Ortho Palladation and Functionalization of l-Phenylalanine Methyl Ester†

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Ortho Palladation and Functionalization of L-Phenylalanine Methyl Ester†

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The ortho-metalated complex (*S,S*)-[$Pd_2\{\kappa^2(C,N)$-$C_6H_4CH_2CH(CO_2Me)NH_2$-2$\}_2(\mu$-Br$)_2$] (**1b**) can be prepared by refluxing in acetonitrile equimolecular amounts of $Pd(OAc)_2$ and L-phenylalanine methyl ester hydrochloride, followed by addition of an excess of NaBr. Complex **1b** reacts with 4-picoline to give the mononuclear derivative (*S*)-[$Pd\{\kappa^2(C,N)$-$C_6H_4CH_2CH(CO_2Me)NH_2$-2$\}_2$Br(NC_5H_4Me-4)] (**2**), whose crystal structure has been determined by X-ray diffraction. The precursor of **1b**, (*S,S*)-[$Pd_2\{\kappa^2$-(C,N)-$C_6H_4CH_2CH(CO_2Me)NH_2$-2$\}_2(\mu$-Cl$)_2$] (**1a**), could not be isolated in a pure form, but it can be used as the starting material for the synthesis of functionalized derivatives of the phenylalanine methyl ester. Thus, CO and RNC (R = Xy, ^{t}Bu) insert into the Pd−C bond of **1a** to afford, after depalladation, (*S*)-1-oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (**3**) and (*S*)-1-R-3-(methoxycarbonyl)-3,4-dihydroisoquinolinium triflate (R = ^{t}Bu (**4**), Xy (**5**)), respectively. Reaction of complex **1b** with bromine or iodine affords *trans*-(*S,S*)-[$PdBr_2\{NH_2CH(CO_2Me)CH_2C_6H_4$-X-2$\}_2$] (X = Br (**6**), I (**7**)), which further reacts with 1,10-phenanthroline (phen) to give [$PdBr_2$(phen)] and (*S*)-2-X-phenylalanine methyl ester (X = Br (**8**), I (**9**)).

Introduction

Ortho palladation of (*S*)-phenylalanine (L-phenylalanine) raises an interesting problem. If the free amino acid is used, N,O-chelates involving the deprotonated carboxyl group may be formed,[1] as has been described for other amino acids.[2] For instance, 4-iodo-L-phenylalanine reacts with $[PdCl_2(PEt_3)]_2$ to give the N,O-chelate complex (*S*)-[$Pd\{\kappa^2(N,O)$-$NH_2CH(CH_2$-C_6H_4I-4)$CO_2\}$Cl(PEt_3)].[3] The carboxylate groups of amino acids can be prevented from coordinating to the metal by using ester derivatives.[4,5] Still, a second problem remains: ortho metalation of primary amines has been reported to be difficult, especially if the metallacycle to be formed is a six-membered ring.[6] This second issue has been avoided by using functionalized[7] or N-substituted[4,8] amino groups. However, ortho metalation of primary amines is difficult, but it can be carried out if appropriate experimental conditions are used.[9−14]

Ortho-palladated (*S*)-phenylalanine complexes are interesting for at least three reasons. First of all, palladium complexes containing amino acids as ligands[15−17] as well as cyclopalladated complexes[17,18] have attracted great interest because their potential cytotoxic activity. Second, they can be useful precursors to prepare functionalized derivatives of L-phenylalanine, since complexes containing cyclopalladated amines have found widespread application in organic synthesis.[19−21] Among the possible derivatives, the ortho-halogenated amino acids are particularly interesting, as they are not easily prepared by other methods, such as direct electrophilic substitution, and, in addition, they can be used for preparing other amino acids through palladium-catalyzed reactions. Barluenga et al. have recently reported a regioselective method to prepare ortho-iodinated phenylalanine-containing peptide sequences,[22] but the

† Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday.

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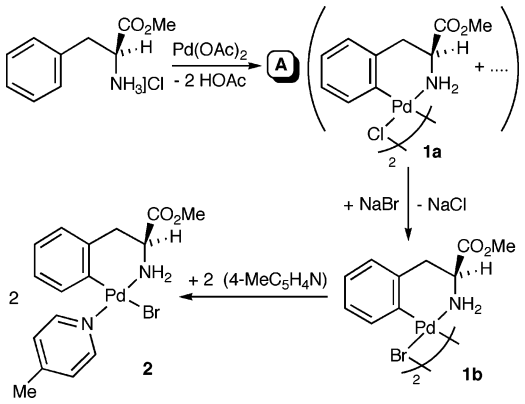
method cannot be applied to the methyl ester of the amino acid.[23] Finally, optically active palladacycles are suitable auxiliary reagents for the resolution of racemic mixtures and determination of enantiomeric purity and absolute configuration of chiral phosphines,[12,24] amino acids,[25] and other ligands.[26]

Fuchita et al. reported the cyclopalladation of (*R*)-2-phenylglycine methyl ester, an amino acid derivative with an unprotected amino group which gives a five-membered palladacycle, by reacting palladium acetate with the hydrochloride salt of the amino acid ester in acetone.[27] Nevertheless, the same reaction conditions were reported to fail when trying to prepare the analogous compound containing (*S*)-phenylalanine methyl ester, our target complex in this article.

Insertion of CO into the Pd−C bond of ortho-palladated tertiary amines has been widely investigated,[8,19,28−30] whereas the same reaction with primary benzylamines has been only superficially examined. Thus, a preliminary communication by Parkins et al. in 1984 described the reaction of $[Pd(\kappa^2(C,N)\text{-}C_6H_4CH_2NH_2\text{-}2)I]_2$ with CO in methanol at room temperature to give phthalimidine and palladium metal, although experimental procedures and the yield were not stated.[31] Dyke et al. in 1986 observed a similar reaction using chloroform or benzene as solvent, although the expected phthalimidine was not obtained pure.[32] We report here that (*S*)-1-oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline can be obtained by carbonylation of ortho-palladated (*S*)-phenylalanine methyl ester. This is a particularly interesting compound,[33] as it has been extensively used to study the steric course and stereospecificity of α-chymotrypsin-catalyzed reactions.[34,35] It has also been used as an antiallergic agent, to prevent the physical manifestation of atopic allergic reactions.[36] Recently, a convenient large-scale synthesis of the *R* enantiomer has been reported, using the amino acid methyl ester and triphosgene as starting materials.[37]

Scheme 1



The reaction of five-membered cyclopalladated benzylamines and isocyanides allows the isolation of the corresponding isoindolinium salts.[31,38] Here we report that the six-membered cyclopalladated (*S*)-phenylalanine methyl ester allows the synthesis of tetrahydroisoquinolines.

Results and Discussion

Synthesis and Structure of Ortho-Metalated Complexes. When (*S*)-$PhCH_2CH(CO_2Me)NH_2{\cdot}HCl$ (L-phenylalanine hydrochloride) is reacted with $Pd(OAc)_2$ in a 1:1 molar ratio in acetonitrile for 6 days, the orange solid **A** is isolated, whose ^1H NMR shows very broad signals that cannot be easily assigned. Nevertheless, in the aromatic region of the spectrum, there are signals corresponding to the ortho-metalated and the non-ortho-metalated aryl ring of the starting amino acid derivative. There are also two signals in the region corresponding to the OMe groups, whose relative integrals indicate an average molar ratio of 1:0.3. On the other hand, no acetate signals are present. The components of the mixture cannot be separated by fractional crystallization or by chromatography, although its reactivity shows that the ortho-metalated complex (*S*,*S*)-$[Pd_2\{\kappa^2(C,N)\text{-}C_6H_4CH_2CH(CO_2Me)NH_2\text{-}2\}_2(\mu\text{-}Cl)_2]$ (**1a**) is the main component (Scheme 1). Thus, this mixture **A** can be used as the starting material to synthesize in good yields some derivatives of **1a**.

