Determination of Enantiomer Purity of β- and γ-Amino Acids by NMR Analysis of Diastereoisomeric Palladium Complexes

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Dedicated to Professor *Günter Helmchen* on the occasion of his 60th birthday

Like α-amino acids, β- and γ-amino acids form spirobicyclic complexes (see **2** and **3**) by reaction with the chiral di-μ-chlorobis{2-[1-dimethylamino-$\varkappa N$)-ethyl]phenyl-$\varkappa C$}dipalladium complexes **1** under basic conditions (*Scheme 1* and X-ray structures in *Fig. 1*). The diastereoisomeric complexes formed with mixtures of enantiomers of either the amino acids or the dichloro-dipalladium complexes give rise to marked chemical-shift differences in the ^{1}H- and ^{13}C-NMR spectra (*Figs. 2–4*) to allow determination of the enantiomer purities. A simple procedure is described by which β- and γ-amino acids (which may be generated *in situ* from Boc- or Fmoc-protected precursors) are converted to the Pd complexes and subjected to NMR measurements. The effects of solvent, temperature, and variation of the aryl group in the chiral derivatizing Pd reagent are described (*Figs. 4* and *5*). The methyl esters of β-amino acids can also be employed, forming diastereoisomeric chloro[(amino-$\varkappa N$)aryl-$\varkappa C$][(amino-$\varkappa N$)alkanoate]palladium complexes **6** for determining enantiomer ratios (*Scheme 6*). The new method has great scope, as demonstrated for β^2-, β^3-, $\beta^{2,3}$-, $\beta^{2,2,3}$-, γ^2-, γ^3-, γ^4-, and $\gamma^{2,3,4}$-amino acid derivatives.

1. Introduction. – Analytical methods for determining enantiomer purities have become very important in the past decade due to the explosively growing attention to the synthesis and application of enantiomerically pure compounds. In our own work, β-amino acids, homologs of α-amino acids, and the β-peptides derived therefrom, have become the center of interest during the past five years [1]. β-Peptides form secondary structures, including helices [2][3], pleated sheets [2][4], and turns [4][5], they are stable to mammalian peptidases [2][6], and they are promising candidates for drugs [7]. There is a growing need for enantiomerically pure β-, and also γ-amino acids [8–11], and various approaches to their stereoselective syntheses have been developed [3][8–13].

On the other hand, determination of enantiomer purity and also of absolute configuration of these compounds is still a challenge[2]). To the best of our knowledge, no *general* method for this purpose has been developed so far, albeit enantiomer

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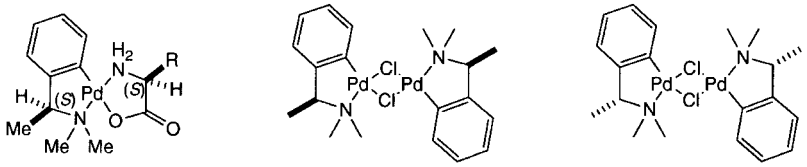
[2]) The method of choice for the preparation of β^3-amino acids on a research-laboratory scale is the *Arndt-Eistert* homologation of α-amino acids, which has been shown to be free of racemization except when performed with phenylglycine [12][14]. For the preparation of β^2-amino acids we have, so far, used exclusively the *Evans* auxiliary approach [3][13][15], which does not always provide enantiomerically pure compounds. $\beta^{2,3}$-Amino acids are accessible by α-alkylation of enantiomerically pure β^3-amino acids through doubly lithiated intermediates, a method developed by us more than a decade ago [3][16][17]. γ-Amino acids have been prepared by double homologation of α-amino acids [8][18] or by addition of *Evans*-type enolates to nitro olefins, and hydrogenation [10].

purities of several β- and γ-amino acids have been determined by HPLC and NMR spectroscopy [14][19][20][3]). This is in contrast to the situation with α-amino acids where a broad arsenal of modern analytical methods is available for the determination of enantiomer ratios. For chromatographic resolution by HPLC and GC on either a chiral or achiral stationary phase, the α-amino acids are usually derivatized [21][22]. Separation of the free amino acids is also possible by HPLC [23], whereas, for GC analysis, the generation of volatile amino acid derivatives is essential [22]. A recently developed alternative to chromatographic methods is capillary electrophoresis (CE), where only tiny amounts of reagents, solvents, and chiral selectors are required [24]. NMR is a well-established method, and enantiomer purity of α-amino acids can be determined by means of chiral derivatizing agents (CDAs), chiral solvating agents (CSAs), and chiral lanthanide shift reagents [20][25].

Chiral metal complexes such as **1** have been widely used as resolving agents for various racemic mixtures [26], as CDAs for determination of enantiomer purity [27] and of absolute configuration [28], as chiral templates [29], and as catalysts [30] for asymmetric synthesis. Compound **1** was also used for determining enantiomer ratios in α-amino acids by forming [(amino-$\varkappa N$)aryl-$\varkappa C$][(amino-$\varkappa N$)alkanoato-$\varkappa O$]palladium complexes **A** [31]. We have now found that the chiral metal complexes **1** (and naphthalenyl analogs) can be used as derivatizing agents for NMR determination of enantiomer ratios of a wide range of β- and γ-amino acids with various substitution patterns. Also, assignment of the absolute configuration of β^2-amino acids is possible, by means of complexes derived from the di-μ-chlorobis[(amino-$\varkappa N$)-aryl-$\varkappa C$]dipalladium complexes (*R*,*R*)-**1** or (*S*,*S*)-**1**.



A (*S*,*S*)-**1** (*R*,*R*)-**1**

Results and Discussion. – The chloro-bridged metal complex **1** is known to react with α-amino acids to give spirobicyclic square-planar [(amino-$\varkappa N$)alkanoato-$\varkappa O$]-palladium complexes **A** [31]. In these, the amino acid is coordinated to the Pd-atom *via* the amino group and a carboxylate O-atom to form a metallacycle. ^{1}H-NMR Spectra of diastereoisomers of complexes **A** show good resolution of signals from diastereoisotopic groups of protons, and determination of the enantiomer purity of various α-amino acids has been possible [31]. We wondered whether the complexes **1** can also be used for derivatizing and determining enantiomer purities of β- and γ-amino acids. The corresponding six- and seven-membered metallacycles would have stereogenic centers next to the amino group (β^3- or γ^4-amino acids) or next to the carboxylate group (β^2- or

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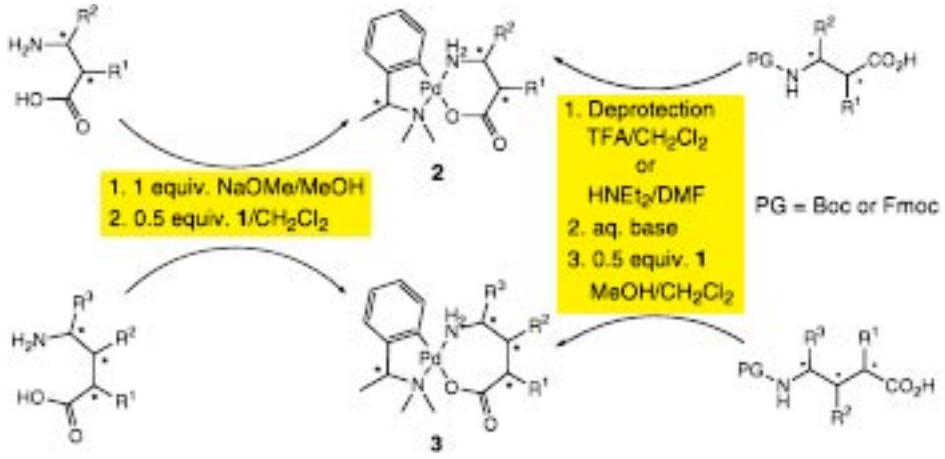
3) So far, attempts to derivatize β-amino acids and to determine enantiomer ratios by gas chromatography have been unsuccessful.

4) For our nomenclature of β- and γ-amino acids, see [3]; the superscript indicates the position of the side chain along the C_3 or C_4 chain of the corresponding amino acid.

γ^2-amino acids)[4]), so that we expected that their NMR spectra would show sizeable chemical-shift differences for diastereoisomeric complexes.

In fact, β- and γ-amino acids react smoothly with the chiral Pd complexes (*S*,*S*)-**1** and (*R*,*R*)-**1** to give complexes **2** and **3** (*Scheme 1*, left side).

Scheme 1. *Generation of Diastereoisomeric Pd Complexes* **2** *and* **3** *from Free and Protected β- and γ-Amino Acids.* For examples, see *Fig. 2*



Addition of a base (NaOMe) is required to generate the corresponding carboxylate from the free amino acid. Since *N*-Boc- and *N*-Fmoc-protected α-, β-, and γ-amino acids (Boc = (*tert*-butoxy)carbonyl; Fmoc = (9*H*-fluoren-9-yl)methoxycarbonyl) are widely used in peptide synthesis, we developed a procedure for generating metal complexes **2** and **3** directly from protected precursors without having to isolate the free amino acids (*Scheme 1*, right side): after standard deprotection with CF_3COOH (TFA)/CH_2Cl_2 (Boc) or Et_2NH/DMF (Fmoc) and addition of a base, the amino carboxylates generated react with **1** *in situ* to give the corresponding metal complexes[5]). It is noteworthy that generation of **2** and **3** is not sensitive to the presence of H_2O or air, and, therefore, aqueous amino acid solutions can be employed in this procedure (see *Exper. Part*).

To ensure that the new complexes have structures resembling those of the α-amino acids[6]), the structures of the [β-(amino-$\varkappa N$)butanoato-$\varkappa O$] complexes **2a** and **2i** were determined by X-ray diffraction (*Fig. 1*)[7]).

