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Design of Stable β-Sheet-Based Cyclic Peptide Assemblies Assisted by Metal Coordination: Selective Homo- and Heterodimer Formation

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Abstract: Metal-directed supramolecular construction represents one of the most powerful tools to prepare a large variety of structures and functions. The ability of metals to organize different numbers and types of ligands with a variety of geometries (linear, trigonal, octahedral, etc.) expands the supramolecular synthetic architecture. We describe here the precise construction of homo- and heterodimeric cyclic peptide entities through coordination of a metal (Pd, Au) and to β-sheet-type hydrogen-bonding interactions. The selective coordination properties of the appropriate metal allow control over the cross-strand interaction between the two peptide strands.

Keywords: cyclic peptides · dimers · gold · metal tweezers · self-assembly

Organometallic and coordination complexes have become established as very versatile tools—not only as a catalyst but also for their potential applications in molecular electronics and materials science.[1,2] Metal alkynyl derivatives are amongst the most intriguing of these complexes and gold acetylides are perhaps the most appealing to their luminescent properties and their geometrical and electronic properties.[3] In addition to the interest in gold complexes due to their novel catalytic properties,[4] gold acetylides have also aroused great interest in supramolecular construction[5] and sensing due to the combination of the linear coordination geometry, the linearity of the acetylene moiety, and the known tendency of gold to interact with itself (aurophilia).[6] Gold(I) compounds also have several potential roles in biologically related chemistry, due to their relatively low toxicity and its lability.[7] Finally, peptides that carry functional organometallics are envisioned to provide novel systems in which biological and metal-related properties are combined to create useful assembly components for the preparation of supramolecular functional materials. However, only a few works on this aspect have been currently reported.[8]

In recent years we have been interested in the preparation of biocompatible supramolecular ensembles, such as peptide nanotubes.[9,10] For this reason, we started a program for the development of cyclic peptides that assemble through β-sheet-type interactions to form homo- and/or heterodimeric species in a controlled way.[11] β-sheet-based structures have become a powerful tool in supramolecular chemistry, biology, and nanotechnology since chemists learned to control the formation of multiple aggregates and to tailor the solubility.[12] However, further understanding of the β-sheet formation process and structure must be achieved to address medical problems, such as Alzheimer's and Parkinson's diseases, amongst others.[13] Part of our program is devoted to understanding the structural basis of the nanotube interactions in an effort to control precisely the nanotube structure, a possibility that would allow the development of further applications. We envisaged that metal–ligand interactions would be a useful tool not only to control and induce the supramolecular process of nanotube formation, but also to modulate the electronic and spectroscopic properties.[14] We present a one-step route aimed at the precise β-sheet register control based on a metal-directed assembly process that induces the exclusive formation of homo- and/or heterodimeric entities with precise interpeptide arrangements.

In our preliminary studies we showed that cyclic peptides that lack *Cn* symmetry form several (*n*) nonequivalent dimers—such as hexapeptide **CP1**, which forms three dimers **D(A_{ccw})1**, **D(A_{cw})1**, and **D(*S*)1** (Scheme 1).[15,16] Although backbone–backbone interactions in the dimers are almost identical, they can be distinguished by the different cross-strand pairwise relationship between the α-amino acid components of the cyclic monomers. The dimer ratios depend on several factors, such as side-chain substitution, backbone skeleton, and so on. For example, **CP1**, a 3-aminocyclohexanecarboxylic acid (γ-Ach)-based cyclic peptide that contains one serine, forms the three nonequivalent dimers in 1:1:2 ratios. The major supramolecular diastereomer is the one in which the serines are in register. Although we initially attributed this finding to the formation of an additional hydrogen-bonding interaction between the hydroxyl groups of serines, other CPs that contain this amino acid, such as the 3-aminocyclopentanecarboxylic acid