Other reaction conditions (solvent, temperature, time) were tested to prepare **1a**: (i) acetonitrile at 80 °C for 4−8 h; (ii) toluene at 60 or 75 °C for 12 h; (iii) acetic acid at 60 °C for 24 h. In all cases, decomposition to Pd(0) took place and the mixture obtained was not as rich in **1a** (tested by ^1H NMR) as in **A**. However, we succeeded in isolating the pure bromo-bridged dinuclear ortho-metalated complex (*S*,*S*)-$[Pd_2\{\kappa^2(C,N)\text{-}C_6H_4CH_2CH(CO_2Me)NH_2\text{-}2\}_2(\mu\text{-}Br)_2]$ (**1b**), by reacting the mixture **A** with NaBr and recrystallizing the crude product. 4-Picoline (pic) splits the bromide bridges in complex **1b** to give the mononuclear complex (*S*)-$[Pd\{\kappa^2(C,N)\text{-}C_6H_4CH_2CH(CO_2Me)NH_2\text{-}2\}_2Br(pic)]$ (**2**). Of the two possible isomers for

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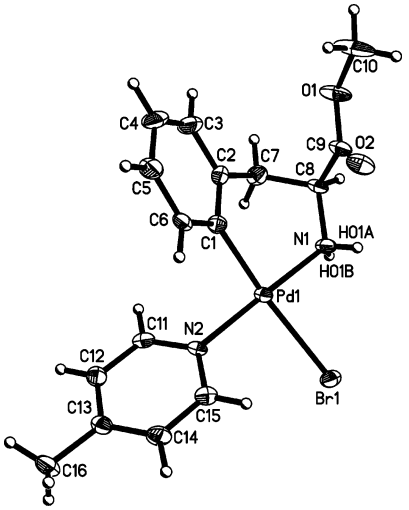

Figure 1. Thermal ellipsoid plot (50% probability) of **2** along with the labeling scheme. Selected bond lengths (Å) and angles (deg): Pd(1)−Br(1) = 2.5458(6), Pd(1)−N(1) = 2.066(4), Pd(1)−C(1) = 1.999(5), Pd(1)−N(2) = 2.054(4); Br(1)−Pd(1)−N(1) = 85.39(12), N(1)−Pd(1)−C(1) = 92.19(18), C(1)−Pd(1)−N(2) = 90.22(17), N(2)−Pd(1)−Br(1) = 92.81(11).

complex **2**, only the one with the two nitrogen atoms in mutually trans positions is obtained, as proved by ^{1}H and ^{13}C NMR and X-ray diffraction studies. This is the normal behavior for benzylamine palladacycles,[21,39] although a notable exception has recently been reported.[40]

The ^{1}H and ^{13}C NMR spectra of complexes **1b** and **2** are in agreement with the proposed structures. The ^{1}H NMR spectrum of complex **1b** shows a set of three different signals, corresponding to the four remaining protons in the ortho-metalated ring: H3 (see numbering scheme in the Experimental Section) as a doublet at 7.38 ppm, H5 as a triplet at 6.88 ppm, and H4 and H6 as a multiplet between 6.76−6.82 ppm. A similar pattern is observed in the ^{1}H NMR spectrum of the mononuclear complex **2**, although in this case H3 is significantly shifted to lower frequencies ($\Delta\delta = -0.92$ ppm) due to the anisotropic shielding from the picoline ring.[41] In the ^{13}C NMR spectra of complexes **1b** and **2**, the resonances due to the carbon atoms bonded to Pd (140.8 ppm, **1b**; 147.4 ppm, **2**) are deshielded with respect to that of the corresponding free ligand (129.3 ppm in DMSO-d_6), as observed in other cyclopalladated complexes.[13,14,42]

The crystal structure of complex **2** (Figure 1) shows the palladium atom in a distorted-square-planar environment (mean deviation of the plane 0.09 Å) with a dihedral angle of 8.3° between the N(1)−Pd(1)−C(1) and N(2)−Pd(1)−Br(1) planes. The chelated amino acid ligand forms a six-membered metallacycle with a boat conformation. These features are similar to those of analogous complexes containing other phenethylamine derivatives.[11,13] The nitrogen atom of the amine and the nitrogen atom of 4-picoline are mutually trans, and the pyridine ring is rotated 65.3° with respect to the phenyl ring to avoid steric hindrance.

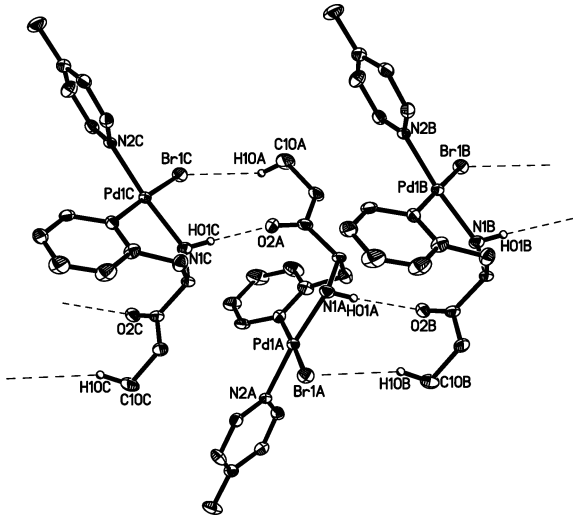

Figure 2. View of the hydrogen bond interactions along the *b* axis in complex **2**. Only Pd and atoms involved in the H bonding are labeled. Details (including symmetry operators) are given in the Supporting Information.

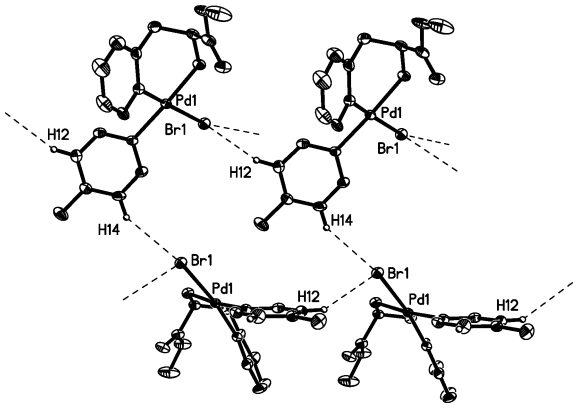

Figure 3. View of the hydrogen bond interaction between aromatic hydrogen and bromine atoms in complex **2**. Only Pd and atoms involved in the H bonding are labeled. Details (including symmetry operators) are given in the Supporting Information.

Each molecule of complex **2** is connected to four other molecules through hydrogen bonds, giving a three-dimensional network. Along the *b* axis, two adjacent molecules (A and C; Figure 2) are associated through a double interaction between the bromine atom of molecule C and one hydrogen of the methyl group of molecule A (Br1C···H10A−C10A) and between one hydrogen of the amino group of molecule C and the oxygen atom of the carbonyl group of molecule A (N1C−H01C···O2A). In addition, the same bromine atom is associated with two aromatic picoline hydrogens, each belonging to other two different molecules (Figure 3).

Reaction with Carbon Monoxide. Synthesis of (*S*)-1-Oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (3). As stated in the Introduction, two previous works described the reaction of $[Pd(\kappa^2(C,N)\text{-}C_6H_4CH_2NH_2\text{-}2)I]_2$ with CO to give phthalimidine and palladium metal, although the experimental procedures and the yield were not stated in the first work[31] and the phthalimidine was not obtained pure in the other.[32] The reaction of the mixture **A** with CO in $CHCl_3$ at room temperature has allowed us to prepare (*S*)-1-oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (**3**) (Scheme 2). The good isolated yield (64% from phenylalanine methyl ester hydrochloride) also proves that **A** is mainly the ortho-metalated complex **1a**.