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[5]) A slight excess (*ca.* 1.05 equiv.) of the protected amino acid derivative is usually employed. Excess of amino acid is easily removed from the metallacyclic product by extraction of a $CHCl_3$ solution with $NaHCO_3$ (see *Exper. Part*). Preferred formation of one diastereoisomer by kinetic resolution has not been observed: reaction of (*S*,*S*)-**1** with a *ca.* 10-fold excess of *rac*-H-β^3-HAla-OH led to formation of the two diastereoisomeric complexes in an exactly 1:1 ratio (by NMR analysis).

[6]) *I.e.*, *trans*-positions of the two N-atoms and of the aryl C-atom with respect to the carboxylato O-atom in a square-planar coordination polyhedron about the Pd-atom.

[7]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-147215 (**2a**) and No. CCDC-147216 (**2i**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

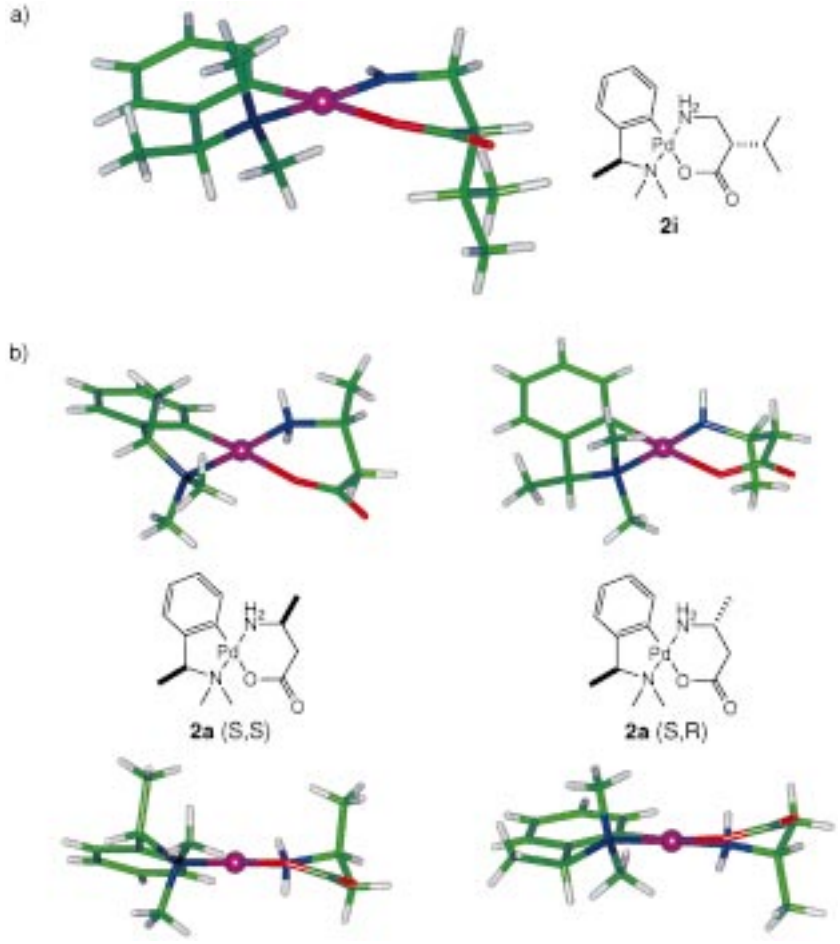

Fig. 1. *X-Ray crystal structures of Pd complexes* **2a** *and* **2i**. C-Atoms in green, O-atoms in red, N-atoms in blue, H-atoms in grey, Pd-atoms in violet. The views have been generated with the program *Insight II* (v. 98.0). The structures were determined by Dr. *B. Schweizer*. *a*) Molecular structure of **2i** · 2 $CHCl_3$ ((*S*,*S*)-diastereoisomer, the $CHCl_3$ molecules are omitted for clarity). *b*) Molecular structure of **2a**. The unit cell contains two independent molecules, one of the (*S*,*S*)- and one of the (*S*,*R*)-form. Note that both the five- *and* the six-membered rings have different conformations in the two diastereoisomers.

The Pd-atom has, indeed, a slightly distorted square-planar ligand coordination, and the amino acid ligand is coordinated to Pd *via* the N- and a carboxylato O-atom to form a six-membered metallacycle. Interestingly, the side chains of the amino acid ligands in all three molecules of the X-ray structures are in axial positions of the six-membered rings. The structure of **2a** contains two independent molecules in the unit cell, the (*S*,*S*)-(*Fig. 1, b*, left side) and the (*S*,*R*)-diastereoisomer (*Fig. 1, b*, right side), which have different conformations of both the five- and the six-membered metallacycles. Whereas the Me group of the amino acid ligand is in an axial position at the six-membered ring in

both diastereoisomeric structures, the Me group of the chiral amine ligand adopts an axial position on the five-membered ring of the (*S,S*)-isomer and an equatorial position of the (*S,R*) isomer. Especially the Me_2NCH, the Me but also the Me_2N protons of the chiral amine ligand have significantly different chemical environments in the two diastereoisomers, which cause the large chemical-shift differences observed in the NMR spectra (*Figs. 2–4*)[8].

To demonstrate the broad applicability of the Pd complex **1** as CDA for determining the enantiomer purities of β- and γ-amino acids, a large number of diastereoisomeric complexes (see **2a**–**m** and **3a**–**e**) were generated from a wide variety of β- and γ-amino acids with different substitution patterns, and subjected to ^{1}H-NMR (*Fig. 2*), and ^{13}C-NMR measurements (*Fig. 3*).

The largest and most useful shift differences (in Hz) are indicated in the corresponding positions of the *Formulae* of *Figs. 2* and *3*. In many of the cases tested there was a pair of ^{1}H-NMR signals with base-line separation that could be used for reliable integration. In *Fig. 4*, we show some representative ^{1}H-NMR spectra. The chemical-shift differences of H-atoms on the chiral amine ligand are especially large (up to 134.5 Hz at 300 MHz for the Me_2NCH signals of **3e**), and the corresponding signals are generally those most suitable for determining the diastereoisomer ratios of complexes **2** and **3**. Thus, in the shift ranges of δ *ca.* 1.5 ppm (Me), δ 2.5–2.9 ppm (Me_2N) and δ *ca.* 4 ppm (Me_2NCH), there exist three spectroscopic windows for signal integration, which minimizes problems arising from signal overlap with resonances of the amino acid ligand. To some extent, the chemical-shift differences depend on the solvent used; in many cases CD_3OD is the solvent of choice, but sometimes mixtures of $CDCl_3/CD_3OD$ or C_6D_6/CD_3OD give somewhat better results (*Fig. 2*)[9]. Inadequate line separation may be improved by lowering the temperature as shown for the β-HAla derivative **2a** in *Fig. 4, b*. A 'side effect' of lowering the temperature is that the NH_2 signal moves to lower field, which can be an advantage, 'clearing' the shift range around δ 4 ppm[10]). Elimination of the sometimes interfering NH_2 resonances can also be achieved simply by keeping a solution in CD_3OD of the corresponding metal complex for several days at room temperature, which causes NH_2/ND_2 exchange.

The Me_2NCH resonances of diastereoisomeric metal complexes **2g**–**j** generated from various β^2-amino acids are shown in *Fig. 4, c*. The complexes of *trans*-configuration of the side chain and Me group all show a lower-field shift for the Me_2NCH signals, as compared to their *cis*-isomers. This effect can be used for assigning the absolute configuration of β^2-amino acids: reaction of a non-racemic mixture of (*R,R*)-**1** and (*S,S*)-**1** of known composition with an enantiomerically pure β^2-amino acid of unknown absolute configuration generates the *cis*/*trans*-isomers of the corresponding metal complexes in unequal amounts. Integration of the Me_2NCH signals provides the information necessary to assign the absolute configuration to the β^2-amino acid by

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[8]) Complexes of the naphthalenyl analogs show low resolution of these signals, probably because the Me group of the chiral-amine ligand is locked in an axial position (*cf.* [32]).

[9]) The use of pure $CDCl_3$ or C_6D_6 can lead to significant line broadening.

[10]) NH_2 Resonances sometimes overlap with the Me_2NCH resonances of the chiral-amine ligand.