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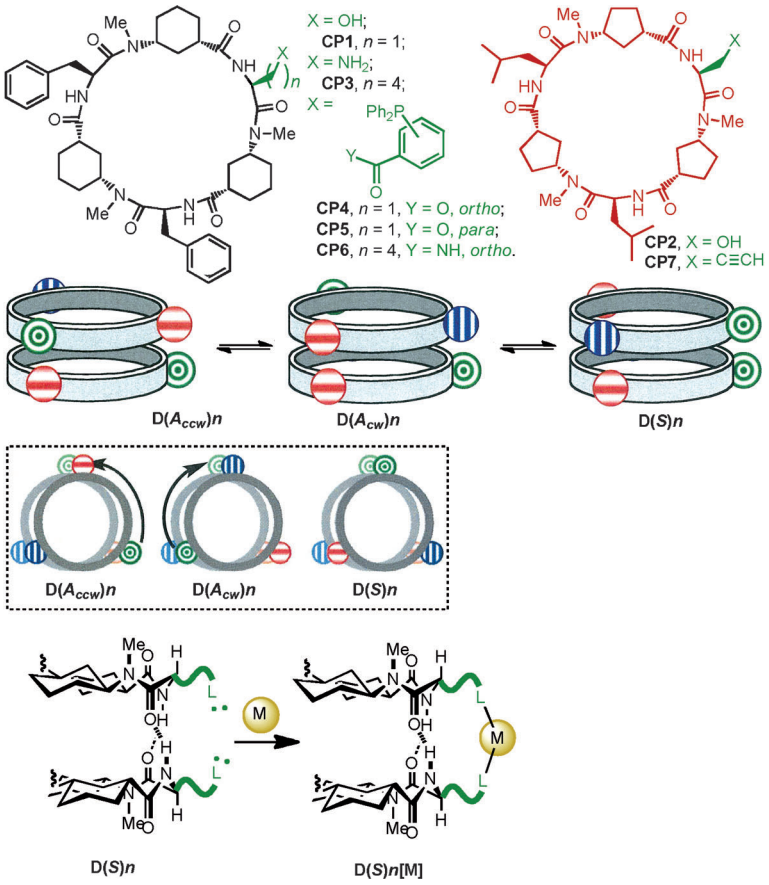


Scheme 1. Cyclic peptides containing γ-Ach (**CP1**, **CP3–6**) and γ-Acp (**CP2** and **CP7**) residues and model of the three nonequivalent dimers (**D(*A*$_{ccw}$)*n***, **D(*A*$_{cw}$)*n***, and **D(*S*)*n*** in which *n* is 1 to 7) formed by these non-*C*3 symmetric peptides. At the bottom, top view of the schematic representation of the three nonequivalent dimers derived with the nomenclature proposed for these systems and schematic representation of metal chelating properties of *syn*-dimer (**D(*S*)*n***).

(γ-Acp)-based **CP2**, did not show any special preference for being on register. **CP2** forms the three corresponding dimers (**D(*A*$_{ccw}$)2**, **D(*A*$_{cw}$)2**, and **D(*S*)2**) in an almost equimolecular ratio. Diastereoisomer control was recently achieved by means of salt-bridged interactions in CPs that contain one Lys and Glu.[16b] Interestingly, the equilibrium can be shifted to any other dimeric form through the addition of an external chemical signal, such as divalent anions or cations. Unfortunately, these groups are not sensitive enough to the addition of one equivalent of a specific metal and therefore cannot be used in sensing or other such applications. Based on these results we believe that the use of improved metal ligands, such as phosphines or alkynes, covalently linked to the CP could bring additional sensitivity to this equilibrium (Scheme 1) along with additional structural and chemical information and complexity towards nanotechnological applications. In an effort to learn about the organometallic and supramolecular properties of this system we decided to study complex formation on dimeric models, paying attention not only to the formation of homomeric but also heteromeric aggregates.[17]