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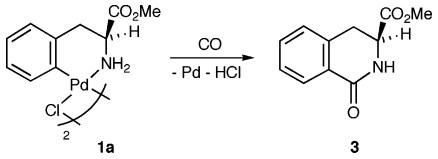
Scheme 2. Synthesis of (*S*)-1-Oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (3)



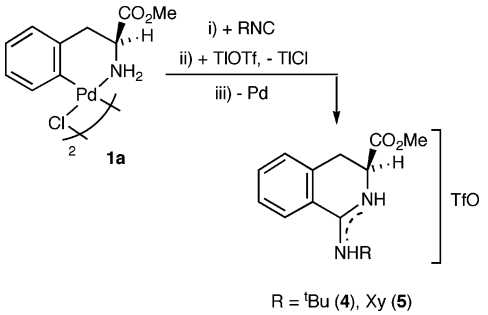
The reaction conditions used to prepared the tetrahydroisoquinoline derivative **3** are milder than those used in analogous reactions to prepare 2-methylphthalimidine from ortho-palladated *N*,*N*-dimethylbenzylamine (xylene, 100 °C, and 1 atm of CO pressure[28] or CH_2Cl_2, room temperature, and 2 atm of CO pressure[29]) but similar to those used to prepare 2-methyl-3-(carboxymethyl)phthalimidine from ortho-palladated *N*,*N*-dimethylphenylglycine,[8] although in the latter, a nitrogen atmosphere was used. As mentioned in the Introduction, **3** has been used to study the steric course and stereospecificity of α-chymotrypsin-catalyzed reactions[34,35] and as an antiallergic agent, to prevent the physical manifestation of atopic allergic reactions.[36] Compound **3** has been synthesized mostly by cyclation of *N*-acyl-*β*-arylethylamines, through procedures that involve some drastic reaction conditions or moisture-sensitive catalysts.[34,43] Recently, a convenient large-scale synthesis of the *R* enantiomer has been reported, using the amino acid methyl ester and triphosgene as starting materials.[37]

Orito et al. have reported a Pd(II)-catalyzed carbonylation of *N*-alkyl-*ω*-arylalkylamines to afford five- or six-membered benzolactams.[44] Under these conditions, carbonylation of primary amines does not produce benzolactams but ureas. The key step in these reactions seems to be the metalation of the amine. This result is not surprising, since ortho metalation of primary amines does not occur under the reaction conditions used when an excess of amine is present.[45] Our method, although not catalytic, allows the synthesis of a benzolactam from a primary amine and CO.

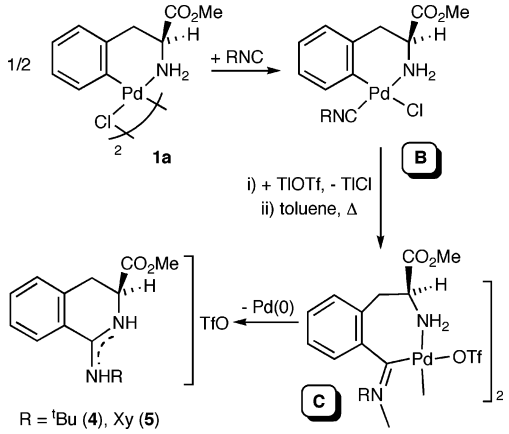
Reactions with Isocyanides. Synthesis and Structure of (*S*)-1-R-3-(methoxycarbonyl)-3,4-dihydroisoquinolinium Triflate (R = ^{t}Bu (4), 2,6-$Me_2C_6H_3$ (Xy) (5)). It has been reported that the reaction of cyclopalladated benzylamines and isocyanides in refluxing toluene allows the isolation of the corresponding isoindolinium salts.[31,38] The present availability of cyclopalladated phenethyl amines prompted us to extend this work to the synthesis of six-membered N-heterocycles. Thus, the mixture **A** was treated with isocyanide (RNC, R = ^{t}Bu, Xy) and thallium(I) triflate (1:2:2). After TlCl was removed, the resulting solution was refluxed in toluene for 7 h, upon which time formation of Pd(0) was observed. From the mother liquors, the tetrahydroisoquinoline derivatives **4** and **5** could be isolated (Scheme 3).

According to previous studies,[8,38,46] it is reasonable to assume that the first step in the formation of the tetrahydroisoquinoline

Scheme 3



Scheme 4. Proposed Reaction Pathway for the Synthesis of 4 and 5



derivative is the coordination of the isocyanide to the ortho-metalated fragment to give the adduct **B**, followed by insertion into the Pd−C bond to give the iminoacyl complex **C** (Scheme 4). There are some examples of such dimeric bridging iminoacyl palladium complexes.[29,47] The instability of this triflato derivative and the strain of the seven-membered ring can explain its decomposition and the formation of palladium(0) and the salt **4** or **5**.

These reactions can be performed without thallium triflate, but the yields are lower. In addition, a mixture of the chloride salts and the free bases are obtained (tested by ^{1}H NMR).

Recently, Saluste et al. have reported the palladium-catalyzed synthesis of cyclic amidines, starting from 2-bromobenzylamine or 2-bromophenethylamine, ^{t}BuNC, and Cs_2CO_3.[48] Nevertheless, it is necessary to point out the restricted availability of 2-halobenzylamines and the limitations of the process, which seems to give only good yields for *tert*-alkyl isocyanides.

The ^{1}H and ^{13}C NMR spectra of compounds **4** and **5** are in agreement with the proposed structures. Additionally, the crystal structures of both compounds have been determined by X-ray diffraction (Figures 4 and 5). The similar N−C bond distances in the groups N(2)−C(9)−N(1) (N(2)−C(9) = 1.3215(18) Å, C(9)−N(1) = 1.3248(18) Å) (**4**) and N(1)−C(17)−N(2) (N(1)−C(17) = 1.318(3) Å, C(17)−N(2) = 1.312(3) Å) (**5**) and the significantly longer distances of N(1) and N(2) with their other neighbors (N(2)−C(10) = 1.4990(17) Å, N(1)−C(8) = 1.4625-

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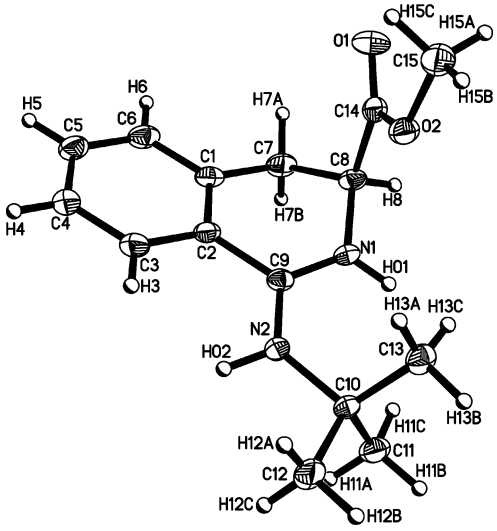


Figure 4. Thermal ellipsoid plot (50% probability) of the cation of **4** along with the labeling scheme. Selected bond lengths (Å) and angles (deg): N(2)−C(10) = 1.4990(17), N(2)−C(9) = 1.3215(18), N(1)−C(9) = 1.3248(18), N(1)−C(8) = 1.4625(16), C(2)−C(9) = 1.4809(18); C(9)−N(2)−C(10) = 129.35(12), C(9)−N(1)−C(8) = 122.87(12), N(1)−C(9)−N(2) = 121.78(13), N(1)−C(9)−C(2) = 118.46(12), N(2)−C(9)−C(2) = 119.75(12).