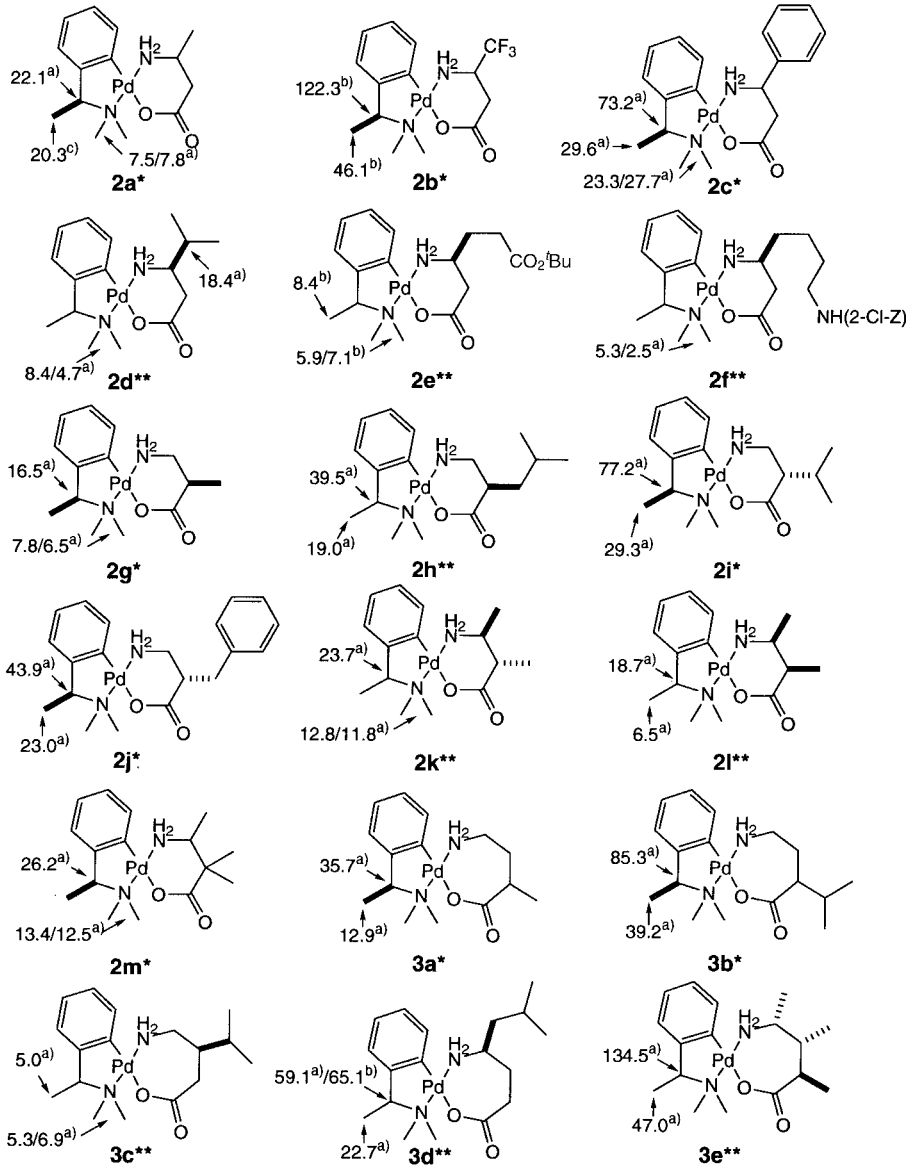


Fig. 2. *Chemical-shift differences in the ^{1}H-NMR spectra of diastereoisomeric complexes* **2** *and* **3** *generated from racemic or enantiomerically enriched amino acids and* (S,S)-**1** (*), *or from enantiomerically pure amino acids and mixtures of* (R,R)-**1** *and* (S,S)-**1** (**). The spectra were measured with a 300-MHz instrument. The values given here for selected H-atoms are in Hz. The solvents used were [a]) CD_3OD, [b]) $CDCl_3/CD_3OD$, [c]) C_6D_6/CD_3OD.

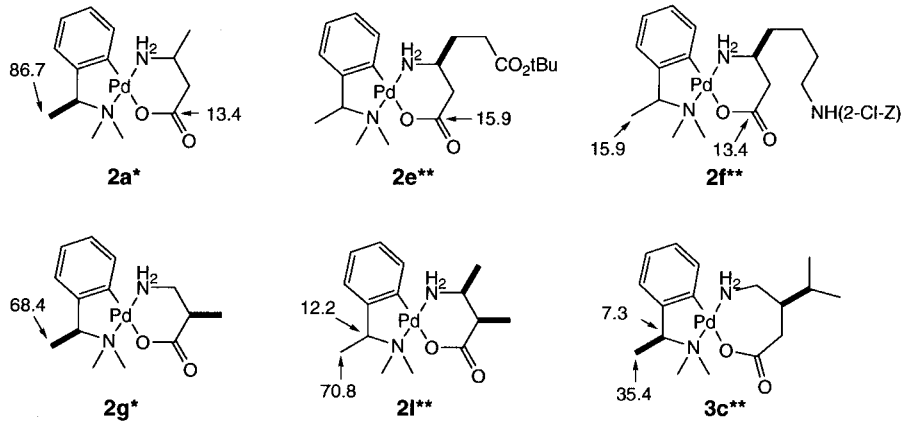


Fig. 3. *Chemical-shift differences in the ^{13}C-NMR spectra of diastereoisomeric complexes* **2** *and* **3** *generated from racemic or enantiomerically enriched amino acids and (*S,S*)-***1*** (*), or from enantiomerically pure amino acids and mixtures of (*R,R*)-***1*** and (*S,S*)-***1*** (**). The spectra were measured with a 300-MHz instrument. The values given here for selected C-atoms are in Hz. The solvent used was CD_3OD.*

analogy (see *Fig. 4, c*). On the other hand, the absolute configuration of the enantiomers in an enantiomerically enriched sample of a β^2-amino acid can be assigned by generating the diastereoisomers of the corresponding metal complexes from enantiomerically pure (*S,S*)-**1** or (*R,R*)-**1**.

In some cases ^{1}H-NMR separation of signals from diastereoisomeric complexes is too small (*e.g.*, **2e** and **2f** in *Fig. 2*), and the diastereoisomer ratio has to be determined by a time-consuming quantitative ^{13}C-NMR measurement (*cf. Fig. 3*). Therefore, we have checked whether the chiral metal complex **4**, the naphthalenyl analog of **1**, might be a more useful alternative. The chloro complex **4** reacts smoothly with β-amino acids to give [(amino-$\varkappa N$)alkanoato-$\varkappa O$] complexes **5** (*Fig. 5, a*). While separations of the corresponding ^{1}H-NMR signals from these naphthalenyl complexes are generally small, which is especially true for the Me_2NCH, Me, and Me_2N resonances of the chiral-amine ligand[8]), diastereoisomer ratios can sometimes be determined in the part of the spectrum arising from the amino acid moieties (for an example, see *Fig. 5, c* compound **5c**).

Metal complex **1** can also be used for determining the enantiomer purities of β-amino acid *esters*, which react to give diastereoisomeric complexes **6**. The structure of these complexes, as shown in *Fig. 6*, is related to that of similar compounds formed with α-amino acid esters [33][34]. Surprisingly large chemical-shift differences in the ^{1}H-NMR spectra of diastereoisomeric complexes **6** are observed (*Fig. 6, b*), even for complex **6c** derived from a β^2-amino acid methyl ester, with a 1,6-distance between the stereogenic center of the CDA and of the amino acid component (*Fig. 6, c*). The large shift difference between the CO_2Me protons in the two diastereoisomers would suggest that the carbonyl O-atom is coordinated to the Pd center. This should lead to a shift of the C=O frequency (*ca.* 100 cm^{-1} [33]); however, the IR spectra in $CHCl_3$ of the amino acid ester (ν(CO) = 1730 cm^{-1}) and of the complex **6c** (ν(CO) = 1723 cm^{-1}) differ very

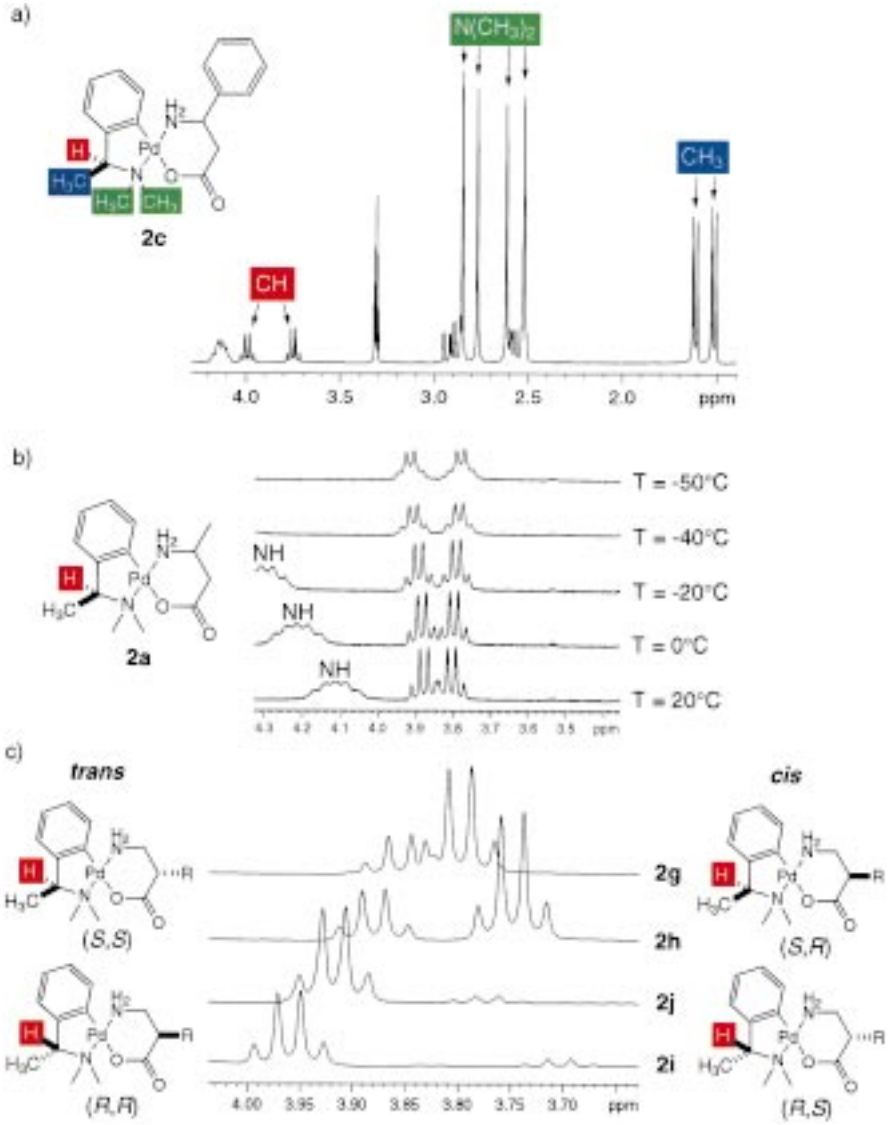


Fig. 4. *Chemical-shift differences in the ^{1}H-NMR spectra* (300 MHz, CD_3OD) *of diastereoisomeric complexes derived from various β-amino acids. a*) ^{1}H-NMR Spectrum of **2c** (prepared from *rac*-H-β^3-HPhg-OH and (*S*,*S*)-**1**). *b*) ^{1}H-NMR Spectrum of **2a** (prepared from *rac*-H-β^3-HAla-OH and (*S*,*S*)-**1**) at variable temperatures. *c*) Me_2NCH Resonances of *cis*/*trans*-isomers of β^2-amino carboxylato complexes **2g** – **2j**; the signal arising from the *trans*-isomers is at lower field.