Results and Discussion

Cyclic peptides **CP4–6** were prepared and these bear *ortho*- or *para*-substituted diphenylphosphinobenzoate moieties linked to a Ser or Lys side chain. The peptides were prepared from **CP1** by reaction with the corresponding (*o*,*p*)-phosphinobenzoic acids in the presence of *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), and 1-hydroxybenzotriazole (DMAP) in dichloromethane and **CP3** by reaction with the corresponding *o*-phosphinobenzoic acids in the presence of *N*,*N*-diisopropylethylamine (DIEA) and [*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate] (HATU) in dichloromethane. In nonpolar solvents these peptides exit as a mixture of three nonequivalent dimers in almost equimolecular ratios (**D(*A*,*S*)4**, **D(*A*,*S*)5**, and **D(*A*,*S*)6**) as evidenced by the appearance of several peaks between $\delta = 8.00$ and 8.80 ppm corresponding to the three amide protons involved in hydrogen-bonding interactions that are forming three nonequivalent dimers. For example, **CP4** showed nine doublets (see Figure 1 or the Supporting Information for other peptides). In this case, the three dimers are not formed in an equimolecular ratio, with the less abundant dimer apparently the one in which both phosphine-bearing side chains are in register (**D(*S*)4**). In principle, only one of the three dimers, the *syn* form, can coordinate metals as supramolecular bidentate ligands and metal coordination should therefore restrict the interdimer equilibria towards this form (Scheme 1).

This hypothesis was initially tested with the formation of palladium complexes. Thus, addition of palladium acetate to a deutorochloroform solution of **CP4** (Figure 1) immediately led to the formation of a single dimer, signified by the appearance of three new doublets in the NMR spectrum at $\delta = 8.71$, 8.66, and 8.04 ppm and the shift of the aromatic proton signal from $\delta = 7.94$ to 7.85 ppm. In addition, other signals—such as the three methyl groups, which now appear as one singlet per methyl group ($\delta = 3.17$, 2.49, and 2.45 ppm)—also provide clear evidence of the formation of the new complex. Addition of only 0.5 equivalents of metal with respect to CP concentration (1.0 equiv per dimer) was

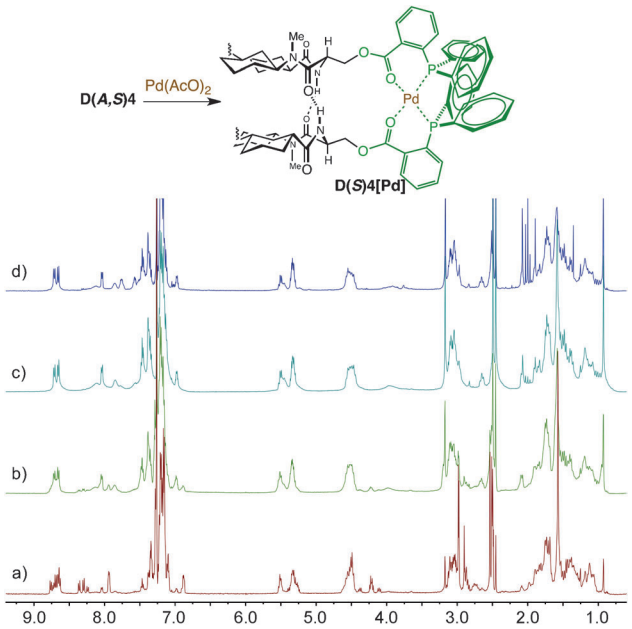
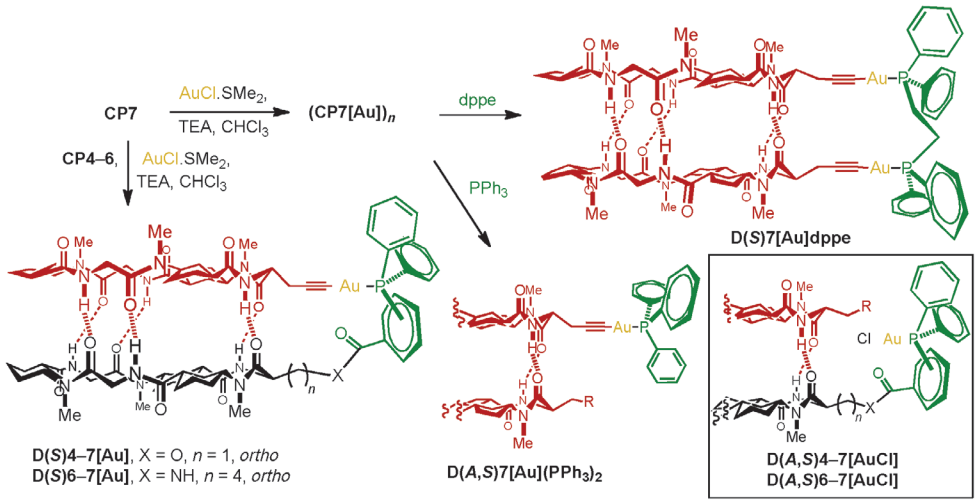