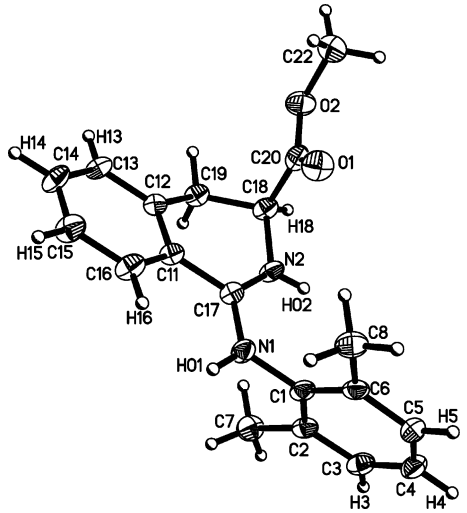


Figure 5. Thermal ellipsoid plot (50% probability) of the cation of **5** along with the labeling scheme. Selected bond lengths (Å) and angles (deg): N(1)−C(1) = 1.443(3), N(1)−C(17) = 1.318(3), N(2)−C(17) = 1.312(3), N(2)−C(18) = 1.457(3), C(17)−C(18) = 1.479(3); C(1)−N(1)−C(17) = 124.45(19), C(17)−N(2)−C(18) = 122.54(19), N(2)−C(17)−N(1) = 120.8(2), N(2)−C(17)−C(11) = 119.22(19), N(1)−C(17)−C(11) = 120.00(19).

(16) Å (**4**); N(1)−C(1) = 1.443(3) Å, N(2)−C(18) = 1.457(3) Å (**5**)) suggest that a delocalization of electron density occurs among the atoms N(2), C(9), and N(1) in **4** and N(1), C(17), and N(2) in **5**. Additionally, the angles C(9)−N(2)−C(10) (129.35(12)°) in **4** and C(17)−N(1)−C(1) (124.45(19)°) in **5** are far from the sp^3 hybridization for N(2) and N(1), respectively, if a lone pair were assumed on these atoms. The atoms C(8), N(1), C(9), C(2), N(2), and C(10) in **4** and C(18), N(2), C(17), C(11), N(1), and C(1) in **5** are coplanar (mean deviations from the plane 0.0459 and 0.0417 Å, respectively).

In both compounds, the cationic units are connected to the triflate groups through hydrogen bonds (nine interactions with three different triflates for compound **4** and six interactions with three different triflates for compound **5**). In the cation of compound **5**, there is also a hydrogen bond between the oxygen atom of the C═O group and one aromatic hydrogen of the phenyl ring (O1A···H15D−C15D). This interaction leads to zigzag chains along the *b* axis (see Figure 6).

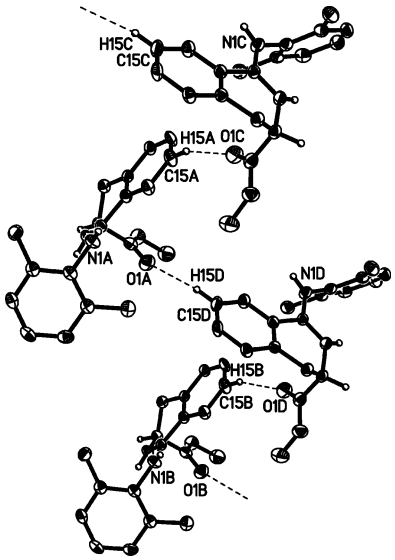


Figure 6. View of the hydrogen bond interaction between aromatic hydrogen and oxygen atoms of the C═O group in complex **5**. Only atoms involved in the H bonding are labeled. Details (including symmetry operators) are given in the Supporting Information.

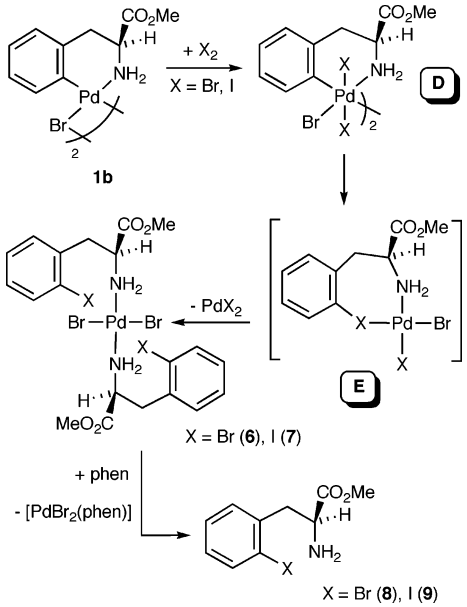
Synthesis and Structure of 2-Halo Derivatives. Stoichiometric aromatic halogenation of tertiary amines through cyclopalladated complexes is a known process.[19,49,50] However, the extension to the corresponding primary amines has only very recently been reported by us.[14] The reaction of complex **1b** with Br_2 or I_2, in CH_2Cl_2 at room temperature, afforded *trans*-$[PdBr_2\{NH_2CH(CO_2Me)Me_2CH_2C_6H_4X\text{-}2\}_2]$ (X = Br (**6**), I (**7**)) in good yields (Scheme 5). We have proposed that the initial step of the reaction is the oxidative addition of iodine or bromine to give a Pd(IV) complex (see **D** in Scheme 5).[14] This complex would then undergo a reductive elimination, to give **E**, followed by a symmetrization process, leading to **6** or **7** and PdX_2. A Pd(II) complex similar to the proposed intermediate **E** has been reported by Espinet et al.[50] Pure palladium bromide or palladium iodide was quantitatively isolated from the reaction mixture by filtration, as a dark brown solid. It is interesting to note that, when I_2 is used as an oxidative agent, only PdI_2 and the dibromo complex **7** are formed. These solids were then reacted with PPh_3 (1:2) to give $[PdBr_2(PPh_3)_2]$ or $[PdI_2(PPh_3)_2]$, which were characterized by ^{31}P NMR.

(*S*)-2-Bromophenylalanine methyl ester (**8**) and (*S*)-2-iodophenylalanine methyl ester (**9**) were conveniently prepared by reacting the corresponding precursor (**6** or **7**) with 1,10-phenanthroline (phen). The iodo derivatives **7** and **8** decompose slowly at room temperature. The byproduct in these reactions, $[PdBr_2(phen)]$, precipitates from the reaction mixtures and can be easily separated from the final amines by filtration (Scheme 5). Curiously, an analogous complex, $[PdCl_2(phen)]$, has been reacted with various amino acids in the presence of a base to prepare palladium(II) N,O-chelated amino acidato complexes with cytotoxic activity.[16]

(49) Onishi, M.; Hiraki, K.; Iwamoto, A. *J. Organomet. Chem.* **1984**, *262*, C11. Dunina, V. V.; Gorunova, O. N.; Grishin, Y. K.; Kuz'mina, L. G.; Churakov, A. V.; Kuchin, A. V.; Howard, J. A. K. *Russ. Chem. Bull.* **2005**, *54*, 2073.

(50) Bartolome, C.; Espinet, P.; Martín-Álvarez, J. M.; Villafañe, F. *Inorg. Chim. Acta* **2003**, *347*, 49.

Scheme 5. Proposed Reaction Pathway for the Synthesis of 2-Halo Derivatives of Phenylalanine Methyl Esters 8 and 9



Substitution of the Pd atom by bromine or iodine was confirmed by ^{13}C NMR spectroscopy. The resonance due to the aromatic carbon atom bonded to Br or I (δ 124.7 (**8**), 100.8 (**9**)) is shifted to lower frequency with respect to the corresponding signals in the cyclometalated complex **1b** (δ 140.8) and in the free ligand (δ 129.3, DMSO-d_6). This is a well-known effect.[51] In addition, the ^1H NMR spectra of the 2-halo amino acid methyl esters **8** and **9** showed the signals corresponding to the NH_2 groups shifted to lower frequency with respect to those of **6** and **7**, as expected upon palladium decoordination.

Conclusions

Using the appropriate experimental conditions, L-phenylalanine methyl ester can be ortho-metalated. The crystal structure of the mononuclear complex containing 4-picoline has been determined by X-ray diffraction. The cyclopalladated compound is an excellent starting material to prepare, in a stereospecific form, functionalized derivatives of this amino acid, as tetrahydroisoquinolines and 2-halo phenylalanine methyl esters.