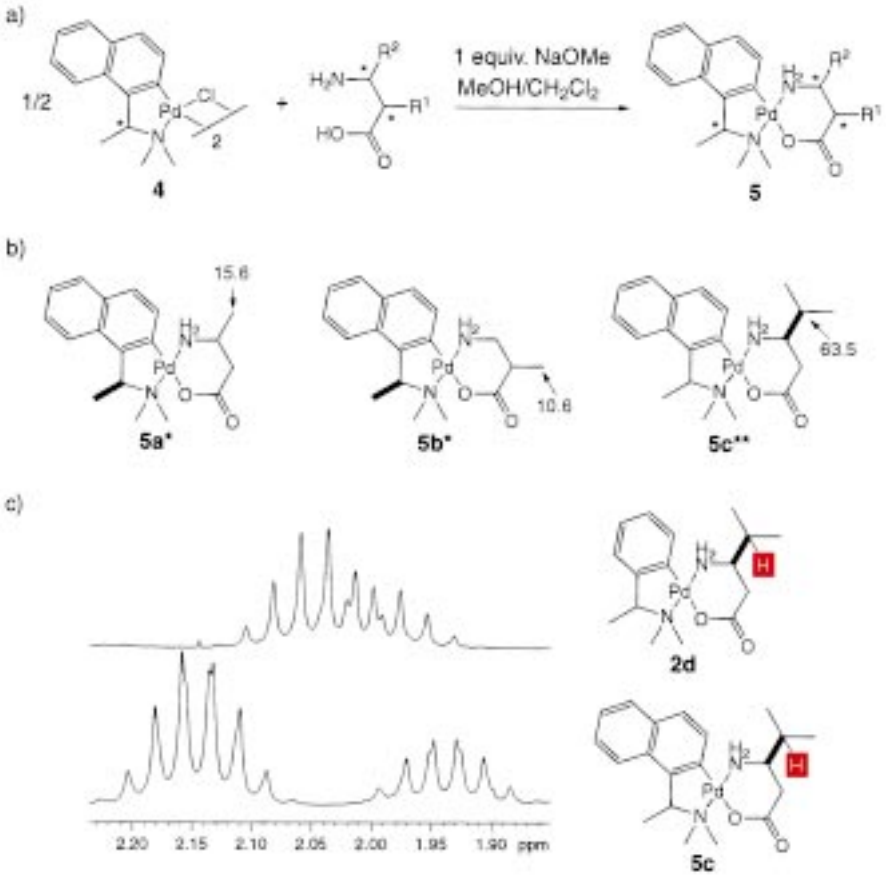
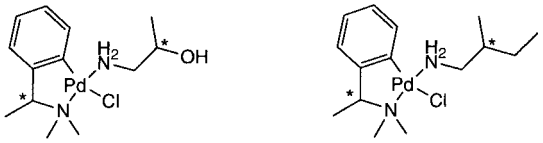


Fig. 5. *Generation of naphthalenyl analogs* **5** *of the complexes* **2** *and comparison of the* ^{1}*H-NMR spectra. a*) Generation of diastereoisomeric Pd complexes **5** from free β-amino acids. *b*) Diastereoisomers of **5** prepared from racemic amino acids and (*S*,*S*)-**4** (*) or from enantiomerically pure amino acids and mixtures of (*R*,*R*)-**4** and (*S*,*S*)-**4** (**). Resolution of ^{1}H-NMR signals (300 MHz, CD_3OD) is given for selected protons (values in Hz). *c*) ^{1}H-NMR Resonances (300 MHz, CD_3OD) of diastereoisomers of **2d** and **5c** prepared from enantiomerically pure Boc-(*S*)-β^3-HVal-OH (*cf. Scheme 1*, right) and a mixture of (*R*,*R*)-**1** and (*S*,*S*)-**1**, and (*R*,*R*)-**4** and (*S*,*S*)-**4** ((*R*,*R*)/(*S*,*S*) 30:70), respectively.

little. Still, an interaction between the O-atom and the metal, at least on the NMR time scale, must be present[11]).

[11]) This is also compatible with the observation of large shift differences among the Me_2NCH, Me, and Me_2N protons of the aminoaryl ligand in the diastereoisomers of **i** but not those of **ii**!



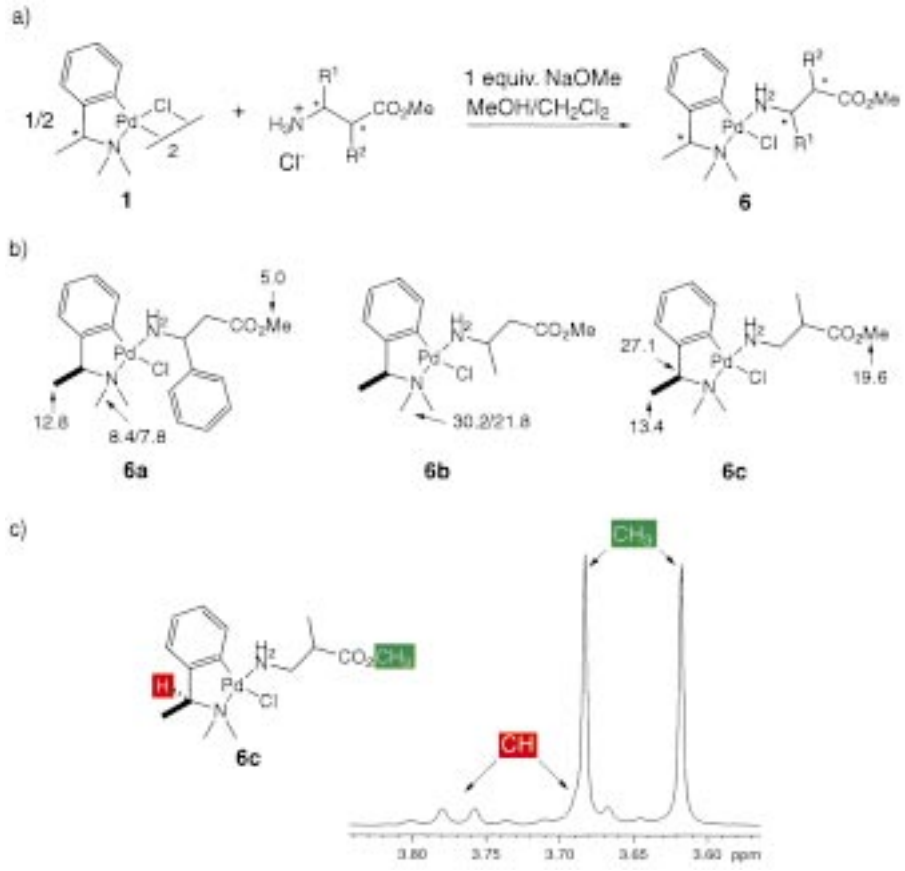
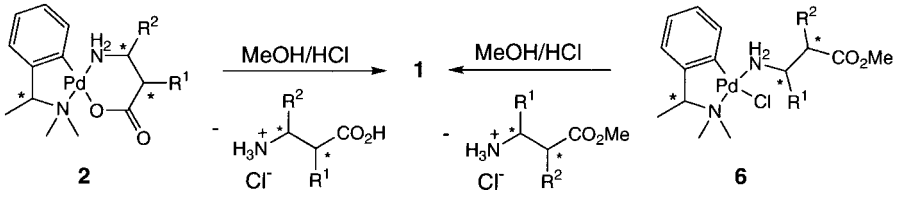


Fig. 6. *Diastereoisomeric Pd complexes* **6** *prepared from hydrochlorides of* rac-*β-amino acid esters and (*S,S*)-***1***, and separation of their [1]H-NMR signals. a*) Generation of Pd complexes **6**. *b*) Diastereoisomers of **6** and resolution of ^{1}H-NMR signals (300 MHz, $CDCl_3$) given for selected protons (values in Hz). *c*) ^{1}H-NMR Resonances (300 MHz, $CDCl_3$) of diastereoisomers of **6c**.

The chiral derivatizing agent **1** and also the amino acid components of the complexes **2**, **3**, **5**, and **6** can be easily recovered after use. As shown for complexes **2** and **6** in *Scheme 2*, treatment of a MeOH solution with aqueous HCl solution destroys the complexes and regenerates the chiral metal complex **1** and the amino acid component.

Scheme 2. *Recovery of Chiral Derivatizing Agent* **1** *from Amino Acid or Amino Acid Ester Complexes*



Because of their different solubility in $CHCl_3$ and H_2O, separation of the two components is very simple (see *Exper. Part*).

Conclusion. – A general NMR method is now available for determining the enantiomer purities of β- and γ-amino acids and of β-amino acid methyl esters by means of chiral metal complexes such as **1** and **4**. The examples presented demonstrate the broad scope of the method, which is applicable to β- and γ-amino acids with various substitution patterns, including β^2-, β^3-, $\beta^{2,3}$-, $\beta^{2,2,3}$-, γ^2-, γ^3-, γ^4-, and $\gamma^{2,3,4}$-amino acids, as well as to β^2- and β^3-amino acid[4]) methyl esters. The procedure is characterized by a small preparative effort and a fast determination procedure. In favorable cases, the enantiomer purity of an amino acid can be determined by ^{1}H-NMR spectroscopy within a few hours. Chiral derivatizing agents **1** and **4** can be easily prepared by a one-step procedure from commercially available compounds (see *Exper. Part*). In addition, it is possible to derive the absolute configuration of β^2-amino acids from the NMR spectra of the complexes formed with **1**. The starting materials can be recovered by cleaving the metal complexes with 1N aqueous HCl solution.

We thank Dr. *B. Schweizer* for the determination of the X-ray crystal structures. We gratefully acknowledge financial support of the *Deutsche Forschungsgemeinschaft* (grant No. BO 1663/1-1 to *A. B.*). We thank *M. Brenner*, *T. Hintermann*, *S. Abele*, *T. Sifferlen*, *Y. Mahajan*, and *A. Jacobi* for the generous donation of samples of various β- and γ-amino acids and amino acid derivatives.