Figure 1. Homodimer equilibrium of **CP4** to form one single dimer (**D(*S*)4[Pd]**) directed by palladium coordination and ^{1}H NMR spectroscopy upon addition of a) 0.0, b) 0.5, c) 1.0, and d) 2.0 equivalents of palladium acetate per dimer, respectively.

enough to shift completely the equilibrium towards the dimer **D(*S*)4[Pd]** (Figure 1). Phosphorus NMR spectra showed the downfield shift of phosphorous signal upon the addition of palladium (form $\delta = -6.0$ to 11.1 ppm, see Figure 1 in the Supporting Information). Further addition of Pd (more than two equivalents) did not lead to any change in the NMR spectrum, thus confirming the stability of the chelate complex. Tetracoordination of palladium must occur by simultaneous interaction of the metal with both the carbonyl and phosphine of each 2-phosphinobenzoate moiety. On the other hand, the lysine-derived **CP6**, which has a longer spacer between the phosphine moiety and the CP skeleton, was also treated with palladium acetate (see Figure S2 in the Supporting Information). Initial addition of one equivalent of palladium with respect to the dimer led to the appearance of a new species, with the preferred formation of a single dimer, probably **D(*S*)6[Pd]**, which is indicated by the doublet at $\delta = 8.70$ ppm. It should be pointed out that, in contrast with **CP4**, the formation of this dimer required several hours. Further addition of palladium gave rise to the formation of new, different complexes, as evidenced by proton NMR spectra. The ^{31}P NMR spectrum contained only one signal (at $\delta = 29.9$ ppm) after addition of one equivalent of Pd per dimer. At least two nonequivalent dimers can be differentiated, as shown by the three doublets in the NH region for each dimer ($\delta = 8.80$, 8.75, and 8.18 ppm for one dimer, and $\delta = 8.72$, 8.69, and 8.25 ppm for the other one). These two dimers could correspond to the **D(A_{ccw})6** and **D(A_{cw})6** forms, in which each phosphine is coordinated to one palladium atom. The absence of **D(*S*)6** could be attributed to the flexibility of the CP/phosphine spacer, which reduces its chelating properties.

On the other hand, **CP5**, which has the *para*-oriented phosphine moiety, does not form the same type of complex. Upon addition of palladium the distribution of aromatic protons in the ^{1}H NMR spectrum, together with the phosphorus NMR spectrum (in which the signal at $\delta = -7.5$ ppm disappears as a new signal is formed at $\delta = 25.8$ ppm), suggests some changes at the phosphine moiety, which initially we associated to metal coordination. In contrast to the previous discussed isomer, neither the NH proton signals nor *N*-methyl groups change in ratio or shift upon addition of palladium. One additional feature of the *para*-derivative ligand is the appearance of a new peak in the mass spectrum (1103, $[M+16]^+$) which corresponds to the oxidized phosphine. This rapid oxidation precludes coordination to the palladium and hence the interdimer equilibrium cannot be restricted. Thus, whereas the Pd complex of *ortho*-oriented derivatives (**CP4** and **CP6**) can be stored at room temperature for several hours without evidence of oxidation, the *para*-oriented analogue is oxidized in a few seconds even on using degased solvents. These results confirm the equilibrium control through metal coordination with homodimers, with only one complex formed on addition of the metal provided that the supramolecular bidentate ligand has the appropriate geometry to coordinate the metal.

