Inorganic Chemistry

Article

pubs.acs.org/IC

Synthesis of New Gold(I) Thiolates Containing Amino Acid Moieties with Potential Biological Interest

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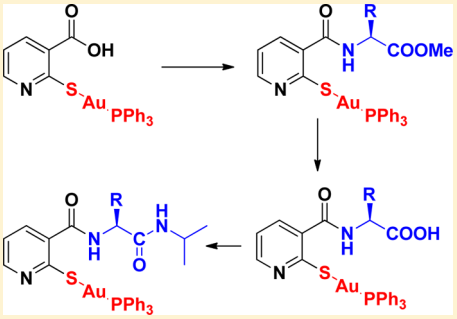
Supporting Information

ABSTRACT: The reaction of the gold(I) complex [Au(SpyCOOH)(PPh_3)], which contains nicotinic acid thiolate, with several amino acid esters such as glycine methyl ester or the enantiomerically pure L isomers of alanine methyl ester, phenylalanine methyl ester, valine methyl ester, methionine methyl ester, and proline methyl ester produces the gold(I) derivatives with the new thiolate containing amino acid ester ligands [Au{SpyCONHCH(R)COOMe}(PPh_3)]. The reaction of these amino acid ester derivatives with LiOH in methanol and acidification with $KHSO_4$ until pH 3−4 afford the corresponding acids, which are water-soluble species. These amino acid compounds can be further coupled with other amines, such as, for example, isopropylamine, to give the corresponding amide derivatives. The species with glycine methyl ester and valine methyl ester have been characterized by X-ray crystallography, showing, in the second case, only one of the enantiomers, which proves that retention of the configuration after reaction occurs.



INTRODUCTION

Thiolate metal complexes are very important in many areas of research: (a) in bioinorganic chemistry mainly because of their presence in very diverse metalloproteins and metalloenzymes,[1,2] (b) in medicine as structural models for bioinorganic medicines[3] or the use of gold thiolates in the treatment of arthritis,[4,5] (c) in material chemistry as precursors for chemical surface deposition of layers of metal or sulfides from the vapor phase,[6−8] (d) in catalysis for the chemistry relating to S−C bond cleavage reactions and desulfurization,[9] or carbon−heteroatom bond formation,[10] and (e) in nanoscience because thiolates stabilize the formation of metal nanoparticles because of their outstanding capability to form self-assembled monolayers.[11,12] Noble metal nanoparticles functionalized with biological thiolates are versatile agents with several biomedical applications, including their use in diagnostic assays,[13] thermal ablation and radiotherapy enhancement,[14] or drug delivery.[15]

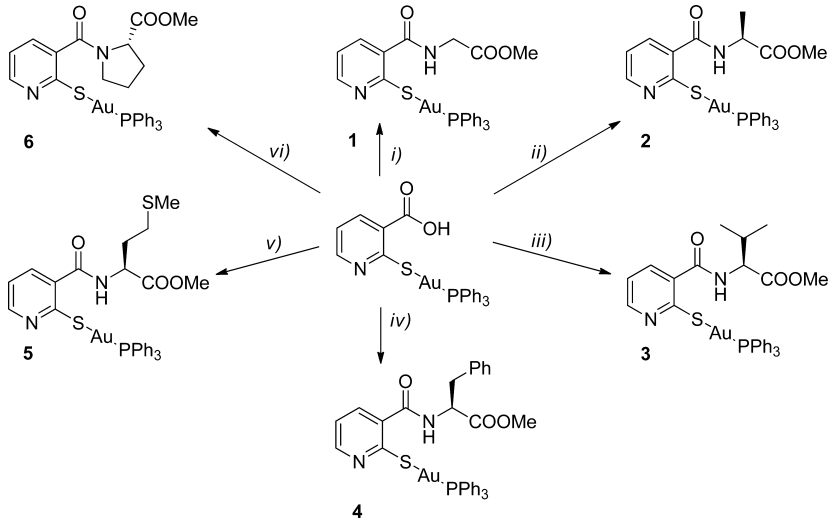
Following the success of the antiarthritic drug Auranofin, a gold(I) thiolate bearing a carbohydrate moiety, as a good antiproliferative agent, many other gold(I) derivatives of carbohydrates were prepared[16] and tested for biological activity, as well as others with thiolates derived from DNA bases, some of them with antitumoral activity by themselves as the thiopurine or thioguanine derivatives.[17,18] In this sense, we think that the synthesis of gold(I) thiolate complexes with thiolates bearing amino acid moieties could be interesting in view of the possible biological properties because the amino acids can serve as good carriers to deliver the gold atom to the biological target and because in tumoral cells the amino acid receptors are overexpressed and, consequently, the complexes could be more selective to abnormal cells.[19] Not many gold(I) derivatives with amino acids have been reported. Ligand-exchange reactions of gold phosphine[20] and gold cyano complexes[21] with cysteine or glutathione have been investigated. Gold(I) phosphine complexes with N-substituted glycines have been reported.[22] Human glutathione reductase (hGR) or thioredoxine reductase are important targets for gold compounds,[23] and the crystal structure of a gold(I) complex with hGR[24] and also a gold protein with the $AuPEt_3$ fragment bonded to a histidine rest[25] have been reported and could give interesting insight in the biological function of gold compounds. The reduction of a nonemissive gold(III) complex with intracellular glutathione gives the corresponding gold(I) glutathione derivative, which shows promising anticancer activity, accompanied by the release of a fluororescent ligand, thus serving in cellular thiol detection.[26] Stoichiometric 1:1 complexes with amino acids have only been described for cysteine-protected derivatives with phosphine or N-heterocyclic carbenes,[27] and thus we believe it is an interesting goal in order to prepare gold(I) complexes with more biologically compatible ligands.

With this proposal, we first considered the nicotinic acid thiolate gold complex [Au(SpyCOOH)(PPh_3)], previously synthesized by Nomiya et al., who demonstrated its antibacterial activity.[28] This complex possesses an acid moiety that is adequate for functionalization with biological groups such as the amino acids.

Received: February 14, 2013

   dx.doi.org/10.1021/ic4003803 | *Inorg. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of the Gold Thioamino Acid Derivatives[a]



[a](i) Glycine methyl ester, DIPEA, PyBOP; (ii) alanine methyl ester, DIPEA, PyBOP; (iii) valine methyl ester, DIPEA, PyBOP; (iv) phenylalanine methyl ester, DIPEA, PyBOP; (v) methionine methyl ester, DIPEA, PyBOP; (vi) proline methyl ester, DIPEA, PyBOP.

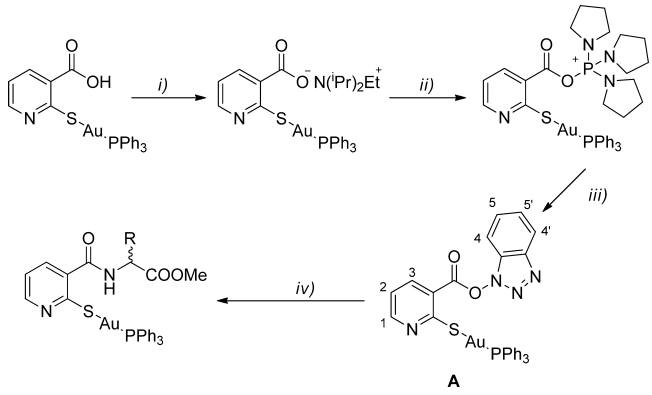
Here we report on the synthesis of gold thiolate complexes functionalized with amino acid esters. In these cases, the gold phosphine unit serves as a protecting group for the thiol because in normal reactions coupling with amino acids is necessary to protect the groups not involved in the reaction. The new thiolate containing amino acid ester complexes can be easily converted into their amino acid derivatives, and also coupling of the amino acids with amines affords the amido derivatives. The characterization of the complexes demonstrates that the configuration of the amino acid is retained upon reaction with the gold complex. The ease of functionalization of these complexes opens a broad field in the preparation of gold derivatives containing biological molecules with potential medicinal properties.

RESULTS AND DISCUSSION

Synthesis and Characterization. The phosphine thiolate complex [Au(SpyCOOH)(PPh_3)] can be readily prepared by a procedure slightly different from that published,[28] that is, by the reaction of [AuCl(PPh_3)] with mercaptoniconitic acid in acetone in the presence of K_2CO_3, yielding the product in high yield. This complex presents an acid moiety on the thiolate ligand that can be used for coupling with amino acid esters such as glycine methyl ester or the enantiomerically pure L isomers of alanine methyl ester, valine methyl ester, phenylalanine methyl ester, methionine methyl ester, and proline methyl ester. The reaction in acetonitrile of the gold complex with diisopropylethylamine (DIPEA), followed by the addition of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and the corresponding amino acid ester, gave after workup complexes **1**–**6** in good yield (Scheme 1). The gold phosphine unit acts as a protecting group of the thiol because in normal reactions coupling with amino acids is necessary to protect the groups not involved in the reaction.