Experimental Part

1. *General*. Abbreviations: Boc: (*tert*-butoxy)carbonyl, Fmoc: (9*H*-fluoren-9-yl)methoxycarbonyl, FC: flash chromatography, h.v.: high vacuum (0.01 – 0.1 Torr), β-HXaa: β-homoamino acid, γ-HHXaa: γ-homohomoamino acid, TFA: trifluoroacetic acid, DMF: dimethyl formamide. Et_3N was distilled over CaH_2. A *ca.* 1M solution of MeONa in MeOH was prepared by dissolving Na metal (50 mmol) in MeOH (50 ml). The exact molarity was determined by titration with 0.1M HCl against phenolphthalein as indicator. Amino acids and amino acid derivatives were prepared according to literature procedures [3][8][10][12 – 14][35 – 37]. *rac*-3-Aminobutanoic acid, *rac*-3-amino-2-methylpropanoic acid, and *rac*-3-amino-3-phenylpropanoic acid were purchased from *Fluka* and *Aldrich*. Amino acid methyl ester hydrochlorides were prepared from the free amino acids by esterification with $SOCl_2$/MeOH. All other reagents were used as received from *Fluka*, *Aldrich*, and *Strem*. FC: *Fluka* silica gel *60* (40 – 63 mm); at *ca.* 0.2 bar. M.p.: *Büchi-510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1620-FT-IR* spectrometer, in cm^{-1}. NMR Spectra: *Varian Gemini 300* (^{1}H: 300 MHz, ^{13}C: 75 MHz); chemical shifts (δ) in ppm, *J* values in Hz; chemical shifts of diastereoisomers in the ^{13}C-NMR spectra are indicated by an asterisk. MS: *VG ZAB2-SEQ* (FAB, in a 3-nitrobenzyl-alcohol matrix) spectrometer; *m/z* (% of basis peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

2. *Preparation of Di-μ-chlorobis{2-[1-(dimethylamino-κN)ethyl]phenyl-κC}dipalladium* (**1**) *and Di-μ-chlorobis{1-[1-(dimethylamino-κN)ethyl]naphthalen-2-yl-κC}dipalladium* (**4**). Complexes **1** and **4** ((*R*,*R*)- and (*S*,*S*)-isomers, resp.) were prepared by slight modifications of the literature procedures [38]: To a soln. of $Na_2PdCl_4 \cdot 3\ H_2O$ (5 mmol) in MeOH (25 ml (**1**) or 12 ml (**4**)) the corresponding chiral amine (5 mmol) and Et_3N (5 mmol) were added and stirred overnight. The resulting precipitate was filtered off, washed with MeOH, and dried under h.v. FC ($CHCl_3$) yielded the pure compounds.

3. *Generation of Pd Complexes* **2**, **3**, *and* **5**. 3.1. *From Free Amino Acids: General Procedure 1* (*GP 1*). To a soln./suspension of the free amino acid (0.2 mmol) in MeOH (10 – 15 ml), a 1M soln. of MeONa in MeOH (200 μl) was added and the mixture was stirred for 15 – 20 min. A soln. of complex **1** or **4** (0.1 mmol) in CH_2Cl_2 (3 ml) was added, and the resulting colorless soln. was stirred for 1 – 2 h at r.t. After evaporation, the residue was treated with $CHCl_3$ or $CHCl_3$/MeOH (*ca.* 100 : 1) and H_2O. The org. phase was washed with $NaHCO_3$ and H_2O. Evaporation and drying under h.v. yielded a colorless residue, which was investigated by NMR spectroscopy.

3.2. *From Boc-Protected Amino Acids: General Procedure 2* (*GP 2*). To a soln. of the Boc-protected amino acid (0.2 mmol) in CH_2Cl_2 (2 ml), TFA (2 ml) at 0° (ice bath) was added. After 15 min, the mixture was allowed

to warm to r.t. and stirred for further 2 h. The solvent was evaporated, and the residue was dried under h.v. After addition of a soln. of Na_2CO_3 (2–3 mmol) in H_2O (2 ml) and subsequent dilution with MeOH (15 ml), a soln. of complex **1** or **4** (*ca.* 0.095 mmol) in CH_2Cl_2 (3 ml) was added, and the resulting colorless soln. was stirred for 1–2 h at r.t. Similar workup as described in *GP 1* yielded a colorless residue, which was investigated by NMR spectroscopy.

3.3. *From Fmoc-Protected Amino Acids: General Procedure 3* (*GP 3*). To a soln. of the Fmoc-protected amino acid (0.2 mmol) in DMF (2 ml), Et_2NH (0.2 ml) was added, and the mixture was stirred for 2 h. After evaporation, the residue was dried under h.v. and treated with H_2O (2–3 ml) and a 1M soln. of MeONa in MeOH (200 µl). $CHCl_3$ was added, and the aq. phase (which contains the free amino carboxylate) was extracted with $CHCl_3$ (3×). After dilution with MeOH (15 ml), a soln. of complex **1** (*ca.* 0.095 mmol) in CH_2Cl_2 (3 ml) was added, and the resulting colorless soln. was stirred for 1–2 h at r.t. Similar workup as described in *GP 1* yielded a colorless residue, which was investigated by NMR spectroscopy.

4. *Generation of Pd Complexes* **6**: *General Procedure 4* (*GP 4*). To a soln. of the amino acid methyl ester hydrochloride (0.2 mmol) in MeOH (10 ml), a 1M solution of MeONa in MeOH (200 µl) was added, and the mixture was stirred for 15 min. A soln. of **1** (0.1 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 1 h at r.t. The solvent was evaporated, $CHCl_3$ was added, and the org. phase was washed with H_2O. The solvent was evaporated, and the residue was dried under h.v. and investigated by NMR spectroscopy.

5. *Cleavage of Complexes* **2** *and* **6**: *General Procedure 5* (*GP 5*). To a soln. of the corresponding metal complex (0.1 mmol) in MeOH (2 ml), 400 µl of 1N aq. HCl were added, and the mixture was stirred for 5–10 min. After addition of H_2O and $CHCl_3$, the org. phase was evaporated to yield crude **1**, which could be purified by FC ($CHCl_3$). Evaporation of the aq. phase provided the crude amino acid hydrochloride or amino acid methyl ester hydrochloride.

6. *Products. [3-(Amino-κN)butanoato-κO][2-[(1S)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**2a**). From *rac*-3-aminobutanoic acid (H-β^3-HAla-OH) and (*S,S*)-**1** according to *GP 1*. IR ($CHCl_3$): 3328*w*, 3055*w*, 2983*m*, 2875*w*, 1596*vs*, 1576*s*, 1455*w*, 1438*w*, 1386*m*, 1336*w*, 1274*w*, 1102*w*, 1078*w*, 941*w*, 919*w*, 658*w*. ^{1}H-NMR (300 MHz, CD_3OD): 7.00–6.86 (*m*, 3 arom. H); 6.75–6.71 (*m*, 1 arom. H); 4.53 (br., NH), 4.11 (br., NH), 3.87 (*q*, *J* = 6.6, 0.5 H, Me_2NCH); 3.80 (*q*, *J* = 6.6, 0.5 H, Me_2NCH); 3.12 (*m*, CH), 2.78 (*s*, 1.5 H, MeN); 2.75 (*s*, 1.5 H, MeN); 2.54 (*s*, 1.5 H, MeN); 2.52 (*s*, 1.5 H, MeN); 2.46–2.31 (*m*, CH_2); 1.56 (*d*, *J* = 6.5, 1.5 H, Me); 1.53 (*d*, *J* = 6.5, 1.5 H, Me); 1.28 (*d*, *J* = 6.5, 1.5 H, Me); 1.26 (*d*, *J* = 6.5, 1.5 H, Me); line separation was improved by lowering the temp. ^{13}C-NMR (75 MHz, CD_3OD): 180.75 (180.57*); 155.38 (155.09*); 144.32 (144.06*); 131.93–123.30 (arom. C); 75.87 (75.68*); 51.41 (51.01*); 48.10 (48.00*); 45.73 (45.52*); 44.80 (44.71*); 22.55 (22.29*); 20.34 (19.19*). FAB-MS: 357.0 ([100, $[M+1]^+$). For elemental analysis, a sample of **2a** was crystallized from a $CHCl_3$ soln. by layering with pentane. Colorless crystals. M.p. 216–218° (dec.). Anal. calc. for $C_{14}H_{22}N_2O_2Pd$ (356.74): C 47.13, H 6.22, N 7.85; found: C 46.90, H 6.13, N 7.77.

[3-(Amino-κN)-4,4,4-trifluorobutanoato-κO][2-[(1S)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium (**2b**). From *rac*-3-amino-4,4,4-trifluorobutanoic acid and (*S,S*)-**1** according to *GP 1*. ^{1}H-NMR (300 MHz, $CDCl_3$/CD_3OD (*ca.* 7:1)): 6.97–6.76 (*m*, 3 arom. H); 6.51–6.48 (*m*, 1 arom. H); 4.02 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.61 (*q*, *J* = 6.4, 0.5 H, Me_2NCH); 3.46 (*m*, CH), 2.76 (*s*, 1.5 H, MeN); 2.67 (*s*, 1.5 H, MeN); 2.61–2.42 (*m*, 5 H, MeN, CH_2); 1.51 (*d*, *J* = 6.5, 1.5 H, Me); 1.36 (*d*, *J* = 6.5, 1.5 H, Me).