The above-mentioned properties of gold acetylide complexes motivated us to prepare a new peptide bearing a terminal alkyne (**CP7**). We envisaged that this CP could be used in the supramolecular construction of both homo- and heterodimeric complexes. As expected, in nonpolar solvents, such as deuterochloroform, **CP7** forms three nonequivalent dimers (**D(A_{ccw})7**, **D(A_{cw})7**, and **D(*S*)7**) in almost equimolecular ratio. We envisaged that gold acetylides would coordinate to bidentate ligands, such as 1,2-bis(diphenylphosphino)ethane (dppe) with two gold acetylides oriented towards the same direction, perhaps assisted by gold–gold interactions.[7] To this end, we added **CP7** to a THF/MeOH (3:2) solution of gold chloride in the presence of base (triethylamine) to give a precipitate of the acetylide complex **(CP7[Au])$_n$**.[18] Addition of this precipitate to a chloroform solution of dppe induces the solubilization of the gold complex and the formation of dimer **D(*S*)7[Au]dppe** (Scheme 2 and Figure S3 in the Supporting Information), in which the phosphorus atoms are coordinated to the gold atoms of each CP in the dimer. The formation of this dimer is clearly evidenced by the simplification of amide signals ($\delta = 8.38$, 8.25 and 8.21 ppm) in the NMR spectrum. Phosphorus NMR spectra showed one new signal at $\delta = 19.7$ ppm and this confirms the existence of only one type of phosphorus and its coordination to the metal. On the other hand, addition of triphenylphosphine to a suspension of gold complex **(CP7[Au])$_n$** also induces solubilization and the formation of a gold–phosphine complex (**D(*A*,*S*)7[Au](PPh$_3$)$_2$**, Scheme 2). The ^{1}H NMR spectrum of this complex is similar to the one observed for the dppe derivative (**D(*S*)7[Au]dppe**; see Figure S4 in the Supporting Information), but careful evaluation of amide proton signals suggests the formation of at least two dimers. The number and



Scheme 2. Homo and hetero-inter-dimer equilibrium of **CP7** based on the formation of gold acetylide complexes. For simplicity most of the α-amino acid side chains have been removed, the three nonequivalent dimers of triphenylphosphine complex are represented with the R group as an isopropyl or an acetylene moiety (bottom-center). Inset: heterodimeric gold complex formed before the addition of triethylamine, in which gold chloride is coordinated to the phosphine moiety, the lack of interaction with the complementary CP (**CP4** or **CP6**) allow the formation of the three nonequivalent dimers, denoted by an R group that could be the phenyl or the acetylide moieties.

ratio of dimers could not be established; although it appears that the two dimers are those in which gold complexes are not in register (**D(A_{ccw})7[Au](PPh$_3$)$_2$** and **D(A_{cw})7[Au]-(PPh$_3$)$_2$**). These equilibria suggest that gold–gold interactions are not playing an important role in stabilizing the *S* form, perhaps due to the steric repulsion of triphenylphosphine moieties or to the existence of some geometrical constraints.[19]