Experimental Section

General Procedures. Infrared spectra were recorded on a Perkin-Elmer 16F-PC-FT spectrometer. C, H, N, and S analyses and melting point determinations were carried out as described elsewhere.[9] Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ with Bruker Avance 300 and 400 spectrometers. Chemical shifts are referenced to TMS (^1H and $^{13}C\{^1H\}$) or H_3PO_4 ($^{31}P\{^1H\}$). Signals in the ^1H and ^{13}C NMR spectra of all complexes were assigned with the help of HSQC and HMBC techniques. FAB MS measurements were carried out from liquid samples using 3-nitrobenzyl alcohol as a matrix in a VG Autospec E apparatus. Chromatographic separations were carried out by TLC on silica gel 60 ACC (70−230 mesh). Reactions were carried out at room temperature without special precautions against moisture. L-Phenylalanine methyl ester hydrochloride, 4-methylpyridine (4-picoline), 2,6-dimethylphenyl isocyanide (xylyl isocyanide), *tert*-butyl isocyanide, PPh_3 (Fluka), 1,10-phenanthroline hydrate (Merck), and palladium acetate (Johnson Matthey) were used as received. TlOTf ($TlSO_3CF_3$) was prepared by reaction of $Tl_2CO_3$and HSO_3CF_3 (1:2) in water and recrystallized from acetone/Et_2O.

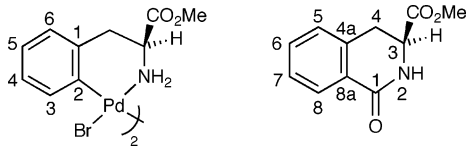
Caution! *Special precautions should be taken in handling thallium(I) compounds because of their toxicity.*

Synthesis of (*S,S*)-[Pd$_2${κ^2(*C,N*)-C$_6$H$_4$CH$_2$CH(CO$_2$Me)NH$_2$-2}$_2$(μ-Br)$_2$] (1b). L-Phenylalanine methyl ester hydrochloride (1.00 g, 4.64 mmol) was added to a solution of $Pd(OAc)_2$ (1.04 g, 4.64 mmol) in acetonitrile (60 mL), and the resulting solution was stirred at room temperature for 6 days. A small amount of metallic palladium was formed. The mixture was filtered through a plug of $MgSO_4$, the filtrate was concentrated to dryness, the residue was dissolved in CH_2Cl_2 (5 mL), and Et_2O (30 mL) was added to precipitate an orange solid which was filtered, washed with Et_2O (2 × 2 mL), and air-dried (1.26 g). ^1H NMR of this solid in $CDCl_3$ shows very broad peaks, difficult to assign, but the analysis of the aromatic region indicates a 1:0.35 mixture of the ortho-metalated complex [Pd$_2${κ^2(*C,N*)-C$_6$H$_4$CH$_2$CH(CO$_2$Me)NH$_2$-2}$_2$(μ-Cl)$_2$] and other non-ortho-metalated species such as [Pd$_2$(μ-Cl)Cl{NH$_2$CH(CO$_2$Me)CH$_2$Ph}$_2$] and [Pd$_2$Cl$_2${NH$_2$CH(CO$_2$Me)CH$_2$Ph}$_2$]. This mixture **A** could not be separated, either by fractional crystallization or by chromatography. To a solution of mixture **A** (950 mg) in acetone (50 mL) was added NaBr (1.5 g, 19.4 mmol). The reaction mixture was stirred for 12 h, and acetone was evaporated. The residue was taken up in CH_2Cl_2 (30 mL), the suspension was filtered through a plug of $MgSO_4$, the filtrate was concentrated to dryness, and Et_2O (30 mL) was added. The orange solid obtained was filtered, washed with Et_2O (2 × 2 mL), and air-dried to afford crude complex **1b**. Yield: 631 mg, 0.866 mmol, 49%. An analytically pure sample of complex **1b** was obtained by recrystallization of CH_2Cl_2/Et_2O. Mp: 147 °C dec. Anal. Calcd for $C_{20}H_{24}Br_2N_2O_4Pd_2$ (729.03): C, 32.95; H, 3.32; N, 3.84. Found: C, 33.49; H, 3.54; N, 4.15. IR (cm^{-1}): ν(NH) 3280, 3234; ν(CO) 1732. ^1H NMR (300 MHz): δ 3.31 (dd, 1 H, CH$_2$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 3.7 Hz), 3.51 (s, 3 H, OMe), 3.82 (br d, 1 H, CH$_2$), 4.23 (br s, 2 H, NH$_2$), 4.30 (br s, 1 H, CH), 6.76−6.82 (m, 2 H, H4 and H6, C$_6$H$_4$), 6.88 (t, 1 H, H5, C$_6$H$_4$, $^3J_{HH}$ = 7.2 Hz), 7.38 (d, 1 H, H3, C$_6$H$_4$, $^3J_{HH}$ = 7.5). $^{13}C\{^1H\}$ NMR (75.45 MHz): δ 45.5 (s, CH$_2$), 49.8 (s, CH), 52.8 (s, OMe), 124.7 (s, CH, C5, C$_6$H$_4$), 125.3 (s, CH, C4, C$_6$H$_4$), 127.5 (s, CH, C6, C$_6$H$_4$), 134.4 (s, C, C1, C$_6$H$_4$), 136.9 (s, CH, C3, C$_6$H$_4$), 140.8 (s, C, C2, C$_6$H$_4$), 172.3 (s, CO).

The mixture **A** was used as the starting material for the synthesis of compounds **3**−**5**. Crude complex **1b** was used as the starting material for the synthesis of complexes **2**, **6**, and **7**.

Chart 1 gives the numbering scheme for complex **1b** and tetrahydroisoquinoline derivatives.

Chart 1. Numbering Scheme for Complex 1b and Tetrahydroisoquinoline Derivatives



Synthesis of (*S*)-[Pd{κ^2(*C,N*)-C$_6$H$_4$CH$_2$CH(CO$_2$Me)NH$_2$-2}$_2$Br(NC$_5$H$_4$Me-4)] (2). 4-Picoline (60 μL, 0.616 mmol) was added to a solution of crude complex **1b** (150.0 mg, 0.206 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was stirred at room temperature for 2 h. The solution was concentrated to ca. 1 mL, and Et_2O (20 mL) was added to precipitate a small amount of a yellow solid, which was separated by filtration. The filtrate was concentrated to dryness, and the residue was vigorously stirred in *n*-hexane (30 mL). The yellow solid obtained was filtered, washed with *n*-hexane (2 × 5 mL), and air-dried to afford complex **2**. Yield: 123 mg, 0.269 mmol, 65%. Mp: 156 °C dec. Anal. Calcd for $C_{16}H_{19}BrN_2O_2Pd$ (457.644): C, 41.99; H, 4.18; N, 6.12. Found: C, 41.88; H, 4.30; N, 6.21. IR (cm^{-1}): ν(NH) 3316, 3248;

(51) Prestsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tablas para la determinación estructural por métodos espectroscópicos*; Springer-Verlag Ibérica: Barcelona, Spain, 1998.