In the amino acid coupling reaction, PyBOP is used as the carboxylic acid activating agent and DIPEA is used as a base to produce nucleophilic attack of the amino group to the activated carboxylic acid ester such as benzoxitriazole (which is very good leaving group) to place the new amide bond in complexes **1**–**6**. The general mechanism, as well as the structure of the reagents, is shown in Scheme 2. The reaction intermediate **A** has been

Scheme 2. Synthesis of New Complexes[a]



[a](i) DIPEA, (ii) PyBOP, (iii) BzO^-, and (iv) $H_2NCHRCOOMe$.

isolated and characterized by NMR spectroscopy, showing in the ^1H NMR spectra the resonances arising at the pyridine group H1 as a multiplet, H2 as a doublet of doublets, and H3 as a doublet of doublets, together with those of the benzotriazole unit H4–H4′ as a doublet and the H5–H5′ signal overlapped with the resonances of the phenylphosphine protons.

The amino acid ester conjugates were purified by column chromatography and characterized by means of multinuclear and 2D NMR spectroscopy. The ^1H NMR spectra of glycine methyl ester, alanine methyl ester, and valine methyl ester show resonances of the corresponding amino acid ester, the pyridine protons, and the phenylic protons. The ^1H NMR spectra of phenylalanine methyl ester, methionine methyl ester, and proline methyl ester appear as a mixture of rotamers. Normally, in amino acids and peptides, rotational freedom exists around the NH–CαH, CαH–R, and CαH–CO bonds (in this case, in the conformational analysis, the C(pyridine)–CO and C(pyridine)–S bonds must also be taken into account). However, if in the molecule is present an element that hinders or prevents rotation (such as a protecting group or a bulky side chain) freedom in rotation is lost and the molecule presents different conformations that cannot pass each other by free rotation, unless in the NMR time scale and at room temperature.

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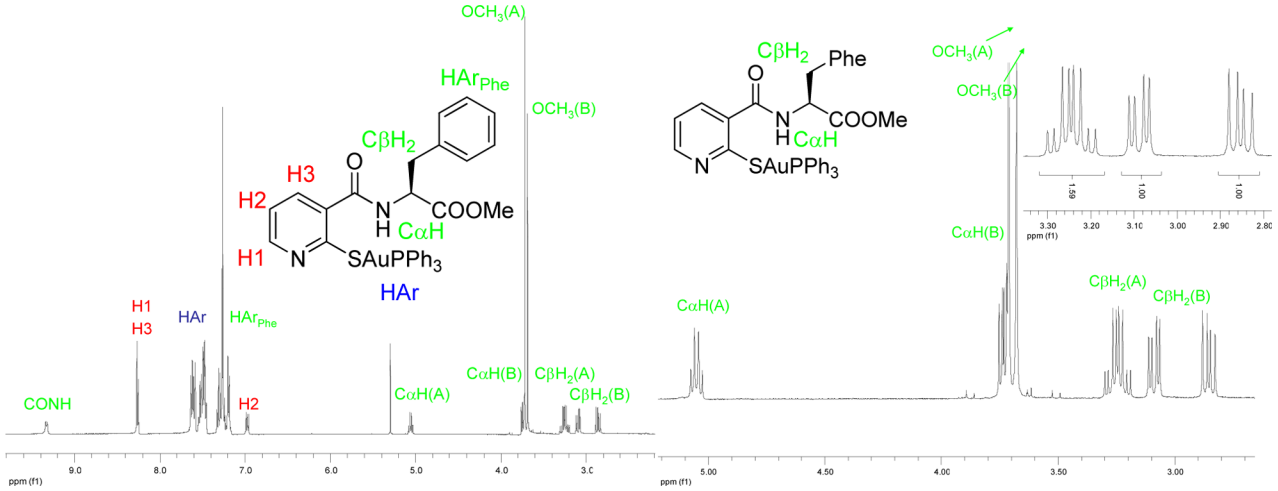
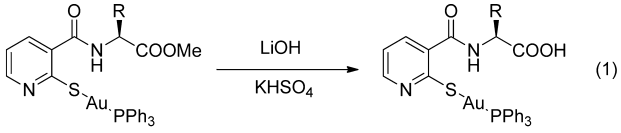


Figure 1. ^{1}H NMR spectra of complex **4** showing the presence of the two rotamers.

These conformations/configurations are called rotamers. The signals have been assigned with the 2D correlation spectroscopy (COSY) NMR spectra. For the phenylalanine derivative, the ratio is 1:0.8, for the methionine 1:1, and for the proline 1:0.75. As an example, the spectra of the phenylalanine derivative can be seen in Figure 1. The proton for C*α* of phenylalanine appears as a doublet of triplets for each rotamer, with quite different chemical shifts. The protons for the C*β*H_2 group are diastereotopic and appear also different for both rotamers with very different coupling constants; for both rotamers, the signal is an ABX system, but for rotamer B, the coupling constant is smaller than that for A. In these resonances is where the ratio for both rotamers can be calculated because others appear overlapped.

The $^{31}P\{^{1}H\}$ NMR spectra present a unique resonance for all of the complexes corresponding to the phosphorus of triphenylphosphine; in all the cases; the chemical shift, as expected, is very similar to that of the starting material. $^{13}C\{^{1}H\}$ NMR APT spectra for compounds **1**-**6** show the resonances for the coupled amino acid ester and the new amide group, as well as those of the pyridine and triphenylphosphine moieties. The assignment of the resonances was made with the $^{1}H-^{13}C$ heteronuclear single quantum coherence and $^{1}H-^{13}C$ heteronuclear multiple-bond correlation experiments. The IR spectra present, among others, absorptions for the amide unit at around 3200 (br, w) and 1640 (s) and for the ester group at around 1740 (s). The mass spectra (positive-mode electrospray ionization, ESI^{+}) present for all of the compounds the molecular peak $[M+H]^{+}$, together with the association fragment $[M + AuPPh_3]^{+}$.

The corresponding acid derivatives were obtained by hydrolysis of amino acid esters using LiOH, which is less basic than the normally used NaOH, trying to avoid racemization or decomposition of the gold compounds. Thus, the reactions of complexes **1**−**6** with LiOH, followed by neutralization with $KHSO_4$ (pH 3−4), to avoid protonation of the thiolate ligand and then decomposition of the gold complex, lead to the acid species **7**−**12** (eq 1).



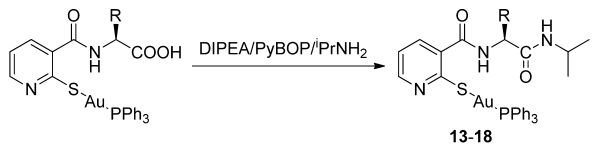
(1)

7-12

Aa = Gly (**7**), Ala (**8**), Phe (**9**), Val (**10**), Met (**11**), Pro (**12**)

In the ^{1}H NMR spectra, similar resonances for the amino acids are observed, with the exception of the methyl group of the ester precursor, which has disappeared. The protons for the COOH group are not observed, but this usually happens, with it being a mobile proton, and the observation depends on the solvent and concentration. The resonance of the amide protons appears at higher fields than those in the corresponding precursors. In these compounds, no rotamers are observed, with the exception of the proline derivative, probably because of the less steric hindrance caused by removal of the methyl group in the ester and because of the possibility of formation of hydrogen bonds between the carboxylic group and the amide proton, which would favor one of the configurations. All of the resonances were assigned with the aid of 2D COSY NMR experiments. The IR spectra show absorptions of the new carboxylic group around 3400−2900 (s, br) and 1730 (s) cm^{-1}. The absorption for the carbonyl of the amide group appears around 1660 (s) cm^{-1}, and the one for the ester group has disappeared. The mass spectra (ESI+) for these complexes show the presence of the molecular peak $[M]^{+}$ and the protonated species $[M + H]^{+}$ and the addition of a $AuPPh_3$ fragment, $[M + AuPPh_3]^{+}$.

The coupling of amino acid derivatives with an amine such as isopropylamine produces the secondary amides (eq 2).



(2)

13-18

Aa = Gly (**13**), Ala (**14**), Phe (**15**), Val (**16**), Met (**17**), Pro (**18**)

The conditions used were the same as those used in the preparation of the ester family. In this case, there is more steric hindrance about the carboxylic acid, but the amine is more nucleophilic than amino acid ester in the first reactions.

In the ^{1}H NMR spectra of the new amide derivatives, it is possible to observe the resonances for the two amide groups; the one with the isopropyl group appears more shielded than the first one probably because the isopropyl group is a better donor group than the ester. In the complexes with a chiral carbon center, the methyl groups of the isopropylamine appear as inequivalent. The $^{31}P\{^{1}H\}$ NMR spectra present a unique resonance for the phosphorus atom of triphenylphosphine with

dx.doi.org/10.1021/ic4003803 | Inorg. Chem. XXXX, XXX, XXX−XXX

very small variation in the chemical shift, as observed for the rest of the complexes. The IR spectra show that the absorption arising at the carboxylic group has disappeared and the ones for the amide groups appear around 3270 (w, br) and 1640 (s) cm^{-1}. In the mass spectra (ESI^+), the molecular peak $[M]^+$, the protonated $[M + H]^+$, and the one with an additional $AuPPh_3$ fragment, $[M + AuPPh_3]^+$, are observed for all of the complexes.