One of the special features of self-assembling cyclic peptides that contain γ-amino acids is their tendency to form, in addition to homodimers, heterodimers that are more stable than the corresponding homoderivatives.[17] This versatile equilibrium, which is similar to that in natural systems, opens the opportunity to create new molecular tools and applications.[20] Encouraged by this special feature, we decided to evaluate the formation of heterodimers in which the metal would be coordinated to two different ligands, such as an alkyne and a phosphine. We envisaged that to achieve the optimal linear gold coordination it would be necessary to use the cyclic peptide with the longest spacer between peptide backbone and the phosphine moiety (Figure 2). Thus, we began by evaluating **CP6**, which solubilized the gold complex precipitate (**(CP7[Au])$_n$**) immediately on mixing. The ^{1}H NMR spectrum showed the formation of a new dimer that was identified as the gold complex heterodimer (Figure 2c and Figure S5 in the Supporting Information). The amide signals at $\delta = 8.69$ and 8.61 ppm were assigned for Leu and $\delta = 8.42$ ppm for Phe residues; thus confirming the exclusive formation of **D(*S*)6–7[Au]**. The ^{31}P NMR spectrum showed one signal at $\delta = 40.1$ ppm that was attributed to the phosphine coordinating the gold ion (Figure S5 in the Supporting Information). The mass spectrum contained a peak (*m*/*z*: 2128.8, $[M+Ag]^+$) that coincides with the heterodimeric complex coordinated to gold.[21] The stability of the gold complex is remarkable; it can be purified by HPLC and stored at room temperature for several weeks without detectable decomposition. The heterodimeric gold derivative can also be formed in situ simply by mixing the two peptides (**CP6** and **CP7**) with gold chloride in the presence of base (triethylamine). The formation of the complex was followed by ^{1}H NMR spectroscopic experiments (see Figure 2 and Figure S6 in the Supporting Information). The initial mixture of the two peptides gave a

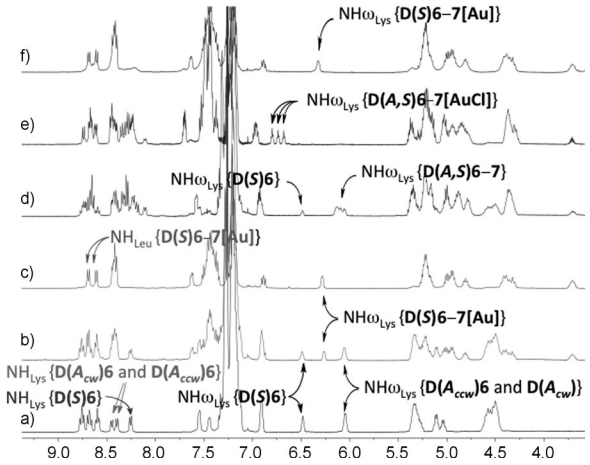
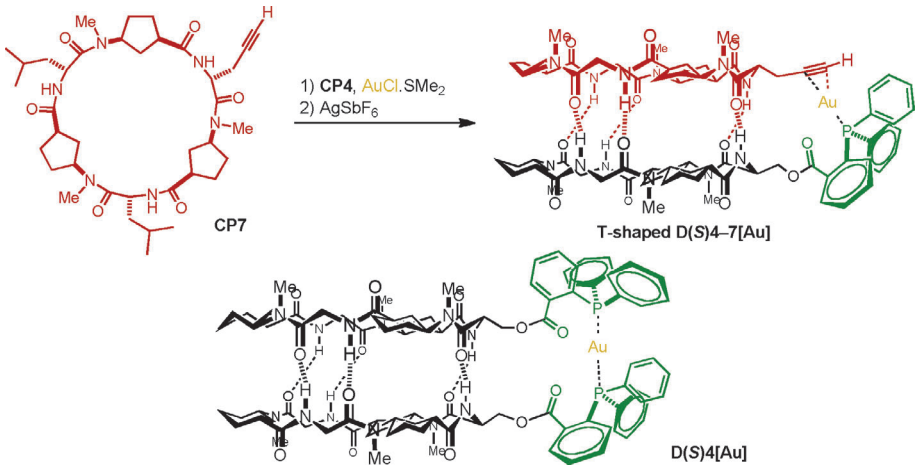