ν(CO) 1726. ^{1}H NMR (300 MHz): δ 2.36 (s, 3 H, Me), 3.25 (m, 1 H, CH_2), 3.51−3.61 (m, 2 H, CH + CH_2), 3.70 (s, 3 H, OMe), 4.24 (m, 2 H, NH_2), 6.46 (d, 1 H, H3, C_6H_4, $^3J_{HH}$ = 7.8 Hz), 6.73 (td, 1 H, H4, C_6H_4, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 2.0 Hz), 6.88−6.96 (m, 2 H, H5 + H6, C_6H_4), 7.04 (d, 2 H, *o*-C_5H_4N, $^3J_{HH}$ = 6.1 Hz), 8.51 (d, 2 H, *m*-C_5H_4N, $^3J_{HH}$ = 6.4 Hz). ^{13}C{^{1}H} NMR (75.45 MHz): δ 21.1 (s, Me), 44.8 (s, CH_2), 50.5 (s, CH), 53.0 (s, OMe), 124.5 (s, CH, C5, C_6H_4), 125.5 (s, CH, C4, C_6H_4), 125.7 (s, CH, *m*-C_5H_4N), 126.8 (s, CH, C6, C_6H_4), 134.5 (s, CH, C3, C_6H_4), 135.8 (s, C1, C_6H_4), 147.7 (s, C2, C_6H_4), 149.7 (s, C, *p*-C_5H_4N), 153.2 (s, CH, *o*-C_5H_4N), 171.8 (s, CO).

Single crystals of **2**, suitable for an X-ray diffraction study, were obtained by slow evaporation of a solution of **2** in $CHCl_3$.

Synthesis of (*S*)-1-Oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (3). CO was bubbled through a suspension of **A** (from 119 mg, 0.552 mmol of phenylalanine methyl ester hydrochloride) in $CHCl_3$ (40 mL) for 1 h, and the resulting mixture was stirred for 12 h under a CO atmosphere. Decomposition to metallic palladium was observed. The mixture was filtered through a plug of Celite, and the filtrate was concentrated to dryness to give compound **3** as a colorless liquid. Yield: 72.0 mg, 0.351 mmol, 64% with respect to phenylalanine methyl ester hydrochloride. Anal. Calcd for $C_{11}H_{11}NO_3$ (205.213): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.77; N, 6.65. IR (cm^{-1}): ν(NH) 3348, 3258; ν(CO) 1746, 1674. ^{1}H NMR (400 MHz): δ 3.15, 3.26 (AB part of an "ABX system", 2 H, CH_2, $^2J_{AB}$ = 15.6, $^3J_{BX}$ = 9.7, $^3J_{AX}$ = 5.1 Hz), 3.73 (s, 3 H, OMe), 4.35 (X part of an "ABXM system", 1 H, CH, $^3J_{MX}$ = 2.0 Hz), 6.64 (br s, 1 H, NH), 7.17 (d, 1 H, H5, $^3J_{HH}$ = 7.5 Hz), 7.30 (t, 1 H, H7, $^3J_{HH}$ = 7.5 Hz), 7.40 (td, 1 H, H6, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.4 Hz), 8.00 (dd, 1 H, H8, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2 Hz). ^{13}C{^{1}H} NMR (100.81 MHz): δ 31.1 (s, CH_2), 52.9 (s, OMe), 53.0 (s, CH), 127.4 (s, CH, C5), 127.5 (s, CH, C7), 128.1 (s, CH, C8), 128.3 (s, C8a), 132.5 (s, CH, C6), 136.1 (s, C4a), 165.2 (s, *C*O−NH), 170.8 (s, *C*O_2Me). FAB$^+$-MS: *m*/*z* 206 [(M + 1)$^+$].

Synthesis of (*S*)-1-(*tert*-Butylamino)-3-(methoxycarbonyl)-3,4-dihydroisoquinolinium Triflate (4). ^{t}BuNC (71 μL, 0.628 mmol) was added to a solution of **A** (from 159 mg, 0.738 mmol of phenylalanine methyl ester hydrochloride) in acetone (20 mL), and the mixture was stirred for 10 min. TlOTf (220 mg, 0.624 mmol) was added, and the resulting suspension was further stirred for 15 min. The mixture was filtered through a plug of Celite to remove TlCl. The filtrate was concentrated to dryness, and the remaining residue was suspended in toluene (25 mL) and refluxed for 7 h, upon which time Pd(0) precipitated. Toluene was evaporated, acetone (20 mL) was added, the suspension was filtered through a plug of Celite, and HTfO (0.1 mL, 1.13 mmol) was added. The filtrate was concentrated to dryness, and the residue was dried in the oven at 70 °C for 24 h and then dissolved in CH_2Cl_2 (3 mL). Et_2O (30 mL) was added to precipitate a white solid, which was filtered, washed with Et_2O (2 × 5 mL), and air-dried to afford compound **4**. Yield: 147 mg, 0.358 mmol, 49% from phenylalanine methyl ester hydrochloride. Mp: 151 °C. Anal. Calcd for $C_{16}H_{21}F_3N_2O_5S$ (410.411): C, 46.82; H, 5.16; N, 6.83; S, 7.81. Found: C, 46.85; H, 5.45; N, 6.93; S, 7.67. IR (cm^{-1}): ν(NH) 3304; ν(CN) 1752, 1640. ^{1}H NMR (400 MHz): δ 1.63 (s, 9 H, C*Me*$_3$), 3.30, 3.39 (AB part of an "ABX system", 2 H, CH_2, $^2J_{AB}$ = 16.4, $^3J_{BX}$ = 6.2, $^3J_{AX}$ = 4.4 Hz), 3.68 (s, 3 H, OMe), 4.86 (X part of an "ABXM system", 1 H, CH, $^3J_{MX}$ = 4.6 Hz), 7.31 (d, 1 H, H5, $^3J_{HH}$ = 7.6 Hz), 7.48 (t, 1 H, H7, $^3J_{HH}$ = 7.6 Hz), 7.59 (td, 1 H, H6, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 0.9 Hz), 8.01 (d, 1 H, H8, $^3J_{HH}$ = 7.7 Hz), 8.07 (br s, 1 H, N*H*−^{t}Bu), 8.33 (d, 1 H, N*H*CH, $^3J_{MX}$ = 4.6 Hz). ^{13}C{^{1}H} NMR (100.81 MHz): δ 28.3 (s, C*Me*$_3$), 30.1 (s, CH_2), 51.8 (s, CH), 53.3 (s, OMe), 55.3 (s, *C*Me$_3$), 121.9 (s, C8a), 127.4 (s, CH, C8), 128.8 (s, CH, C7), 128.9 (s, CH, C5), 134.9 (s, CH, C6), 135.0 (s, C4a), 156.5 (s, C1), 169.7 (s, CO).

Single crystals of **4**, suitable for an X-ray diffraction study, were obtained by slow diffusion of *n*-hexane into a solution of **4** in $CHCl_3$.