[3-(Amino-κN)-3-phenylpropanoato-κO][2-[(1S)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium (**2c**). From *rac*-3-amino-3-phenylpropanoic acid (H-β^3-HPhg-OH) and (*S,S*)-**1** according to *GP 1*. ^{1}H-NMR (300 MHz, CD_3OD): 7.52–7.26 (*m*, 5 arom. H); 7.00–6.82 (*m*, 3 arom. H); 6.73–6.68 (*m*, 1 arom. H); 4.77 (br., NH); 4.14 (*m*, CH); 3.99 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.75 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 2.95–2.86 (*m*, 1 H, CH_2); 2.85 (*s*, 1.5 H, MeN); 2.77 (*s*, 1.5 H, MeN); 2.61–2.52 (*m*, 4 H, MeN, CH_2); 1.61 (*d*, *J* = 6.5, 1.5 H, Me); 1.51 (*d*, *J* = 6.5, 1.5 H, Me).

[(3R)-3-(Amino-κN)-4-methylpentanoato-κO][2-[4-(dimethylamino-κN)ethyl]phenyl-κC]palladium (**2d**). From (*R*)-3-{(*tert*-butoxy)carbonyl]amino}-4-methylpentanoic acid (Boc-(*R*)-β^3-HVal-OH), and a mixture (*R,R*)-**1**/(*S,S*)-**1** 30:70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.01–6.88 (*m*, 3 arom. H); 6.77–6.74 (*m*, 1 arom. H); 4.36 (br., NH), 3.92–3.80 (*m*, 2 H, Me_2NCH, NH); 2.77–2.67 (*m*, 4 H, CH, MeN); 2.55 (*s*, 0.9 H, MeN); 2.52 (*s*, 2.1 H, MeN); 2.44–2.39 (*m*, CH_2); 2.11–1.93 (*m*, CH); 1.55 (*d*, *J* = 6.8, Me, minor diastereoisomer); 1.54 (*d*, *J* = 6.6, Me, major diastereoisomer); 1.02–0.95 (*m*, 2 Me).

[O^6-(tert-Butyl) (3S)-3-(amino-κN)hexanedioato-κO][2-[1-(dimethylamino-κN)ethyl]phenyl-κC]palladium (**2e**). From (*S*)-3-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}aminohexanedioic acid 6-(*tert*-butyl) ester (Fmoc-(*S*)-β^3-HGlu(OtBu)-OH) and a mixture (*R,R*)-**1**/(*S,S*)-**1** 30:70 according to *GP 3*. ^{1}H-NMR (300 MHz, CD_3OD): 7.00–6.87 (*m*, 3 arom. H); 6.75–6.73 (*m*, 1 arom. H); 4.60 (br., NH), 4.13 (br., NH), 3.85 (*q*, *J* = 6.5, Me_2NCH); 3.00 (*m*, CH), 2.77 (*s*, MeN); 2.54 (*s*, MeN, minor diastereoisomer); 2.53 (*s*, MeN, major

diastereoisomer); 2.50–2.27 (*m*, 4 H); 2.05–1.81 (*m*, 2 H); 1.54 (*d*, *J* = 6.5, Me); 1.44 (*s*, 3 Me). ^{13}C-NMR (75 MHz, CD_3OD): 180.31 (180.10*); 174.20; 155.24; 144.16; 131.93; 126.05; 125.49; 123.42; 81.92; 75.82; 51.58; 51.32; 51.24; 45.69; 42.39; 33.10; 32.29 (32.12*); 28.44; 19.76.

*((3*S*)-3-(Amino-*κ*N)-7-({[(2-chlorobenzyloxy)carbonyl]amino}heptanoato-*κ*O){2-[1-(dimethylamino-*κ*N)ethyl]phenyl-*κ*C}palladium* (**2f**). From (*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-7-{[(2-chlorobenzyloxy)carbonyl]amino}heptanoic acid (Boc-(*S*)-β^3-HLys(2-Cl-Z)-OH) and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30 : 70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.87–7.24 (*m*, 4 arom. H); 6.99–6.86 (*m*, 3 arom. H); 6.75–6.73 (*m*, 1 arom. H); 5.14 (*s*, CH_2); 4.49 (br., NH), 4.00 (br., NH), 3.82 (*m*, Me_2NCH); 3.31 (ψt, CH_2); 2.94 (*m*, CH), 2.75 (*s*, MeN, major diastereoisomer); 2.74 (*s*, MeN, minor diastereoisomer); 2.52 (*s*, MeN, minor diastereoisomer); 2.51 (*s*, MeN, major diastereoisomer); 2.44–2.33 (*m*, 2 H); 1.76–1.38 (*m*, 9 H). ^{13}C-NMR (75 MHz, CD_3OD): 180.65 (180.48*); 158.56; 155.27; 155.20; 144.33; 144.27; 136.03; 134.22; 131.89; 130.56; 130.53; 130.50; 128.25; 126.12; 125.50; 123.46; 75.77; 64.67; 52.40; 52.34; 51.30; 51.18; 45.66; 42.55; 41.61; 36.92; 36.74; 30.89; 24.40; 19.77 (19.56*).

*{(2*R*)-3-(Amino-*κ*N)-2-methylpropanoato-*κ*O]{2-[(1*S*)-1-(dimethylamino-*κ*N)phenyl-*κ*C}palladium* (**2g**). From enantiomerically enriched (*R*)-3-{[(*tert*-butoxy)carbonyl]amino}-2-methylpropanoic acid (Boc-(*R*)-β^2-HAla-OH) and (*S*,*S*)-**1** according to *GP 2*. IR ($CHCl_3$): 3342*w*, 3240*w*, 3054*m*, 2981*s*, 2874*m*, 1594v*s*, 1559*m*, 1405*s*, 1363*m*, 1318*w*, 1273*w*, 1156*w*, 1076*w*, 1048*w*, 1015*w*, 941*w*, 658*w*. ^{1}H-NMR (300 MHz, CD_3OD): 6.99–6.86 (*m*, 3 arom. H); 6.76–6.69 (*m*, 1 arom. H); 4.45 (br., NH), 4.28 (br., NH), 3.85 (*q*, *J* = 6.5, Me_2NCH, minor diastereoisomer); 3.79 (*q*, *J* = 6.4, Me_2NCH, major diastereoisomer); 2.86–2.65 (*m*, 2 H), 2.78 (*s*, MeN, minor diastereoisomer); 2.75 (*s*, MeN, major diastereoisomer); 2.59–2.47 (*m*, 4 H); 1.54 (*d*, *J* = 6.5, Me, major diastereoisomer); 1.51 (*d*, *J* = 6.5, Me, minor diastereoisomer); 1.31 (*d*, *J* = 6.3, Me, major diastereoisomer); 1.29 (*d*, *J* = 6.3, Me, minor diastereoisomer). ^{13}C-NMR (75 MHz, CD_3OD): 184.39 (184.33*); 155.35 (155.16*); 144.38 (144.19*); 131.94–123.38 (arom. C); 75.82 (75.67*); 51.42 (51.15*); 47.22 (46.98*); 45.77 (45.62*); 43.03 (42.97*); 20.14 (19.24*); 16.15. FAB-MS: 357.0 (77, $[M+1]^+$). For elemental analysis, a sample of **2g** was crystallized from a $CHCl_3$ soln. by layering with pentane. Colorless crystals. M.p. 197–199° (dec.). Anal. calc. for $C_{14}H_{22}N_2O_2Pd$ (356.74): C 47.13, H 6.22, N 7.85; found: C 46.90, H 6.36, N 7.75.

*{(2*R*)-2-[(Amino-*κ*N)methyl]-4-methylpentanoato-*κ*O}{2-[1-(dimethylamino-*κ*N)ethyl]phenyl-*κ*C}palladium* (**2h**). From (*R*)-2-(aminomethyl)-4-methylpentanoic acid ((*R*)-H-β^2-HLeu-OH) and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30 : 70 according to *GP 1*. ^{1}H-NMR (300 MHz, CD_3OD): 7.00–6.85 (*m*, 3 arom. H); 6.78–6.74 (*m*, 1 arom. H); 4.48 (br., NH); 4.22 (br., NH); 3.88 (*q*, *J* = 6.5, 0.3 H, Me_2NCH); 3.75 (*q*, *J* = 6.5, 0.7 H, Me_2NCH); 2.89–2.71 (*m*, 5 H), 2.53–2.48 (*m*, 4 H); 2.36–2.10 (*m*, 1 H); 1.73 (*m*, 1 H); 1.57 (*d*, *J* = 6.6, 2.1 H, Me); 1.51 (*d*, *J* = 6.5, 0.9 H, Me); 1.47 (*m*, 1 H); 1.08–0.97 (*m*, 2 Me).

*{(2*S*)-2-[(Amino-*κ*N)methyl]-3-methylbutanoato-*κ*O}{2-[(1*S*)-1-(dimethylamino-*κ*N)ethyl]phenyl-*κ*C}palladium* (**2i**). From enantiomerically enriched (*S*)-2-(aminomethyl)-3-methylbutanoic acid ((*S*)-H-β^2-HVal-OH) and (*S*,*S*)-**1** according to *GP 1*. IR ($CHCl_3$): 3343*w*, 2988*w*, 2960*w*, 1596v*s*, 1578*s*, 1458*m*, 1401*m*, 1370*w*, 1004*w*, 909*w*, 638*w*. ^{1}H-NMR (300 MHz, CD_3OD): 7.00–6.85 (*m*, 3 arom. H); 6.81–6.75 (*m*, 1 arom. H); 3.96 (*q*, *J* = 6.6, Me_2NCH, major diastereoisomer); 3.70 (*q*, *J* = 6.5, Me_2NCH, minor diastereoisomer); 2.93–2.67 (*m*, 6 H); 2.54 (*s*, MeN, minor diastereoisomer); 2.52 (*s*, MeN, major diastereoisomer); 2.11 (*m*, 1 H); 1.58 (*d*, *J* = 6.5, Me, minor diastereoisomer); 1.48 (*d*, *J* = 6.8, Me, major diastereoisomer); 1.08–0.97 (2 Me). ^{13}C-NMR (75 MHz, CD_3OD): 183.32; 154.74; 144.74; 131.96; 126.10; 125.45; 123.53; 75.46; 55.67; 50.79; 45.29; 41.94; 28.64; 22.00; 20.03; 17.65. FAB-MS: 385.0 (100, $[M+1]^+$). For elemental analysis, a sample of **2i** was crystallized from a $CHCl_3$ soln. by layering with pentane. Colorless crystals. M.p. 88–91°. Anal. calc. for $C_{16}H_{26}N_2O_2Pd \cdot 2\ CHCl_3$ (623.55): C 34.67, H 4.53, N 4.49; found: C 34.86, H 5.09, N 4.48.

