prepared from **4** (0.100 g, 0.127 mmol) and L-cysteine (0.0154 g, 0.13 mmol) as described for **5a**. Obtained: 0.099 g (96% yield). ^{31}P{^{1}H} NMR (DMSO-d_6, rt): δ (ppm) 58.27 (d, P-*trans*-S, $^2J_{P-P}$ = 19.4 Hz), 51.65 (d, P-*trans*-N).

Crystal Structure Determination of Complex 5i·3H$_2$O. Crystals of complex **5i.**3H$_2$O of adequate quality for X-ray measurements were grown by slow diffusion of Et$_2$O into a solution of crude **5i** in MeOH/acetone (95:5) at −18 °C for 3 weeks. A single crystal of dimensions 0.22 × 0.13 × 0.11 mm was mounted at the end of a quartz fiber in a random orientation and covered with epoxy.

Data Collection. Data collection was performed at 100 K on a Bruker Smart CCD diffractometer using graphite-monocromated Mo Kα radiation (λ = 0.71073 Å). A hemisphere of data was collected on the basis of three ω-scan runs (starting ω = −30°) at values of ϕ = 0°, 90°, and 180° with the detector at 2θ = 30°. For each of these runs, frames (606, 435, and 230, respectively) were collected at 0.3° intervals and 10 s per frame. The diffraction frames were integrated using the program SAINT,[12] and the integrated intensities were corrected for absorption with SADABS.[13]

Structure Solution and Refinement. The structures were solved and developed by Patterson and Fourier methods.[14] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at idealized positions and treated as riding atoms, with an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. The structures were refined to F_o^2, and all reflections were used in the least-squares calculations.[15]

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Supporting Information Available: Complete experimental details and characterization data for all complexes and CIF data for the crystal structure determination of complex **5i**·3H$_2$O. This material is available free of charge via the Internet at http://pubs.acs.org.

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