Synthesis of (*S*)-1-((2,6-Dimethylphenyl)amino)-3-(methoxycarbonyl)-3,4-dihydroisoquinolinium Triflate (5). XyNC (80 mg, 0.609 mmol) was added to a solution of **A** (from 143 mg, 0.664 mmol of phenylalanine methyl ester hydrochloride) in acetone (20 mL), and the mixture was stirred for 10 min. TlOTf (200 mg, 0.565 mmol) was added, and the resulting suspension was further stirred for 15 min. The mixture was filtered through a plug of Celite to remove TlCl. The filtrate was concentrated to dryness, and the remaining residue was suspended in toluene (20 mL) and refluxed for 7 h, upon which time Pd(0) precipitated. The mixture was cooled to room temperature, toluene was evaporated, CH_2Cl_2 (45 mL) was added, and the resulting suspension was filtered through a plug of $MgSO_4$. The filtrate was concentrated to ca. 1 mL, and Et_2O (30 mL) was added to precipitate an off-white solid, which was filtered, washed with Et_2O (2 × 5 mL), and air-dried to give compound **5**. Yield: 137 mg, 0.299 mmol, 45% from phenylalanine methyl ester hydrochloride. Mp: 190−192 °C. Anal. Calcd for $C_{20}H_{21}F_3N_2O_5S$ (458.455): C, 52.40; H, 4.62; N, 6.11; S, 6.99. Found: C, 52.20; H, 4.77; N, 6.26; S, 6.74. IR (cm^{-1}): ν(NH) 3226 (b); ν(CN) 2016, 1942; ν(CO) 1752, 1644. ^{1}H NMR (400 MHz): δ 2.22 (s, 3 H, Me, Xy), 2.32 (s, 3 H, Me, Xy), 3.30, 3.44 (AB part of an "ABX system", 2 H, CH_2, $^2J_{AB}$ = 16.3, $^3J_{BX}$ = 6.2, $^3J_{AX}$ = 6.0 Hz), 3.70 (s, 3 H, OMe), 4.53 (X part of an "ABXM system", 1 H, CH, $^3J_{MX}$ = 3.9 Hz), 7.16 (d, 1 H, C*H*CMe, Xy, $^3J_{HH}$ = 7.5 Hz), 7.19 (d, 1 H, C*H*CMe, Xy, $^3J_{HH}$ = 7.2 Hz), 7.26 (t, 1 H, CH, Xy, $^3J_{HH}$ = 7.5 Hz), 7.37 (br s, 1 H, N*H*CH), 7.40 (d, 1 H, H5, $^3J_{HH}$ = 7.7 Hz), 7.59 (t, 1 H, H7, $^3J_{HH}$ = 7.6 Hz), 7.70 (td, 1 H, H6, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0 Hz), 8.50 (d, 1 H, H8, $^3J_{HH}$ = 7.5 Hz), 10.90 (br s, 1 H, N*H*−^{t}Bu). ^{13}C{^{1}H} NMR (100.81 MHz): δ 17.4 (s, Me, Xy), 17.7 (s, Me, Xy), 30.4 (s, CH_2), 51.8 (s, CH), 53.7 (s, OMe), 120.3 (q, CF_3, $^1J_{CF}$ = 319.9 Hz), 120.6 (s, C8a), 128.2 (s, CH, C8), 128.9 (s, CH, C5), 129.3 (s, C−NH, Xy), 129.5 (s, CH, C7), 129.5 (s, *C*HCMe, Xy), 129.6 (s, *C*HCMe, Xy), 130.3 (s, CH, Xy), 135.0 (s, C4a), 135.8 (s, CH, C6), 135.9 (s, *C*Me, Xy), 136.0 (s, *C*Me, Xy), 157.9 (s, C1), 169.2 (s, CO).

Single crystals of **5**, suitable for an X-ray diffraction study, were obtained by slow diffusion of *n*-hexane into a solution of **5** in $CHCl_3$.

Synthesis of *trans*-(*S,S*)-[$PdBr_2${$NH_2CH(CO_2Me)CH_2C_6H_4Br$-2}$_2$] (6). Br_2 (220 mg, 1.376 mmol) was added to a solution of complex **1b** (500.0 mg, 0.686 mmol) in CH_2Cl_2 (25 mL), and the resulting mixture was stirred for 12 h. A dark brown solid was formed, which was filtered out, air-dried, and identified as $PdBr_2$ (180 mg, 0.676 mmol, 98%). The filtrate was concentrated to dryness, the residue extracted with Et_2O (30 mL), the resulting solution filtered through a plug of Celite, and the filtrate concentrated to dryness. The residue was vigorously stirred in *n*-pentane (30 mL), and the dark orange solid that formed was filtered, washed with *n*-pentane (2 × 3 mL), and air-dried to give **6**. Yield: 376.0 mg, 0.481 mmol, 70%. Mp: 54 °C dec. Anal. Calcd for $C_{20}H_{24}Br_4N_2O_4Pd$ (782.438): C, 30.70; H, 3.09; N, 3.58. Found: C, 30.74; H, 3.13; N, 3.45. IR (cm^{-1}): ν(NH) 3268, 3205; ν(CO) 1737. ^{1}H NMR (300 MHz): δ 2.67 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 8.4 Hz), 3.36 (m, 1 H, NH_2), 3.58 (m, 1 H, NH_2), 3.64 (dd, 1 H, CH_2, partially obscured by the OMe, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 6.9 Hz), 3.65 (s, 3 H, OMe), 4.27 (m, 1 H, CH), 7.13 (td, 1 H, H4, C_6H_4, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8 Hz), 7.24−7.34 (m, 2 H, H5 + H6, C_6H_4), 7.56 (dd, 1 H, H3, C_6H_4, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.2 Hz). ^{13}C{^{1}H} NMR (75.45 MHz): δ 40.5 (s, CH_2), 52.7 (s, OMe), 57.9 (s, CH), 125.0 (s, C2, C−Br, C_6H_4), 127.7 (s, CH, C5, C_6H_4), 129.2 (s, CH, C4, C_6H_4), 131.6 (s, CH, C6, C_6H_4), 133.2 (s, CH, C3, C_6H_4), 134.9 (s, C1, *C*−CH_2, C_6H_4), 171.2 (s, CO).

Synthesis of *trans*-(*S,S*)-[$PdBr_2${$NH_2CH(CO_2Me)CH_2C_6H_4I$-2}$_2$] (7). I_2 (500 mg, 1.97 mmol) was added to a solution of complex

Table 1. Crystal Data and Structure Refinement for Compounds 2, 4, and 5

	2	4	5
formula	$C_{16}H_{19}BrN_2O_2Pd$	$C_{16}H_{21}F_3N_2O_5S$	$C_{20}H_{21}F_3N_2O_5S$
fw	457.64	410.41	458.45
cryst syst	monoclinic	monoclinic	monoclinic
space group	$P2_1$	$P2_1$	$P2_1$
temp (K)	100(2)	100(2)	100(2)
a (Å)	8.2295(7)	9.5247(4)	9.3942(7)
b (Å)	9.2912(8)	10.0175(4)	11.5392(9)
c (Å)	11.3389(12)	9.8917(4)	10.2024(8)
α (deg)	90	90	90
β (deg)	91.663(2)	93.333(2)	99.789(2)
γ (deg)	90	90	90
V (Å^3)	866.63(14)	942.21(7)	1089.85(15)
Z	2	2	2
ρ_{calcd} (Mg m^{-3})	1.754	1.447	1.397
μ(Mo Kα) (mm^{-1})	3.383	0.230	0.208
F(000)	452	428	476
cryst size (mm)	0.24 × 0.05 × 0.05	0.50 × 0.35 × 0.17	0.24 × 0.19 × 0.09
θ range (deg)	2.48−27.48	2.06−26.37	2.20−26.37
no. of rflns coll	10 153	10 381	12 039
no. of indep rflns	3930	3831	4419
R_{int}	0.0382	0.0145	0.0281
max, min transmissn	0.8491, 0.4973	0.9619, 0.8935	0.9816, 0.9519
no. of data/ restraints/ params	3930/10/210	3831/1/257	4419/1/291
goodness of fit on F^2	1.024	1.079	1.033
R1 ($I > 2\sigma(I)$)	0.0353	0.0265	0.0399
wR2 (all rflns)	0.0796	0.0677	0.0972
Flack param	0.0035(10)	0.03(5)	−0.08(7)
largest diff peak, hole (e Å^{-3})	1.432, −0.951	0.211, −0.260	0.393,−0.176