Because we have used enantiomerically pure amino acid esters, with the exception of glycine methyl ester, which is not chiral, the angle of optical rotation has been measured in order to know whether there is racemization after the reaction conditions. For the amino acid ester derivatives, positive values are found from 3.97 for PheOMe to 44.1 for ValOMe and a negative value of −50.2 for ProOMe. The acid derivatives present positive values from 5.9 (AlOH) to 30.0 (AlaOH) and negative values of −18 to −56 for ProOH. The amide derivatives present all negative values from −0.44 (ValNH^{i}Pr) to −26.87 (ProNH^{i}Pr).

X-ray Structure Analysis. The crystal structures for the glycine (**1**) and valine (**3**) ester derivatives have been established by X-ray diffraction. Complex **1** crystallizes with two independent molecules; one of those can be seen in Figure 2.

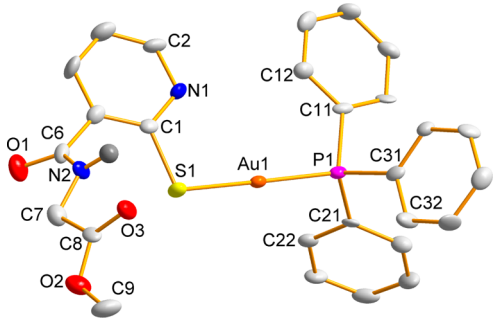


Figure 2. Diagram of **1** with 50% probability ellipsoids. Hydrogen atoms (except NH) are omitted for clarity.

The gold(I) centers in both molecules are in a linear environment with a P−Au−S angles of 178.13(9)° and 177.21(9)°, respectively. The Au−P distances of 2.245(3) and 2.251(3) Å and the Au−S bond lengths of 2.302(3) and 2.305(3) Å are similar to those reported for the starting material, Au−P of 2.254(2) Å and Au−S of 2.295(3) Å.[27] In the thiolate substituent, the new amide bond formed with glycine methyl ester is observed with a C6−N2 distance of 1.334(12) Å.

There are several secondary bonds that can be considered as hydrogen bonds in the molecule. Figure 3 represents the shortest one between one of the oxygen atoms of glycine methyl ester

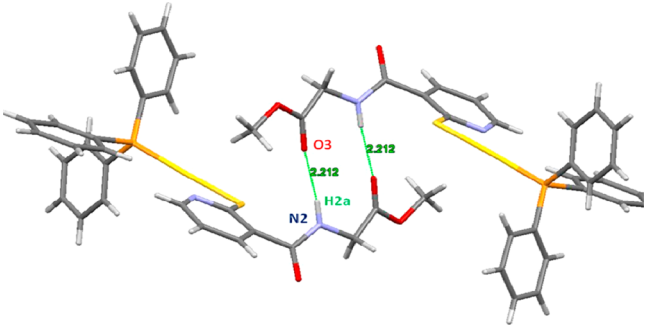


Figure 3. Hydrogen bonds in complex **1**.

and the NH proton, with an O3···H2a distance of 2.211(8) Å and an angle of 163.82(2)°.

The structure of complex **3** is shown in Figure 4. The compound contains a chiral amino acid ester, valine methyl ester,

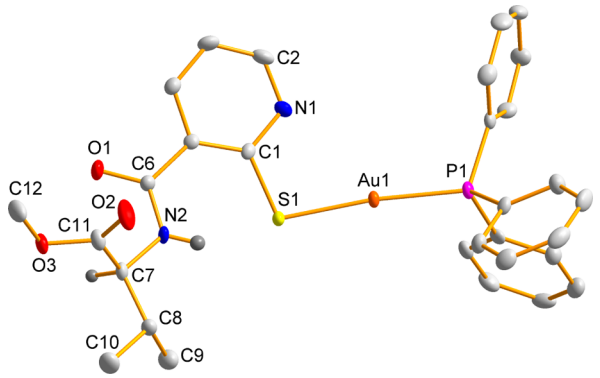


Figure 4. Diagram of **1** with 50% probability ellipsoids. Hydrogen atoms (except NH and chiral CH) are omitted for clarity.

and crystallizes in the noncentrosymmetric group $P2_12_12_1$. Determination of the Flack parameter led to the conclusion that only the *S* enantiomer is present in the molecule (such as the enantiomerically pure valine methyl ester used). Again the gold(I) center is found in a linear geometry with a P−Au−S angle of 174.08(3)°. The distances Au−P and Au−S are 2.2515(7) and 2.3099(7) Å, respectively, which are very similar to those in complex **1**. The amide bond C6−N2 is 1.351(4) Å, which is also on the same order as that of glycine methyl ester.

CONCLUSIONS

Synthesis of the thiolate containing amino acid ester species [Au{SpyCONHCH(R)COOMe}(PPh_3)] was achieved by functionalization of the carboxylic group with amino acid esters in the gold(I) thiolate complex [Au(SpyCOOH)(PPh_3)], in which the gold(I) center serves as a protecting group for the thiol. The new complexes can be easily converted into the water-soluble amino acid species by reaction with LiOH and subsequent treatment with $KHSO_4$. These amino acid species are very versatile compounds that can be further functionalized with other molecules through the acid moiety and, thus, treatment with isopropylamine gave the corresponding amide derivatives. With the exception of the glycine derivative, in all of the cases enantiomerically pure L isomers have been used, and the crystal structure of the valine methyl ester compound shows the presence of the same *S* enantiomer and corroborates that the configuration is retained upon reaction conditions. The ease of functionalization of these complexes opens a broad field in the preparation of gold derivatives containing biological molecules with potential medicinal properties. These studies are being conducted and will be published in due course.

EXPERIMENTAL SECTION

Instrumentation. Carbon, hydrogen, and nitrogen analysis was carried out with a Perkin-Elmer 2400 microanalyzer. Mass spectra were recorded on a Bruker Esquire 3000 Plus, with the ESI technique, and on a Bruker Microflex (matrix-assisted laser desorption ionization time of flight). ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR, including 2D experiments, were recorded at room temperature on a Bruker AVANCE 400 spectrometer (^1H, 400 MHz; ^{13}C, 100.6 MHz) or on a Bruker AVANCE II 300 spectrometer (^1H, 300 MHz; ^{13}C, 75.5 MHz), with chemical shifts (δ, ppm) reported relative to the solvent peaks of the deuterated solvent.[29]

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Starting Materials. [AuCl(PPh$_3$)][30] was prepared according to published procedures and [Au(SpyCOOH)(PPh$_3$)] with a slight variation of the reported procedure.[28] All other reagents were commercially available. Solvents were used as received without purification or drying, except for tetrahydrofuran, which was dried with a SPS solvent purification system.

Synthesis of [Au(SpyCOOBzt)(PPh$_3$)] (A). To a suspension of [Au(SpyCOOH)(PPh$_3$)] (0.613 g, 1 mmol) in acetonitrile (6 mL) was added DIPEA (2.2 mmol). The mixture was stirred for 5 min at room temperature, and then PyBOP was added (1.2 mmol), and the resulting solution was stirred for an additional 45 min. Then the white precipitate was filtered off, and the intermediate complex **A** was obtained as a white solid. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 8.41 (dd, 1H, J = 4.8 and 2.0, *H*1), 8.22 (dd, 1H, J = 7.6 and 2.0, *H*3), 8.07 (d, 1H, J = 8.4, H4), 7.75 (d, 1H, J = 7.8, H4′), 7.67−7.61 and 7.54−7.48 (m, 15H, *ArH*), 7.52 (m, 1H, H5), 7.42 (m, 1H, H5′), 7.06 (dd, 1H, J = 8.0 and 4.8, *H*2). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.9. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 151.6 (*C*H, *C*1), 139.0 (*C*H, *C*3), 134.3 (d, *C*H, J = 14.0, *C*5), 131.7 (*C*H, *C*7), 129.1 (d, *C*H, J = 11.6, *C*6), 128.6 and 124.5 (*C*H, *C*10 and *C*10′), 120.3 and 109.4 (*C*H, *C*9 and *C*9′), 117.6 (*C*H, *C*2).