*{(2*S*)-3-(Amino-*κ*N)-2-benzylpropanoato-*κ*O}{2-[(1*S*)-1-(dimethylamino-*κ*N)ethyl]phenyl-*κ*C}palladium* (**2j**). From enantiomerically enriched (*S*)-2-benzyl-3-{[(9*H*-fluoren-9-yloxy)carbonyl]amino}propanoic acid (Fmoc-(*S*)-β^2-HPhe-OH) and (*S*,*S*)-**1** according to *GP 3*. ^{1}H-NMR (300 MHz, CD_3OD): 7.28–7.14 (*m*, 5 arom. H); 6.99–6.84 (*m*, 3 arom. H); 6.70–6.67 (*m*, 1 arom. H); 4.44 (br., NH), 4.14 (br., NH), 3.92 (*q*, *J* = 6.5, Me_2NCH, major diastereoisomer); 3.77 (*q*, *J* = 6.5, Me_2NCH, minor diastereoisomer); 3.41 (*m*, 1 H); 2.88–2.68 (*m*, 7 H); 2.58 (*s*, MeN, minor diastereoisomer); 2.53 (*s*, MeN, major diastereoisomer); 1.58 (*d*, *J* = 6.5, Me, minor diastereoisomer); 1.50 (*d*, *J* = 6.5, Me, major diastereoisomer).

*{(2*S*,3*S*)-3-(Amino-*κ*N)-2-methylbutanoato-*κ*O}{2-[1-(dimethylamino-*κ*N)ethyl]phenyl-*κ*C}palladium* (**2k**). From (2*S*,3*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-2-methylbutanoic acid and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30 : 70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.00–6.80 (*m*, 4 arom. H); 4.54–4.42 (br., NH); 4.03–3.90 (br., NH); 3.85 (*q*, *J* = 6.7, 0.3 H, Me_2NCH); 3.79 (*q*, *J* = 6.5, 0.7 H, Me_2NCH); 3.01 (*m*, CH); 2.79 (*s*, 0.9 H, MeN); 2.75 (*s*, 2.1 H, MeN), 2.55 (*s*, 2.1 H, MeN); 2.51 (*s*, 0.9 H, MeN); 2.43 (*m*, CH); 1.57–1.30 (3 Me); line separation can be improved by lowering the temp.

*[(2*R*,3*R*)-3-(Amino-κN)-2-methylbutanoato-κO][2-[1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**2l**). From (2*R*,3*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-2-methylbutanoic acid and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30:70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 6.99–6.85 (*m*, 3 arom. H); 6.79–6.75 (*m*, 1 arom. H); 4.70 (br., NH); 3.90 (br., NH); 3.85 (*q*, *J* = 6.5, 0.3 H, Me_2NCH); 3.79 (*q*, *J* = 6.5, 0.7 H, Me_2NCH); 3.08 (*m*, CH); 2.78 (*s*, 0.9 H, MeN); 2.75 (*s*, 2.1 H, MeN); 2.55–2.48 (*m*, 4 H); 1.56 (*d*, *J* = 6.5, 2.1 H, Me); 1.53 (*d*, *J* = 6.8, 0.9 H, Me); 1.28–1.18 (*m*, 2 Me). ^{13}C-NMR (75 MHz, CD_3OD): 183.24; 155.37 (155.17*); 144.38 (144.20*); 132.02–123.25 (arom. C); 75.90 (75.74*); 51.95; 51.48 (51.19*); 47.72; 45.86 (45.62*); 20.43 (19.50*); 18.32; 13.87.

*[(3*R*)-3-(Amino-κN)-2,2-dimethylbutanoato-κO][2-[(1*S*)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**2m**). From enantiomerically enriched (*R*)-3-{[(*tert*-butoxy)carbonyl]amino}-2,2-dimethylbutanoic acid and (*S*,*S*)-**1** according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 6.99–6.79 (*m*, 4 arom. H); 3.86 (*q*, *J* = 6.5, Me_2NCH, major diastereoisomer); 3.78 (*q*, *J* = 6.5, Me_2NCH, minor diastereoisomer); 2.84–2.76 (*m*, 4 H), 2.56 (*s*, MeN, minor diastereoisomer); 2.52 (*s*, MeN, major diastereoisomer); 1.60–1.52 (*m*, 2 Me); 1.29–1.14 (2 Me). ^{13}C-NMR (75 MHz, CD_3OD): 184.07 (184.02*); 155.48 (154.12*); 144.48 (144.15*); 132.20–123.24 (arom. C); 75.93 (75.70*); 56.74; 51.64 (51.05*); 47.89; 45.84 (45.63*); 25.84; 25.26; 20.68 (19.27*); 18.22.

*[4-(Amino-κN)-2-methylbutanoato-κO][2-[(1*S*)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**3a**). From *rac*-4-{[(*tert*-butoxy)carbonyl]amino}-2-methylbutanoic acid (Boc-γ^2-HHAla-OH) and (*S*,*S*)-**1** according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.01–6.83 (*m*, 3 arom. H); 6.74–6.68 (*m*, 1 arom. H); 4.37 (br., NH); 3.90 (br., NH); 3.90 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.72 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 2.94–2.47 (*m*, 3 H); 2.76 (*s*, 1.5 H, MeN); 2.74 (*s*, 1.5 H, MeN); 2.55 (*s*, 1.5 H, MeN); 2.51 (*s*, 1.5 H, MeN); 2.02–1.83 (*m*, 1 H); 1.59 (*d*, *J* = 6.2, 1.5 H, Me); 1.52 (*d*, *J* = 6.6, 1.5 H, Me); 1.45 (*m*, 1 H); 1.15 (*d*, *J* = 6.7, Me).

*{2-[2-(Amino-κN)ethyl]-3-methylbutanoato-κO}[2-[(1*S*)-1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**3b**). From *rac*-2-(2-{[(*tert*-butoxy)carbonyl]amino}ethyl)-3-methylbutanoic acid (Boc-γ^2-HHVal-OH) and (*S*,*S*)-**1** according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.01–6.85 (*m*, 3 arom. H); 6.74–6.69 (*m*, 1 arom. H); 3.96 (*q*, *J* = 6.6, 0.5 H, Me_2NCH); 3.68 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.68 (br., NH); 3.51 (br., NH); 2.94–2.85 (*m*, 1 H); 2.78 (*s*, 1.5 H, MeN); 2.76 (*s*, 1.5 H, MeN); 2.58–2.50 (*m*, 4 H); 2.06 (*m*, 1 H); 1.87 (*m*, 1 H); 1.64 (*d*, *J* = 6.4, 1.5 H, Me); 1.51 (*d*, *J* = 6.5, 1.5 H, Me); 1.39 (*m*, 1 H); 1.07–0.96 (2 Me).

*{(3*R*)-3-[(Amino-κN)methyl]-4-methylpentanoato-κO}[2-[1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**3c**). From (*R*)-3-{[(*tert*-butoxy)carbonyl]amino}methyl)-4-methylpentanoic acid (Boc-(*R*)-γ^3-HHVal-OH) and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30:70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.01–6.88 (*m*, 3 arom. H); 6.79–6.76 (*m*, 1 arom. H); 3.92 (br., NH); 3.81 (*m*, Me_2NCH); 3.10–2.69 (*m*, 4 H); 2.76 (*s*, MeN, major diastereoisomer); 2.74 (*s*, MeN, minor diastereoisomer); 2.51 (*s*, MeN, minor diastereoisomer); 2.48 (*s*, MeN, major diastereoisomer); 1.93 (*m*, 1 H); 1.71 (*m*, 1 H); 1.56 (*d*, *J* = 6.4, Me, minor diastereoisomer); 1.54 (*d*, *J* = 6.5, Me, major diastereoisomer); 1.00–0.95 (2 Me). ^{13}C-NMR (75 MHz, CD_3OD): 182.66 (182.61*); 155.35 (154.25*); 143.62 (143.52*); 131.71; 126.10; 125.60; 123.43; 75.92 (75.82*); 51.75 (51.59*); 46.28 (46.14*); 43.63; 40.15 (40.06*); 32.05 (31.92*); 20.95; 20.85; 20.30 (19.83*).

*[(4*R*)-4-(Amino-κN)-6-methylheptanoato-κO][2-[1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**3d**). From (*R*)-4-{[(*tert*-butoxy)carbonyl]amino}-6-methylheptanoic acid (Boc-(*R*)-γ^4-HHLeu-OH) and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30:70 according to *GP 2*. ^{1}H-NMR (300 MHz, $CDCl_3/CD_3OD$ (*ca.* 6/2): 6.93–6.75 (*m*, 3 arom. H); 6.51–6.47 (*m*, 1 arom. H); 3.82 (*q*, *J* = 6.7, 0.3 H, Me_2NCH); 3.61 (*q*, *J* = 6.5, 0.7 H, Me_2NCH); 3.01 (*m*, 1 H); 2.84 (*m*, 1 H); 2.63 (*s*, MeN); 2.50–2.43 (*m*, 1 H); 2.38 (*s*, MeN, minor diastereoisomer); 2.37 (*s*, MeN, major diastereoisomer); 1.97 (*m*, 1 H); 1.55 (*m*, 2 H); 1.45 (*d*, *J* = 6.5, 2.1 H, Me); 1.38 (*d*, *J* = 6.9, 0.9 H, Me); 1.27 (*m*, 2 H); 0.78 (*m*, 2 Me).