1b (678 mg, 0.93 mmol) in CH_2Cl_2 (25 mL), and the resulting mixture was stirred for 4 h. A dark brown solid was formed, which was filtered out, air-dried, and identified as PdI_2 (305 mg, 0.847 mmol, 91%). The suspension was filtered through a plug of Celite, the filtrate was concentrated to ca. 2 mL, and *n*-pentane (30 mL) was added to precipitate a dark yellow solid, which was filtered, washed with *n*-pentane (2 × 3 mL), and air-dried to give compound **7**. Yield: 715 mg, 0.816 mmol, 88%. Mp: 57 °C dec. Anal. Calcd for $C_{20}H_{24}Br_2I_2N_2O_4Pd$ (876.44): C, 27.41; H, 2.76; N, 3.20. Found: C, 28.38; H, 2.81; N, 3.26. Compound **7** decomposes slowly at room temperature. This could explain the slightly high C analysis found (relative error, 3.5%). IR (cm^{-1}): ν(NH) 3273, 3218; ν(CO) 1738. ^{1}H NMR (300 MHz): δ 3.16 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 8.4 Hz), 3.33 (m, 1 H, NH_2), 3.53 (m, 1 H, NH_2), 3.63 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 6.9 Hz), 3.65 (s, 3 H, OMe), 4.26 (m, 1 H, CH), 6.95 (ddd, 1 H, H4, C_6H_4, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0 Hz), 7.27−7.31 (m, 2 H, H6 + H5, C_6H_4), 7.84 (d, 1 H, H3, C_6H_4, $^3J_{HH}$ = 8.4 Hz). ^{13}C{^{1}H} NMR (75.45 MHz): δ 44.9 (s, CH_2), 52.8 (s, OMe), 58.1 (s, CH), 101.1 (s, C2, C−I, C_6H_4), 128.6 (s, CH, C5, C_6H_4), 129.2 (s, CH, C4, C_6H_4), 130.7 (s, CH, C6, C_6H_4), 138.2 (s, C1, *C*−CH_2, C_6H_4), 140.0 (s, CH, C3, C_6H_4), 171.2 (s, CO).

Synthesis of (*S*)-2-$BrC_6H_4CH_2CH(CO_2Me)NH_2$ (8). 1,10-Phenanthroline hydrate (89.0 mg, 0.450 mmol) was added to a solution of complex **6** (350 mg, 0.447 mmol) in CH_2Cl_2 (25 mL), and the resulting mixture was stirred for 3 h. A yellow solid precipitated, which was filtered, washed with Et_2O, air-dried, and identified as [$PdBr_2$(phen)] by IR spectroscopy (172 mg, 0.385 mmol, 86%). The filtrate was concentrated to dryness, Et_2O (10 mL) was added, and the resulting suspension was filtered through a plug of Celite. The filtrate was concentrated to dryness to give crude **8** as a yellow liquid. This liquid was dissolved in CH_2Cl_2 (1 mL) and subjected to silica gel preparative thin-layer chromatography. Elution with Et_2O gave a colorless band (R_f = 0.4), which was collected and extracted with acetone; the solution was filtered through a plug of Celite, and the filtrate was concentrated to dryness to give pure compound **8** as a yellow liquid. Yield: 92.8 mg, 0.359 mmol, 40%. Anal. Calcd for $C_{10}H_{12}BrNO_2$ (258.12): C, 46.53; H, 4.67; N, 5.43. Found: C, 46.47; H, 4.83; N, 5.28. ^{1}H NMR (300 MHz): δ 1.64 (br s, 2 H, NH_2), 2.92 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.5, $^3J_{HH}$ = 8.7 Hz), 3.26 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.5, $^3J_{HH}$ = 5.7 Hz), 3.70 (s, 3 H, OMe), 3.85 (dd, 1 H, CH, $^3J_{HH}$ = 8.7, $^3J_{HH}$ = 5.4 Hz), 7.11 (ddd, 1 H, H4, C_6H_4, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 6.6, $^4J_{HH}$ = 3.0 Hz), 7.20−7.26 (m, 2 H, H5 + H6, C_6H_4), 7.55 (d, 1 H, H3, C_6H_4, $^3J_{HH}$ = 7.5 Hz). ^{13}C{^{1}H} NMR (100.81 MHz): δ 41.3 (s, CH_2), 51.9 (s, OMe), 54.2 (s, CH), 124.7 (s, C2, C−Br, C_6H_4), 127.3 (s, CH, C5, C_6H_4), 128.4 (s, CH, C4, C_6H_4), 131.5 (s, CH, C6, C_6H_4), 132.9 (s, CH, C3, C_6H_4), 136.9 (s, C1, *C*−CH_2, C_6H_4), 175.2 (s, CO). FAB$^+$-MS: *m*/*z* 258 [(M(^{79}Br) + 1)$^+$], 260 [(M(^{81}Br) + 1)$^+$].

Synthesis of (*S*)-2-$IC_6H_4CH_2CH(CO_2Me)NH_2$ (9). 1,10-Phenanthroline hydrate (148.8 mg, 0.751 mmol) was added to a solution of complex **7** (650 mg, 0.742 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was stirred for 3 h. A yellow solid precipitated, which was filtered, washed with Et_2O, air-dried, and identified as [$PdBr_2$(phen)] by IR spectroscopy (322.0 mg, 0.721 mmol, 97%). The filtrate was concentrated to dryness, Et_2O (10 mL) was added, and the resulting suspension was filtered through a plug of Celite. The filtrate was concentrated to dryness to give crude **9** as a dark yellow liquid. This liquid was dissolved in CH_2Cl_2 (1 mL) and subjected to silica gel preparative thin-layer chromatography. Elution with Et_2O gave a wide colorless band (R_f = 0.4−0.6), which was collected and extracted with acetone; the solution was filtered through a plug of Celite, and the filtrate was concentrated to dryness to give spectroscopically pure compound **9** as a yellow liquid. Yield: 285.3 mg, 0.935 mmol, 63%. Anal. Calcd for $C_{10}H_{12}INO_2$ (305.111): C, 39.37; H, 3.96; N, 4.59. Found: C, 40.01; H, 4.18; N, 4.63. Compound **9** decomposes slowly at room temperature. This could explain the slightly high C analysis found (relative error, 1.6%). ^{1}H NMR (400 MHz): δ 1.79 (br s, 2 H, NH_2), 2.92 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.7, $^3J_{HH}$ = 8.8 Hz), 3.24 (dd, 1 H, CH_2, $^2J_{HH}$ = 13.7, $^3J_{HH}$ = 5.6 Hz), 3.71 (s, 3 H, OMe), 3.85 (dd, 1 H, CH, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 5.6 Hz), 6.94 (td, 1 H, H4, C_6H_4, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8 Hz), 7.22 (dd, 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.7 Hz), 7.29 (td, 1 H, H5, C_6H_4, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2 Hz), 7.84 (dd, 1 H, H3, C_6H_4, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.2 Hz). ^{13}C{^{1}H} NMR (100.81 MHz): δ 45.6 (s, CH_2), 52.0 (s, OMe), 54.5 (s, CH), 100.8 (s, C2, C−I, C_6H_4), 128.2 (s, CH, C5, C_6H_4), 128.6 (s, CH, C4, C_6H_4), 130.7 (s, CH, C6, C_6H_4), 139.7 (s, CH, C3, C_6H_4), 140.2 (s, C1, *C*−CH_2, C_6H_4), 175.0 (s, CO). FAB$^+$-MS: *m*/*z* 306 [(M + 1)$^+$].

X-ray Structure Determinations. X-ray data for compounds **2**, **4**, and **5** are summarized in Table 1. For data collection, crystals were mounted in inert oil on a glass fiber and transferred to a Bruker SMART APEX diffractometer. Data were recorded at low temperature using ω scans. Multiscan absorption corrections were applied. Structures were solved by the heavy-atom method (**2**) or by direct methods (**4**, **5**) and refined anisotropically on F^2 using the program SHELX-97.[52] Hydrogen atoms were refined as follows: NH_2 and NH, free; methyl, rigid group; all others, riding.

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Note Added in Proof. During the correction of the galley proof of this article, the direct iodination of phenylalanine methyl ester has been reported to give a 1:1 mixture of the *ortho*- and *para*-iodo derivatives (53% yield).[53]

(52) Sheldrick, G. M. SHELX-97; University of Göttingen, Göttingen, Germany, 1997.

(53) Barluenga, J.; Alvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2007**, *119*, 1303.

Supporting Information Available: For compounds **2**, **4**, and **5**, tables and figures giving details (including symmetry operators) of hydrogen bonds and all refined and calculated atomic coordinates, anisotropic thermal parameters, and bond lengths and angles and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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