General Procedure for the Synthesis of Complexes 1−6. To a suspension of [Au(SpyCOOH)(PPh$_3$)] (0.613 g, 1 mmol) in acetonitrile (6 mL) was added DIPEA (2.2 mmol). The mixture was stirred for 5 min at room temperature, and then PyBOP was added (1.2 mmol), and the resulting solution was stirred for an additional 45 min. To the resultant green solution was added dropwise and at 0 °C a solution of the corresponding amino acid methyl ester (1.5 mmol) in acetonitrile (4 mL) and DIPEA (1.5 mmol). After the addition, the mixture was stirred for 48 h at room temperature. Acetonitrile was evaporated, and dichloromethane (40 mL) was added. This solution was washed with a saturated $NaHCO_3$ solution in water (3 × 15 mL) and a saturated solution of NaCl (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered off, and evaporated to dryness. The complexes were purified by column chromatography of silica gel using as the eluent a mixture of 3:7 acetone/hexane.

[Au(SpyCOGlyOMe)(PPh$_3$)] (1). Yield: 0.475 g, 69.4%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 9.17 (s, br, 1H, CON*H*), 8.33 (dd, 1H, J = 4.6 and 1.6, *H*1), 8.29 (dd, 1H, J = 8.0 and 1.6, *H*3) 7.62−7.48 (m, 15H, *Ar*), 7.02 (dd, 1H, J = 8.0 and 4.6, *H*2), 4.30 (d, 2H, J = 4.8, C$_\alpha$*H*$_2$), 3.78 (s, 3H). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.6. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 170.3 (COOMe), 166.8 (CONH), 164.7 (*C*, Py), 149.3 (*C*H, *C*1), 139.3 (*C*H, *C*3), 134.3 (d, *C*H, J = 13.9, *C*5), 131.7 (*C*H, *C*7), 129.7 (d, *C*, J = 56.1, C4), 129.2 (d, *C*H, J = 11.4, C6), 118.9 (*C*H, *C*2), 52.3 (OCH$_3$), 42.1 (C$_\alpha$H$_2$). MS (ESI$^+$) m/z: [MH]$^+$ 685.0 (calcd), 684.9 (found); [M + AuPPh$_3$]$^+$ 1143.3. IR (cm^{-1}): 3360 (br, w, *NH*), 1736 (s, *COOMe*), 1645 (s, *CONH*), 1573, 1517, and 1480 (w, *Ar*), 1099 and 1064 (s, *C*−*O*), 746, 709, and 690 (w, *Ar*). Anal. Calcd for $C_{27}H_{24}AuN_2O_3PS$: C, 47.38; H, 3.53; N, 4.09; S, 4.68. Found: C, 46.98; H, 3.92; N, 4.04; S, 4.39. TLC: R_f = 0.4 (1:1 acetone/hexane).

[Au(SpyCOAlaOMe)(PPh$_3$)] (2). Yield: 0.473 g, 67.7%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 9.63 (d, 1H, J = 5.2, CON*H*), 8.38 (dd, 1H, J = 7.6 and 2.0, *H*1), 8.19 (dd, 1H, J = 5.2 and 2.0, *H*3), 7.63−7.47 (m, 15H, *Ar*), 6.98 (dd, 1H, J = 7.6 and 5.2, *H*2), 4.80 ("q", 1H, J = 7.2 Hz, C$_\alpha$*H*), 3.76 (s, 3H), 1.57 (d, 3H, J = 7.2, C$_\beta$*H*$_3$). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.6. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 173.3 (COOMe), 165.9 (CONH), 165.6 (*C*, Py), 148.4 (*C*H, *C*1), 139.4 (*C*H, *C*3), 134.2 (d, *C*H, J = 14.1, *C*5), 131.5 (d, *C*H, J = 2.3, *C*7), 130.4 (*C*, Py), 129.7 (d, *C*, J = 55.2, *C*4), 129.1 (d, *C*H, J = 11.5, *C*6), 118.3 (C$_\alpha$H, *C*2), 52.4 (OCH$_3$), 49.1 (C$_\alpha$H), 18.1 (C$_\beta$H$_3$). MS (ESI$^+$) m/z: [MH]$^+$ 699.1 (calcd), 699.0 (found); [M + AuPPh$_3$]$^+$ 1157.1. IR (cm^{-1}): 3273 (br, w, *NH*), 1739 (s, *COOMe*), 1639 (s, *CONH*), 1570, 1523, and 1479 (w, *Ar*), 1098 and 1069 (s, *CO*), 744, 709, and 690 (w, *Ar*). Anal. Calcd for $C_{28}H_{26}AuN_2O_3PS$: C, 48.14; H, 3.75; N, 4.01; S, 4.59. Found: C, 48.07; H, 3.81; N, 4.09; S, 4.32. TLC: R_f = 0.4 (1:1 acetone/hexane). $[\alpha]_D$: +36.16 (c 1.0 g/mL, CHCl$_3$).

[Au(SpyCOValOMe)(PPh$_3$)] (3). Yield: 0.485 g, 66.8%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: 9.09 (d, 1H, J = 8.0, CON*H*), 8.32 (dd, 1H, J = 4.6 and 2.0, *H*1), 8.28 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.63−7.47 (m, 15H, *Ar*), 7.00 (dd, 1H, J = 7.6 and 4.6, *H*2), 4.78 (dd, 1H, J = 8.0 and 5.0, C$_\alpha$*H*), 3.73 (s, 3H), 2.34 (m, 1H, C$_\beta$*H*), 1.09 (d, 6H, J = 6.8, C$_\delta$*H*$_3$). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.6. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 172.3 (COOMe), 166.5 (CONH), 164.7 (*C*, Py), 149.1 (*C*H, *C*1), 139.3 (*C*H, *C*3), 134.3 (d, *C*H, J = 13.9, *C*5), 131.6 (d, *C*H, J = 2.1, *C*7), 130.0 (d, *C*, J = 47.3, *C*4), 129.2 (*C*, Py), 129.1 (d, *C*H, J = 11.6, *C*6), 118.8 (*C*H, *C*2), 58.5 (C$_\alpha$H), 52.0 (OCH$_3$), 31.2 (C$_\beta$H), 19.4 (C$_\chi$H$_3$), 18.4 (C$_\chi$H$_3$). MS (ESI$^+$) m/z: [MH]$^+$ 727.1 (calcd), 727.1 (found); [M + AuPPh$_3$]$^+$ 1185.2. IR (cm^{-1}): 3290 (w, br, *NH*), 1738 (s, *COOMe*), 1643 (s, *CONH*), 1570, 1522, and 1480 (w, *Ar*), 1099 and 1070 (s, *COOMe*), 744, 709, and 690 (w, *Ar*). Anal. Calcd for $C_{30}H_{30}AuN_2O_3PS$: C, 49.59; H, 4.16; N, 3.86; S, 4.41. Found: C, 49.35; H, 4.47; N, 4.04; S, 3.83. TLC: R_f = 0.4 (1:1 acetone/hexane). $[\alpha]_D$: +44.11 (c 1.0 g/mL, CHCl$_3$).

[Au(SpyCOPheOMe)(PPh$_3$)] (4). Yield: 0.493 g, 63.7%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, ratio 1:0.8:9.33 (d, 1H, J = 6.8, CON*H*), 8.27−8.25 (m, 2H, *H*1 and *H*3), 7.64−7.48 (m, 15H), 7.33−7.18 (m, 5H), 6.99−6.96 (m, 1H, *H*2), 5.06 (A) and 3.75 (B) (dt, 1H, J = 13.6 and 6.8, J = 8.0 and 5.2, C$_\alpha$*H*), 3.72 and 3.69 (s, 3H), 3.28 and 3.22 (A) (ABX, 2H diastereotopic, J = 13.8 and 6.0, J = 14.0 and 6.8, C$_\beta$*H*$_2$), 3.10 and 2.86 (B) (ABX, 2H diastereotopic, J = 13.6 and 5.2, J = 13.6 and 8.0, C$_\beta$*H*$_2$). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.4. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, 172.0 (COOMe), 166.1 (CONH), 165.8 (*C*, Py), 148.4 (*C*H, *C*1), 139.4 (*C*H, *C*3), 136.4 (*C*, *C*8), 134.3 (d, *C*H, J = 13.9, *C*5), 131.7 (d, *C*H, J = 2.2, *C*7), 130.1 (d, *C*, J = 64.0, *C*4), 129.5 and 129.2 (*C*H, R, *C*10), 129.1 (d, *C*H, J = 11.5, *C*6), 128.6 and 128.4 (*C*H, R, *C*9), 126.9 and 126.8 (*C*H, R, *C*11), 118.3 (*C*H, *C*2), 55.8 (A) and 55.0 (B) (C$_a$H), 52.1 (A) and 52.0 (B) (OCH$_3$), 41.1 (A) and 38.2 (B) (C$_\beta$H$_2$). MS (ESI$^+$) m/z: [MH]$^+$ 775.1 (calcd), 775.1 (found); [M + AuPPh$_3$]$^+$ 1233.2. IR (cm^{-1}): 3281 (w, br, *NH*), 1736 (s, *COOMe*), 1640 (s, *CONH*), 1571, 1518, 1495, and 1480 (w, *Ar*), 1100 and 1071 (s, *CO*), 745 and 709 (w, *Ar*). Anal. Calcd for $C_{34}H_{30}AuN_2O_3PS$: C, 52.72; H, 3.90; N, 3.62; S, 4.14. Found: C, 52.81; H, 3.68; N, 3.78; S, 4.01. TLC: R_f = 0.4 (1:1 acetone/hexane). $[\alpha]_D$: +3.97 (c 1.0 g/mL, CHCl$_3$).