*[(2*R*,3*R*,4*R*)-4-(Amino-κN)-2,8-dimethylpentanoato-κO][2-[1-(dimethylamino-κN)ethyl]phenyl-κC]palladium* (**3e**). From (2*R*,3*R*,4*R*)-4-amino-2,3-dimethylpentanoic acid and a mixture (*R*,*R*)-**1**/(*S*,*S*)-**1** 30:70 according to *GP 1*. ^{1}H-NMR (300 MHz, CD_3OD): 7.02–6.74 (*m*, 4 arom. H); 4.62 (br., NH); 4.08 (*q*, *J* = 6.6, 0.7 H, Me_2NCH); 3.63 (*q*, *J* = 6.5, 0.3 H, Me_2NCH); 3.70 (*m*, CH); 2.98 (*m*, CH); 2.75 (*s*, MeN); 2.50 (*s*, 2.1 H, MeN); 2.48 (*s*, 0.9 H, MeN); 1.64 (*d*, *J* = 6.5, 0.9 H, Me); 1.48 (*d*, *J* = 6.9, 2.1 H, Me); 1.42 (*m*, CH); 1.26–1.02 (3 Me).

*[3-(Amino-κN)butanoato-κO][1-[(1*S*)-1-(dimethylamino-κN)ethyl]naphthalen-2-yl-κC]palladium* (**5a**). From *rac*-3-aminobutanoic acid (H-β^3-HAla-OH) and (*S*,*S*)-**4** according to *GP 1*. ^{1}H-NMR (300 MHz, CD_3OD): 7.76–7.28 (*m*, 5 arom. H); 6.98 (*m*, 1 arom. H); 4.65 (br., NH); 4.29 (*q*, Me_2NCH); 4.18 (br., NH); 3.23–3.09 (*m*, CH); 2.73 (*s*, 1.5 H, MeN); 2.72 (*s*, 1.5 H, MeN); 2.67 (*s*, 1.5 H, MeN); 2.65 (*s*, 1.5 H, MeN); 2.51–2.35 (*m*, CH_2); 1.77 (*d*, *J* = 6.2, 1.5 H, Me); 1.76 (*d*, *J* = 6.2, 1.5 H, Me); 1.31 (*d*, *J* = 6.5, 1.5 H, Me); 1.26 (*d*, *J* = 6.5, 1.5 H, Me).

[3-(Amino-κN)-2-methylpropanoato-κO]{1-[(1S)-1-(dimethylamino-κN)ethyl]naphtalen-2-yl-κC}palladium (**5b**). From *rac*-3-amino-2-methylpropanoic acid (H-β^2-HAla-OH) and (*S*,*S*)-**4** according to *GP 1*. ^{1}H-NMR (300 MHz, CD_3OD): 7.76–7.27 (*m*, 5 arom. H); 6.98 (*m*, 1 arom. H); 4.67 (br., 0.5 H, NH); 4.50 (br., NH); 4.28 (*m*, 1.5 H, Me_2NCH, NH); 2.87–2.51 (*m*, 9 H); 1.75 (*d*, *J* = 6.2, 1.5 H, Me); 1.74 (*d*, *J* = 6.2, 1.5 H, Me); 1.34 (*d*, *J* = 7.2, 1.5 H, Me); 1.31 (*d*, *J* = 7.2, 1.5 H, Me).

[(3R)-3-(Amino-κN)-4-methylpentanoato-κO]{1-[1-(dimethylamino-κN)ethyl]naphthalen-2-yl-κC}palladium (**5c**). From (*R*)-3-{[(*tert*-butoxy)carbonyl]amino}-4-methylpentanoic acid (Boc-(*R*)-β^3-HVal-OH) and a mixture of (*R*,*R*)-**4**/(*S*,*S*)-**4** 30:70 according to *GP 2*. ^{1}H-NMR (300 MHz, CD_3OD): 7.77–7.28 (*m*, 5 arom. H); 6.99 (*m*, 1 arom. H); 4.68 (br., NH); 4.30 (*m*, Me_2NCH); 4.16 (br., NH); 3.86 (br., NH); 2.84–2.65 (*m*, CH, 2 MeN); 2.56–2.37 (*m*, CH_2); 2.14 (*m*, 0.7 H, CH); 1.94 (*m*, 0.3 H, CH); 1.78 (*d*, *J* = 6.2, 0.9 H, Me); 1.77 (*d*, *J* = 6.5, 2.1 H, Me); 1.02–0.95 (*m*, 2 Me).

Chloro{2-[(1S)-1-(dimethylamino-κN)ethyl]phenyl-κC}{methyl 3-(amino-κN)-3-phenylpropanoate]palladium (**6a**). From methyl *rac*-3-amino-3-phenylpropanoate hydrochloride (H-β^3-HPhg-OMe · HCl) and (*S*,*S*)-**1** according to *GP 4*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.25 (*m*, 5 arom. H); 7.02–6.76 (*m*, 4 arom. H); 4.63 (*m*, CH); 4.03 (br., NH); 3.72 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.58–3.51 (*m*, 3.5 H, MeO, Me_2NCH); 3.44 (*dd*, 0.5 H); 3.27 (*dd*, 0.5 H); 3.14–3.00 (*m*, 1 H); 2.78 (*s*, 1.5 H, MeN); 2.75 (*s*, 1.5 H, MeN); 2.59 (*s*, 1.5 H, MeN); 2.57 (*s*, 1.5 H, MeN); 1.45 (*d*, *J* = 6.5, 1.5 H, Me); 1.41 (*d*, *J* = 6.5, 1.5 H, Me).

Chloro{2-[(1S)-1-(dimethylamino-κN)ethyl]phenyl-κC}[methyl 3-(amino-κN)butanoate]palladium (**6b**). From methyl *rac*-3-aminobutanoate hydrochloride (H-β^3-HAla-OMe · HCl) and (*S*,*S*)-**1** according to *GP 4*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.07–6.87 (*m*, 4 arom. H); 3.93 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.76–3.71 (*m*, MeO,

Table. *Crystallographic Data for* **2a** *and* **2i**

	2a	**2i**
Empirical formula	$C_{28}H_{44}N_4O_4Pd_2$	$C_{18}H_{28}Cl_6N_2O_2Pd$
Formula weight	713.47	623.52
Crystallized from	$CHCl_3$/pentane	$CHCl_3$/pentane
Crystal temp. [K]	293(2)	200(2)
Crystal size [mm]	0.15 × 0.15 × 0.05	0.40 × 0.30 × 0.20
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions		
a [Å]	9.768(3)	11.516(5)
b [Å]	12.994(1)	14.183(5)
c [Å]	25.045(5)	15.708(4)
α [°]	90	90
β [°]	90	90
γ [°]	90	90
V [Å^3]	3178.8(12)	2565.6(16)
Z	4	4
D_x [g · cm^3]	1.491	1.614
μ [mm^{-1}]	1.167	1.365
2θ Range [°]	$3.3 < 2\theta < 51.9$	$3.9 < 2\theta < 51.9$
Reflections measured	3524	2839
Independent reflections	3496	2839
max. and min.	0.9439 and 0.8443	0.7719 and 0.6112
Data/parameters	2091/343	2672/262
Criterion	$I > 3\sigma(I)$	$I > 3\sigma(I)$
Final *R*	0.0451	0.0394
wR_2	0.1300	0.1043
Goodness of fit	1.110	1.028
Absolute structure parameter	0.01(10)	−0.11(5)
$\Delta\varrho$ (max, min) [e · Å^{-3}]	1.181, −0.825	1.203, −1.327

4 H, CH); 3.59 (*m*, 1.5 H, NH, CH); 3.15 (br., NH); 2.93 (*s*, 1.5 H, MeN); 2.83 (*s*, 1.5 H, MeN); 2.74–2.50 (*m*, CH_2, MeN); 1.66–1.48 (2 Me).

Chloro[2-[(1S)-(dimethylamino-κN)ethyl]phenyl-κC][methyl 3-(amino-κN)-2-methylpropanoate]palladium (**6c**). From methyl *rac*-3-amino-2-methylpropanoate hydrochloride (H-β^2-HAla-OMe · HCl) and (*S*,*S*)-**1** according to *GP 4*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.03–6.77 (*m*, 4 arom. H); 3.77 (*q*, *J* = 6.6, 0.5 H, Me_2NCH); 3.67 (*q*, *J* = 6.5, 0.5 H, Me_2NCH); 3.68 (*s*, 1.5 H, OMe); 3.62 (*s*, 1.5 H, OMe); 3.37–3.09 (*m*, 4 H); 2.92–2.77 (*m*, 4 H); 2.64 (*s*, 1.5 H, MeN); 2.61 (*s*, 1.5 H, MeN); 1.53 (*d*, *J* = 6.5, 1.5 H, Me); 1.49 (*d*, *J* = 6.5, 1.5 H, Me); 1.20 (*d*, *J* = 7.2, 1.5 H, Me); 1.19 (*d*, *J* = 7.2, 1.5 H, Me).

X-Ray Crystal-Structure Determination of **2a** *and* **2i** (see *Table* and *Fig. 1*). The reflections were measured on an *Enraf-Nonius-CAD-4* diffractometer with MoK_α radiation (graphite monochromator, $\lambda = 0.71069$ Å). The structure of **2i** was solved by direct methods with SIR97 [39]. Part of the structure of **2a** was solved by direct methods with SIR97 [39], the remaining non-H-atoms were found from a difference *Fourier* map. Non-H-atoms were refined anisotropically with SHELXL-97 [40]. H-Atoms were calculated at idealized positions and included in the structure-factor calculation with fixed isotropic displacement parameters. The structure of **2i** contains two $CHCl_3$ molecules in the asymmetric unit. The structure of **2a** contains two independent molecules (diastereoisomers) in the unit cell. The crystallographic information files (cif-files) have been deposited at the *Cambridge Crystallographic Data Centre* (*CCDC*).

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