[Au(SpyCOMetOMe)(PPh$_3$)] (5). Yield: 0.463 g. 61.1%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, ratio 1:0.75:9.05 (d, 1H, J = 7.6), 8.30 (dd, 1H, J = 4.8 and 2.0, *H*1), 8.21 (dd, 1H, J = 8.0 and 2.0, *H*3), 7.60−7.45 (m, 15H), 6.98 (dd, 1H, J = 8.0 and 4.8, *H*2), 4.94 (A) and 3.58 (B) ("dt", 1H, J = 7.6 and 5.0, J = 8.3 and 4.9, C$_\alpha$*H*), 3.73 and 3.71 (s, 3H), 2.68 (B) and 2.63−2.58 (A) (ddd and m, 2H, J = 8.4, 6.7, and 1.6, C$_\chi$*H*$_2$), 2.28 (A) and 2.16 (B) (dt and m, 2H diastereotopic, J = 8.6, 7.6, and 5.0, C$_\beta$*H*$_2$), 2.01 (A) and 1.76 (B) (m, 2H diastereotopic, C$_\beta$*H*$_2$), 2.08 and 2.08 (s, 3H). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.6. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, 176.1 and 172.2 (COOMe), 166.4 and 164.6 (CONH), 164.7 (*C*, Py), 149.2 (*C*H, *C*1), 139.0 (*C*H, *C*3), 134.2 (d, *C*H, J = 13.9, *C*5), 131.6 (*C*H, *C*7), 129.9 (d, *C*, J = 41.2, *C*4), 129.1 (d, *C*H, J = 11.5, *C*6), 118.8 (*C*H, *C*2), 53.1 and 52.0 (C$_\alpha$H), 52.3 and 52.3 (OCH$_3$), 33.8 (A) (C$_\chi$H$_2$) and 30.1 (B) (C$_\chi$H$_2$), 31.7 (A) (C$_\beta$H$_2$) and 30.4 (B) (C$_\beta$H$_2$), 15.4 (CH$_3$). MS (ESI$^+$) m/z: [MH]$^+$ 759.1 (calcd), 759.1 (found); [M + AuPPh$_3$]$^+$ 1217.0. IR (cm^{-1}): 1734 (s, *COOMe*), 1645 (s, *CONH*), 1571, 1522, and 1480 (w, *Ar*), 1100 and 1071 (s, *COOMe*), 746 and 709 (w, *Ar*). Anal. Calcd for $C_{30}H_{30}AuN_2O_3PS_2$: C, 47.50; H, 3.99; N, 3.69; S, 8.45. Found: C, 47.41; H, 4.16; N, 3.81; S, 8.48. TLC: R_f = 0.4 (1:1 acetone/hexane). $[\alpha]_D$: +22.4 (c 1.0 g/mL, CHCl$_3$).

[Au(SpyCOProOMe)(PPh$_3$)] (6). Yield: 0.437 g, 60.4%. ^{1}H NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, ratio 1:0.75:8.24 (A) and 8.20 (B) (dd, 1H, J = 5.0 and 1.8, J = 5.0 and 1.8, *H*1), 7.58−7.35 (m, 15H, *Ar*), 7.43 and 7.29 (m and dd, 1H, J = 7.4 and 1.8, *H*3), 6.86 (A) and 6.80 (B) (dd, 1H, J = 7.4 and 5.0, J = 7.6 and 4.8, H2), 4.60 and 4.60 (dd, 1H, J = 8.8 and 3.6, C$_\alpha$*H*), 3.69 (A) and 3.43 (B) (s, 3H), 3.66 ("dd", 2H, J = 6.0 and 2.0, C$_\delta$*H*$_2$), 2.30 (B) and 2.21 and 2.03 (A) (C$_\beta$*H*$_2$, m, 2H each), 1.97 and 1.90 (C$_\chi$*H*$_2$, m, 2H each). ^{31}P NMR [CDCl$_3$, 400 MHz, δ (ppm)]: 37.8. ^{13}C NMR [CDCl$_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, 173.0 and 172.7 (COOMe),

dx.doi.org/10.1021/ic4003803 | *Inorg. Chem.* XXXX, XXX, XXX−XXX

168.7 and 168.4 (CONH), 162.6 and 162.3 (C, Py), 148.6 and 148.5 (CH, C1), 134.9 (CH, C3), 134.1 and 132.0 (d, CH, J = 14.2, J = 9.9, C5), 131.9 and 131.4 (d, CH, J = 2.7, J = 2.3, C7), 134.5 and 129.9 (d, C, J = 27.9, J = 52.4, C4), 129.1 and 128.4 (d, CH, J = 11.3, J = 12.2, C6), 118.1 and 117.9 (CH, C2), 60.0 and 58.5 (C_αH), 52.1 and 51.9 (OCH_3), 47.8 and 46.2 ($C_\delta H_2$), 31.2 and 29.6 ($C_\beta H_2$), 24.8 and 23.0 ($C_\chi H_2$). MS (ESI$^+$) m/z: $[MH]^+$ 725.1 (calcd), 725.1 (found); $[M + AuPPh_3]^+$ 1183.1. IR (cm^{-1}): 1738 (s, *COOMe*), 1629 (s, *CONH*), 1570, 1545, and 1479 (w, *Ar*), 1097 and 1093 (s, *COOMe*), 746 and 709 (w, *Ar*). Anal. Calcd for $C_{30}H_{28}AuN_2O_3PS$: C, 49.73; H, 3.90; N, 3.87; S, 4.43. Found: C, 49.67; H, 4.06; N, 3.78; S, 4.30. TLC: R_f = 0.4 (1:1 acetone/hexane). $[\alpha]_D$: −50.2 (c 1.0 g/mL, $CHCl_3$).

General Procedure for the Synthesis of Complexes 7−12. To a suspension of the corresponding complexes **1−6** (1 mmol) in methanol (20 mL) was added LiOH (0.480 g, 20 mmol). The mixture was stirred at room temperature for a period between 24 and 48 h. The reaction was followed by thin-layer chromatography (TLC) and was complete when the starting compound [R_f = 0.4 (1:1 acetone/hexane)] was strongly retained at the origin of TLC [R_f = 0 (1:1 acetone/hexane)]. At this point, methanol was evaporated and the product dissolved in water. The resulting white solution was acidified dropwise with a saturated solution of $KHSO_4$ until a slightly acidic pH (3−4). Then the solution was extracted three times with dichloromethane, and the organic phase was dried over anhydrous $MgSO_4$, filtered off, and evaporated to yield pure compounds **7−12**.

[Au(SpyCOGlyOH)(PPh$_3$)] (7). Yield: 0.514 g, 76.8%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 8.74 (m, 1H), 8.21 (dd, 1H, J = 4.8 and 2.0, *H*1), 8.00 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.53−7.37 (m, 15H, *Ar*), 6.89 (dd, 1H, J = 7.6 and 4.8, *H*2), 4.03 (d, 2H, J = 4.8, $C_\alpha H$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.4. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 171.9 (COOH), 167.1 (CONH), 163.3 (C, Py), 148.9 (CH, C1), 138.4 (CH, C3), 134.2 (d, CH, J = 13.6, C5), 131.8 (CH, C7), 129.2 (d, CH, J = 10.9, C6), 129.2 (d, C, J = 54.9, C4), 118.9 (CH, C2), 43.4 ($C_a H_2$). MS (ESI$^-$) m/z: 671.1 (calcd), 671.1 (found); $[M + AuPPh_3]^+$ 1129.2. IR (cm^{-1}): 3400−2900 (s, br, *COOH*), 1728 (s, *COOH*), 1657 (s, *CONH*), 1574, 1548, and 1479 (w, *Ar*), 1102 and 1053 (*CO*, s), 743 and 709 (w, *Ar*). Anal. Calcd for $C_{26}H_{22}AuN_2O_3PS$: C, 46.58; H, 3.31; N, 4.18; S, 4.78. Found: C, 46.62; H, 3.42; N, 4.15; S, 4.60.

[Au(SpyCOAlaOH)(PPh$_3$)] (8). Yield: 0.544 g, 79.5%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 9.25 (d, 1H, J = 5.6), 8.33 (dd, 1H, J = 4.6 and 2.0, *H*1), 8.24 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.59−7.42 (m, 15H), 7.02 (dd, 1H, J = 7.6 and 4.6, *H*2), 4.65 ("q", 1H, J = 6.8, $C_\alpha H$), 1.59 (d, 3H, J = 6.8, $C_\beta H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.2. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 173.6 (COOH), 168.3 (CONH), 164.6 (C, Py), 149.6 (CH, C1), 139.1 (CH, C3), 134.2 (d, CH, J = 13.8, C5), 131.7 (d, CH, J = 1.3, C7), 129.6 (C, Py), 129.3 (d, C, J = 57.7, C4), 129.2 (CH, J = 11.5, C6), 119.1 (CH, C2), 50.5 (C_αH), 16.9 (CH_3). MS (ESI$^+$) m/z: $[MH]^+$ 685.1 (calcd), 685.0 (found); $[M + AuPPh_3]^+$ 1143.1. IR (cm^{-1}): 3400−2900 (s, w, *COOH*), 1731 (s, *COOH*), 1637 (s, *CONH*), 1570, 1519, and 1479 (w, *Ar*), 1098 and 1069 (*CO*, s) 743 and 709 (w, *Ar*). Anal. Calcd for $C_{27}H_{24}AuN_2O_3PS$: C, 47.38; H, 3.53; N, 4.09; S, 4.68. Found: C, 47.60; H, 3.90; N, 3.78; S, 4.72. $[\alpha]_D$: +5.9 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOValOH)(PPh$_3$)] (9). Yield: 0.600 g, 84.3%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 9.32 (d, 1H, J = 7.2), 8.35 (dd, 1H, J = 4.8 and 2.0, *H*1), 8.31 (dd, 1H, J = 7.8 and 2.0, *H*3), 7.61−7.44 (m, 15H, *Ar*), 7.02 (dd, 1H, J = 7.8 and 4.8, *H*2), 4.64 (dd, 1H, J = 7.2 and 5.2, $C_\alpha H$), 2.52 (m, 1H, $C_\beta H$), 1.15 (d, 3H, J = 5.2, $C_\chi H_3$), 1.13 (d, 3H, J = 5.2, $C_\chi H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 36.4. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 174.0 (COOH), 167.6 (CONH), 164.6 (C, Py), 149.4 (CH, C1), 139.5 (CH, C3), 134.3 (d, CH, J = 14.0, C5), 131.7 (d, CH, J = 2.3, C7), 129.9 (C, C4), 129.8 (C, Py), 129.2 (d, CH, J = 11.5, C6), 119.0 (CH, C2), 59.4 (C_αH), 30.2 ($C_\beta H_2$), 19.6 ($C_\chi H_3$), 18.3 ($C_\chi H_3$). MS (ESI$^+$) m/z: $[MH]^+$ 713.1 (calcd), 713.1 (found); $[M + AuPPh_3]^+$ 1171.4. IR (cm^{-1}): 3400−3200 (br, *COOH*), 1635 (s, *CONH*), 1565 and 1479 (w, *Ar*), 1097 and 1070 (s, *CO*), 743 and 708 (w, *Ar*). Anal. Calcd for $C_{29}H_{28}AuN_2O_3PS$: C, 48.88; H, 3.96; N, 3.93; S, 4.50. Found: C, 48.71; H, 3.98; N, 3.95; S, 4.51. $[\alpha]_D$: +30.0 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOPheOH)(PPh$_3$)] (10). Yield: 0.542 g, 71.3%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 9.25 (d, 1H, J = 5.2), 8.30−8.29 (m, 1H, *H*1), 8.19 (d, 1H, J = 7.6, *H*3), 7.60−7.44 (m, 15H, *Ar*), 7.22 (m, 5H), 6.97 (dd, 1H, J = 7.4 and 4.6, *H*2), 4.89 ("dd", 1H, J = 12.1 and 6.0, $C_\alpha H$), 3.38 and 3.21 (ABX, 2H diastereotopic, J = 13.9 and 5.2, J = 13.9 and 7.1, $C_\beta H_2$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.1. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 171.8 (COOH), 167.7 (CONH), 164.6 (C, Py), 149.4 (CH, C1), 139.1 (CH, C3), 136.7 (C, C8), 134.2 (d, CH, J = 13.9, C5), 131.7 (CH, C7), 129.8 (C, C4), 129.7 (CH, R, C10), 129.2 (d, CH, J = 11.5, C6), 128.4 (CH, R, C9), 126.7 (CH, R, C11), 118.9 (CH, C2), 55.9 (C_αH), 37.0 ($C_\beta H_2$). MS (ESI$^+$) m/z: $[MH]^+$ 761.1 (calcd), 761.1 (found); $[M + AuPPh_3]^+$ 1219.2. IR (cm^{-1}): 3400−2900 (br, *COOH*), 1725 (s, *COOH*), 1636 (s, *CONH*), 1568 and 1479 (w, *Ar*), 1096 and 1065 (*CO*, s), 743 and 710 (w, *Ar*). Anal. Calcd for $C_{33}H_{28}AuN_2O_3PS$: C, 52.11; H, 3.71; N, 3.68; S, 4.22. Found: C, 52.04; H, 4.00; N, 3.69; S, 4.18. $[\alpha]_D$: −7.64 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOMetOH)(PPh$_3$)] (11). Yield: 0.517 g, 69.5%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 9.12−9.10 (m, 1H), 8.30−8.29 (m, 1H, *H*1), 8.18 (d, 1H, J = 7.4, *H*3), 7.58−7.41 (m, 15H, *Ar*), 6.97 (dd, 1H, J = 7.4 and 4.8, *H*2), 4.74 ("dd", 1H, J = 11.2 and 6.0, $C_\alpha H$), 2.70 ("t", 2H, J = 7.2, $C_\chi H_2$), 2.32 and 2.16 (td and m, 2H diastereotopic, J = 13.2 and 7.6, $C_\beta H_2$), 2.04 (s, 3H). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 36.3. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 170.9 (COOH), 167.7 (CONH), 164.4 (C, Py), 149.3 (CH, C1), 139.1 (CH, C3), 134.2 (d, CH, J = 13.8, C5), 131.7 (d, CH, J = 0.8, C7), 130.0 (d, C, J = 59.7, C4), 129.2 (d, CH, J = 11.5, C6), 119.0 (CH, C2), 53.8 (C_αH), 31.0 ($C_\beta H_2$), 30.3 ($C_\chi H_2$), 15.4 (CH_3). MS (ESI$^+$) m/z: $[MH]^+$ 745.1 (calcd), 745.1 (found); $[M + AuPPh_3]^+$ 1203.1. IR (cm^{-1}): 3400−3000 (br, *COOH*), 1719 (s, *COOH*), 1639 (s, *CONH*), 1571, 1515, and 1479 (w, *Ar*), 1098 and 1069 (s, *CO*), 743 and 710 (w, *Ar*). Anal. Calcd for $C_{29}H_{28}AuN_2O_3PS_2$: C, 46.78; H, 3.79; N, 3.76; S, 8.61. Found: C, 46.62; H, 3.82; N, 3.71; S, 8.43. $[\alpha]_D$: +8.19 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOProOH)(PPh$_3$)] (12). Yield: 0.485 g, 68.3%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, ratio 1:0.95:8.29 (A) and 1:0.95:7.98 (B) (dd, 1H, J = 4.8 and 1.8, J = 5.2 and 1.8, *H*1), 7.49−7.37 (m, 15H, *Ar*), 7.52 and 7.43 (m, 1H, *H*3), 6.92 (A) and 6.75 (B) (dd, 1H, J = 7.6 and 4.8, J = 7.6 and 5.2, *H*2), 4.69 (A) and 4.30 (B) (dd, 1H, J = 8.2 and 3.4, J = 8.2 and 2.2, C_αH), 3.71 and 3.56 (rotamer A, H diastereotopic) and 3.47 (rotamer B) ("td" (A) and "q" (B), 2H, J = 11.6 and 8.0 (A), J = 7.0 (B), $C_\delta H_2$), 2.41 and 2.05 (rotamer A, H diastereotopic) and 2.06 (B) (m, 2H, $C_\beta H_2$) and 1.92 (A) and 1.73 (B) (m, 2H, $C_\chi H_2$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 36.6. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, 175.7 (COOH), 168.3 (CONH), 159.9 (C, Py), 149.1 and 148.1 (CH, C1), 135.8 (CH, C3), 135.5 and 129.3 (d,C, J = 54.0, C4), 134.0 (d, CH, J = 13.8, C5), 131.8 (CH, C7), 129.3 (d, CH, J = 11.2, C6), 119.4 and 118.4 (CH, C2), 61.8 and 60.4 (C_αH), 48.7 and 46.0 ($C_\delta H_2$), 31.6 and 28.0 ($C_\beta H_2$), 24.7 and 23.0 ($C_\chi H_2$). MS (ESI$^+$) m/z: $[MH]^+$ 711.1 (calcd), 711.1 (found); $[M + AuPPh_3]^+$ 1169.1. IR (cm^{-1}): 3500−3100 (br, *COOH*), 1608 (s, *CONH*), 1568 and 1479 (w, *Ar*), 1097 and 1093 (s, *CO*), 744 and 708 (w, *Ar*). Anal. Calcd for $C_{29}H_{26}AuN_2O_3PS$: C, 49.02; H, 3.69; N, 3.94; S, 4.51. Found: C, 49.14; H, 4.04; N, 3.95; S, 4.81. $[\alpha]_D$: −18.56 (c 1.0 g/mL, $CHCl_3$).

General Procedure for the Synthesis of Complexes 13−18. To a solution of the corresponding acid derivatives **6−12** (1 mmol) in acetonitrile (10 mL) was added DIPEA (2.2 mmol). The mixture was stirred at room temperature for 15 min, and PyBOP was added (1.2 mmol). After 15 min, isopropylamine was added (1.1 mmol), and then the mixture was stirred for 36 h. The solvent was evaporated, and the products were purified by silica gel column chromatography using as the eluent 1:1 acetone/hexane.

[Au(SpyCOGlyNH^{i}Pr)(PPh$_3$)] (13). Yield: 0.284 g, 40%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 8.44 ("t", 1H, $CONH_{Gly}$), 8.24 (dd, 1H, J = 5.0 and 2.0, *H*1), 8.07 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.52−7.42 (m, 15H, *Ar*), 6.97 (dd, 1H, J = 7.6 and 5.0, *H*2), 6.70 (d, 1H, J = 6.4, $CONH^i_{Pro}$), 4.10 (d, 2H, J = 6.0, $C_\alpha H_2$), 4.03 (septsex, 1H, J = 6.8, $C^i_{Pro}H$), 1.10 (d, 6H, J = 6.8, $C^i_{Pro}H_3$).

dx.doi.org/10.1021/ic4003803 | *Inorg. Chem.* XXXX, XXX, XXX−XXX

^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.3. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 168.2 ($CONH^{i}_{Pro}$), 167.2 ($CONH_{Gly}$), 164.7 (*C*, Py), 148.2 (*CH*, *C*1), 139.2 (*CH*, *C*3), 134.3 (d, *CH*, J = 12.8, *C*6), 131.9 (d, *CH*, J = 4.4, *C*7), 129.3 (d, CH, J = 14.7, *C*5), 129.2 (*C*, J = 57.2, *C*4), 118.7 (*CH*, *C*2), 44.1 ($C_{\alpha}H_2$), 41.7 ($C^{i}_{Pro}H$), 22.7 ($C^{i}_{Pro}H_3$). MS (ESI$^-$) m/z: 712.1 (calcd), 712.1 (found); [M + $AuPPh_3$]$^+$ 1170.2. IR (cm^{-1}): 3278 (*NH*, br), 1637 (s, *CONH*), 1571 and 1480 (m, *Ar*), 1098 and 1071 (m, *CO*), 745 and 709 (w, *Ar*). Anal. Calcd for $C_{29}H_{29}AuN_3O_2PS$: C, 48.95; H, 4.11; N, 5.91; S, 4.51. Found: C, 48.60; H, 4.21; N, 5.82; S, 4.82. TLC: R_f = 0.2 (1:1 acetone/hexane).

[Au(SpyCOAlaNH^{i}Pr)(PPh$_3$)] (14). Yield: 0.308 g, 42.5%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 8.34 (d, 1H, J = 2.0, $CONH_{Ala}$), 8.32 (dd, 1H, J = 8.8 and 2.0, *H*1), 8.10 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.62−7.45 (m, 15H), 7.01 (dd, 1H, J = 7.6 and 4.8, *H*2), 6.85 (d, 1H, J = 6.8, $CONH^{i}_{Pro}$), 4.72 ("q", 1H, J = 7.4, $C_{\alpha}H$), 4.06 ("dq", 1H, J = 6.6 and 13.2, $C^{i}_{Pro}H$), 1.51 (d, 3H, J = 7.2, $C_{\beta}H_3$), 1.16 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$), 1.15 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 35.9. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 171.2 ($CONH^{i}_{Pro}$), 167.1 ($CONH_{Ala}$), 164.9 (*C*, Py), 149.0 (*CH*, *C*1), 138.7 (*CH*, *C*3), 134.3 (d, *CH*, J = 14.2, *C*5), 131.6 (d, *CH*, J = 2.3, *C*7), 131.1 (*C*, Py), 129.7 (d, *C*, J = 73.3, *C*4), 129.2 (d, *CH*, J = 11.5, *C*6), 118.7 (*CH*, *C*2), 50.0 ($C_{\alpha}H$), 41.5 ($C^{i}_{Pro}H$), 22.7 ($C^{i}_{Pro}H_3$), 17.7 ($C_{\beta}H_3$). MS (ESI$^+$) m/z: [MH]$^+$ 726.1 (calcd), 726.1 (found); [M + $AuPPh_3$]$^+$ 1184.2. IR (cm^{-1}): 3280 (br, *CONH*), 1637 (s, *CONH*), 1571, 1512, and 1480 (w, *Ar*), 1099 and 1069 (w, *CO*), 745 and 709 (w, *Ar*). Anal. Calcd for $C_{30}H_{31}AuN_3O_2PS$: C, 49.66; H, 4.31; N, 5.79; S, 4.42. Found: C, 49.48; H, 4.37; N, 5.51; S, 4.32. $[\alpha]_D$: −1.88 (c 0.5 g/mL, $CHCl_3$). TLC: R_f = 0.2 (1:1 acetone/hexane).

[Au(SpyCOValNH^{i}Pr)(PPh$_3$)] (15). Yield: 0.331, 44%. ^{1}H NMR [$CDCl_3$, 300 MHz, δ (ppm), J (Hz)]: 8.43 (d, 1H, J = 8.8, $CONH_{Val}$), 8.33 (dd, 1H, J = 4.8 and 2.0, *H*1), 8.16 (dd, 1H, J = 7.6 and 2.0, *H*3), 7.64−7.45 (m, 15H), 7.02 (dd, 1H, J = 7.6 and 4.8, *H*2), 6.71 (d, 1H, J = 7.6, $CONH^{i}_{Pro}$), 4.61 (dd, 1H, J = 8.8 and 4.4, $C_{\alpha}H$), 4.09 (m, 1H, $C^{i}_{Pro}H$), 2.55 (m, 1H, $C_{\beta}H$), 1.16 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$), 1.15 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$), 1.02 (d, 3H, J = 6.8, $C_{\chi}H_3$), 1.01 (d, 3H, J = 6.8, $C_{\chi}H_3$). ^{31}P NMR [$CDCl_3$, 300 MHz, δ (ppm)]: 36.3. ^{13}C NMR [$CDCl_3$, 300 MHz, δ (ppm), J (Hz)]: 170.2 ($CONH^{i}_{Pro}$), 167.3 ($CONH_{Val}$), 164.4 (*C*, Py), 149.1 (*CH*, *C*1), 139.0 (*CH*, *C*3), 134.3 (d, *CH*, J = 14.0, *C*5), 131.7 (d, *CH*, J = 2.5, *C*7), 131.1 (*C*, Py), 129.7 (d, *C*, J = 56.1, *C*4), 129.2 (d, *CH*, J = 11.5, *C*6), 118.9 (*CH*, *C*2), 59.7 ($C_{\alpha}H$), 41.6 ($C^{i}_{Pro}H$), 29.7 ($C_{\beta}H$), 22.9 and 22.7 ($C^{i}_{Pro}H_3$), 19.8 and 17.5 ($C_{\chi}H_3$). HRMS (ESI$^+$) m/z: [MH]$^+$ 754.1925 (calcd), 754.1077 (found); [M + $AuPPh_3$]$^+$ 1212.2. IR (cm^{-1}): 3285 (br, *NH*), 1633 (s, *CONH*), 1571, 1524, and 1480 (w, *Ar*), 1100 and 1071 (w, *CO*), 746 and 710 (w, *Ar*). Anal. Calcd for $C_{32}H_{35}AuN_3O_2PS$: C, 51.00; H, 4.68; N, 5.58; S, 4.25. Found: C, 49.95; H, 4.58; N, 5.50; S, 4.09. TLC: R_f = 0.2 (1:1 acetone/hexane). $[\alpha]_D$: −0.44 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOPheNH^{i}Pr)(PPh$_3$)] (16). Yield: 0.353 g, 44.1%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 8.36 (d, 1H, J = 8.0, $CONH_{Phe}$), 8.28 (dd, 1H, J = 4.8 and 2.0, *H*1), 7.98 (dd, 1H, J = 8.0 and 2.0, *H*3), 7.61−7.46 (m, 15H), 7.28−7.16 (m, 5H), 6.95 (dd, 1H, J = 8.0 and 4.8, *H*2), 6.54 (d, 1H, J = 7.6, $CONH^{i}_{Pro}$), 4.93 (" td", 1H, J = 8.2 and 6.7, $C_{\alpha}H$), 4.03 ("sexd", 1H, J = 13.1 and 6.6, $C^{i}_{Pro}H$), 3.24 (d, 2H, J = 6.4, $C_{\beta Pro}H_2$), 1.07 (d, 3H, J = 6.4, $C^{i}_{Pro}H_3$), 1.05 (d, 3H, J = 6.4, $C^{i}_{Pro}H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 36.0. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 169.7 ($CONH^{i}_{Pro}$), 166.9 ($CONH_{Phe}$), 164.7 (*C*, Py), 148.7 (*CH*, *C*1), 138.4 (*CH*, *C*3), 137.1 (*C*, *C*8), 134.2 (d, *CH*, J = 14.0, *C*5), 131.6 (d, *CH*, J = 2.5, *C*7), 130.2 (*C*, Py), 129.5 (*CH*, R,C10), 129.1 (*CH*, J = 11.5, *C*6), 128.7 (d, *C*, J = 55.4, *C*4), 128.5 (*CH*, R, *C*9), 126.7 (*CH*, R, *C*11), 118.4 (*CH*, *C*2), 55.4 ($C_{\alpha}H$), 41.6 ($C^{i}_{Pro}H$), 37.9 ($C_{\beta}H_2$), 22.6 ($C^{i}_{Pro}H_3$), 22.5 ($C^{i}_{Pro}H_3$). MS (ESI$^+$) m/z: [MH]$^+$ 802.2 (calcd), 802.1 (found); [M + $AuPPh_3$]$^+$ 1260.1. IR (cm^{-1}): 3270 (br, *CONH*), 1729 and 1635 (s, *CONH*), 1571, 1514, and 1480 (w, *Ar*), 1097 and 1017 (s, *C*−*O*), 745 and 709 (w, *Ar*). Anal. Calcd for $C_{36}H_{35}AuN_3O_2PS$: C, 53.93; H, 4.40; N, 5.24; S, 4.00. Found: C, 53.79; H, 4.50; N, 4.36; S, 3.81. TLC: R_f = 0.2 (1:1 acetone/hexane). $[\alpha]_D$: −9.06 (c 1.0 g/mL, $CHCl_3$).

[Au(SpyCOMetNH^{i}Pr)(PPh$_3$)] (17). Yield: 0.345 g, 44%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 8.50 (d, 1H, J = 8.4, $CONH_{Met}$), 8.33 (dd, 1H, J = 4.8 and 1.8, *H*1), 8.11 (dd, 1H, J = 7.6 and 1.8, *H*3), 7.63−7.46 (m, 15H), 7.02 (dd, 1H, J = 7.6 and 4.8, *H*2), 6.79 (d, 1H, J = 7.2, $CONH^{i}_{Pro}$), 4.82 ("dt", 1H, J = 8.2 and 5.1, $C_{\alpha}H$), 4.07 ("dt", 1H, J = 13.2 and 6.6, $C^{i}_{Pro}H$), 2.66 ("t", 2H, J = 7.5, $C_{\chi}H_2$), 2.38−2.30 and 2.14−2.03 (m, 2H diastereotopic, $C_{\beta}H_2$), 2.11 (s, 3H), 1.16 (d, 3H, J = 6.4, $C^{i}_{Pro}H_3$), 1.15 (d, 3H, J = 6.4, $C^{i}_{Pro}H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.3. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: 170.0 ($CONH^{i}_{Pro}$), 167.3 ($CONH_{Met}$), 164.3 (*C*, Py), 149.3 (*CH*, *C*1), 138.7 (*CH*, *C*3), 134.3 (d, *CH*, J = 14.0, *C*5), 131.7 (d, *CH*, J = 2.3, *C*7), 130.3 (d, *C*, J = 70.1, *C*4), 129.2 (d, *CH*, J = 11.5, *C*6), 118.9 (*CH*, *C*2), 53.4 ($C_{\alpha}H$), 41.6 ($C^{i}_{Pro}H$), 31.1 ($C_{\beta}H_2$), 30.5 ($C_{\chi}H_2$), 22.7 ($C^{i}_{Pro}H_3$), 15.3 (CH_3). MS (ESI$^+$) m/z: [MH]$^+$ 786.1 (calcd), 786.1 (found); [M + $AuPPh_3$]$^+$ 1244.2. IR (cm^{-1}): 3263 (br, *CONH*), 1636 (s, *CONH*), 1570, 1512, and 1480 (w, *Ar*), 1099 and 1070 (s, *CO*), 745 and 709 (w, *Ar*). Anal. Calcd for $C_{32}H_{35}AuN_3O_2PS_2$: C, 48.92; H, 4.49; N, 5.35; S, 8.16. Found: C, 49.09; H, 4.38; N, 5.13; S, 8.01. $[\alpha]_D$: −2.66 (c 0.5 g/mL, $CHCl_3$).

[Au(SpyCOProNH^{i}Pr)(PPh$_3$)] (18). Yield: 0.318, 42.3%. ^{1}H NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, ratio 1:0.1; 8.34 (A) and 8.29 (B) (dd, 1H, J = 4.8 and 2.0, J = 4.8 and 2.0, *H*1), 7.62−7.41 (m, 15H), 7.58−7.55 (m, 1H, $CONH^{i}_{Pro}$), 7.46−7.26 (A) and 7.33−7.19 (B) (m, 1H, *H*3), 6.99 (A) and 6.89 (B) (dd, 1H, J = 7.6 and 4.8, *H*2), 4.71 (dd, 1H, J = 7.8 and 2.4, $C_{\alpha}H$), 4.08 ("dt", 1H, J = 13.4 and 6.7, $C^{i}_{Pro}H$), 3.67 and 3.15 ("td" and "q", 2H, J = 13.3 and 6.6, J = 7.4, $C_{\delta}H_2$), 2.28 and 2.17 (diastereotopic H, m, 2H, $C_{\beta}H_2$), 1.89 (m, 2H, $C_{\chi}H_2$), 1.20 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$), 1.18 (d, 3H, J = 6.8, $C^{i}_{Pro}H_3$). ^{31}P NMR [$CDCl_3$, 400 MHz, δ (ppm)]: 37.5. ^{13}C NMR [$CDCl_3$, 400 MHz, δ (ppm), J (Hz)]: mixture of rotamers, 170.4 ($CONH^{i}_{Pro}$), 162.0 ($CONH_{Pro}$), 149.0 (*CH*, *C*1), 134.3 (d, *CH*, J = 13.4, *C*5), 133.9 (*CH*, *C*3), 131.7 (*CH*, *C*7), 129.8 (*C*, *C*4), 129.2 (d, *CH*, J = 11.5, *C*6), 118.7 (*CH*, *C*2), 60.6 and 55.6 ($C_{\alpha}H$), 48.4 and 43.6 ($C_{\delta}H_2$), 41.7 ($C^{i}_{Pro}H$), 29.3 ($C_{\beta}H_2$), 24.5 ($C_{\chi}H_2$), 22.9 ($C^{i}_{Pro}H_3$), 22.7 ($C^{i}_{Pro}H_3$). HRMS (ESI$^+$) m/z: [MH]$^+$ 752.1511 (calcd), 752.1275 (found); [M + $AuPPh_3$]$^+$ 1210.2. IR (cm^{-1}): 3319 (br, *CONH*), 1635 (s, *CONH*), 1572, 1547, and 1480 (w, *Ar*), 1099 and 1073 (s, *CO*), 747, 710, and 691 (w, *Ar*). Anal. Calcd for $C_{32}H_{33}AuN_3O_2PS$: C, 51.13; H, 4.43; N, 5.59; S, 4.27. Found: C, 51.36; H, 4.45; N, 5.95; S, 4.44. $[\alpha]_D$: −26.87 (c 1.0 g/mL, $CHCl_3$).

Crystallography. Crystals were mounted in an inert oil on glass fibers and transferred to the cold gas stream of APEX SMART (**1**) and Xcalibur Oxford Diffraction (**3**) diffractometers equipped with a low-temperature attachment. Data were collected using monochromated Mo Kα radiation (λ = 0.71073 Å). The scan type was ω. Absorption correction based on multiple scans was applied with the program *SADABS*[31] (**1**) or using spherical harmonics implemented in the *SCALE3 ABSPACK*[32] scaling algorithm (**3**). The structures were solved by direct methods and refined on F^2 using the program *SHELXL-97*.[33] All non-hydrogen atoms were refined anisotropically. For complex **1**, hydrogen atoms were included in calculated positions and refined using a riding model; for complex **3**, the hydrogen atoms were located in the difference map. Refinements were carried out by full-matrix least squares on F^2 for all data. Further details of the data collection and refinement and complete bond lengths and angles are given in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic file in CIF format, details of data collection and structure refinement, and bond lengths and angles for compounds **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ic4003803 | *Inorg. Chem.* XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

The authors thank the Ministerio de Economía y Competitividad-FEDER (Grants CTQ2010-20500-C02-01 and CTQ2010-17436)) and DGA-FSE (E77 and E40) for financial support. A.G. thanks to the CSIC for a JAE-predoc fellowship.

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dx.doi.org/10.1021/ic4003803 | *Inorg. Chem.* XXXX, XXX, XXX−XXX