Figure 2. ^{1}H NMR spectra showing the formation of different dimers as a consequence of the equilibrium between **CP6** and **(CP7[Au])$_n$**: a) **D(*A*,*S*)6**, b) after the addition of 0.25 equivalents of **(CP7[Au])$_n$** (mixture of **D(*A*,*S*)6** and **D(*S*)6–7[Au]**), c) after the addition of 1.0 equivalents of **(CP7[Au])$_n$** to form **D(*S*)6–7[Au]**, d) mixture of **CP6** and **CP7** (0.9 equiv) forming **D(*A*,*S*)6–7**, e) after addition of AuCl·SMe$_2$ to give **D(*A*,*S*)6–7[AuCl]**, and f) after addition of 3.0 equivalents of Et$_3$N to form **D(*A*,*S*)6–7[Au]**. The amide protons of lysine side chain (NHLys) are denoted in the figure, which allows us to visualize the formation of different dimers in each mixture.

complex NMR spectrum with multiple NH signals (Figure 2d), which in some cases did not overlap with any of the signals of the corresponding homodimers, which suggests the main formation of the three nonequivalent heterodimers (**D(*A*,*S*)6–7**). This complex NMR spectrum did not allow an accurate estimate of the dimer ratios, although it can be inferred on the basis of preceding examples that correspond to an equimolecular mixture of the three nonequivalent heterodimers. Interestingly, addition of one equivalent of gold chloride led to changes in the aromatic signals of phosphine moieties (^{31}P NMR showed a new signal at $\delta = 29.5$ ppm compared with $\delta = -11.5$ ppm for the starting heterodimer **D-(*A*,*S*)6–7**), although the fingerprint signals of the amide protons still showed the existence of a complex mixture of the three nonequivalent dimers (Figure 2e). The lack of information transfer between the two peptides suggests that the alkyne moiety does not interact with the metal, which must remain coordinated to the chloride. Under these conditions gold-complex dimeric structure must exist as a mixture of the three nonequivalent dimers (**D(*A*,*S*)6–7[AuCl]**) in an equimolecular ratio as can be inferred by the three triplets at $\delta = 6.80$, 6.74, and 6.68 ppm that correspond to the amide proton of lysine side chains of each dimer. Addition of triethylamine (three equivalents) removed the terminal alkyne proton and led to the formation the gold acetylide (Scheme 2f and Figure S6 in the Supporting Information), the NMR spectra (^{1}H and ^{31}P) of which are identical to that obtained through the gold-acetylide preformation method.

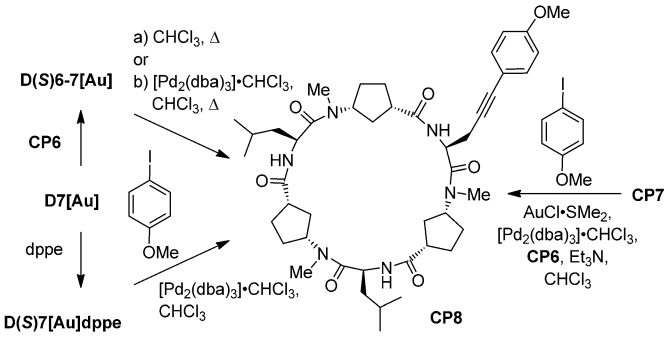
The good results obtained with **CP6** led us to investigate heterodimer formation involving the ligand with the shorter spacer (**CP4**). The addition of **(CP7[Au])$_n$** to a chloroform solution of **CP4** gave linear gold complex **D(*S*)4–7[Au]** (Scheme 2), as indicated by the simplification of the NH signals (see Figure S7 in the Supporting Information) in the NMR spectra and confirmed by mass spectrometry (*m*/*z*: 2087.8, $[M+Ag]^+$).[21] This result was quite surprising because we believed that the spacer between CP and the phosphine moiety was too short to accommodate the linear coordination of gold. We were interested in observing the formation of the gold π-complex as a straightforward route to vinylidenemetal complexes.[22] In this T-shaped gold complex the metal is η^2-bonded to the alkyne, through which the reaction mechanism is generally thought to proceed,[23] but such complexes have not yet been well-characterized. Furthermore, **D(*S*)4–7[Au]** can also be formed in one step by mixing both CPs with gold chloride followed by addition of triethylamine. In this case formation of the complex takes longer and several equivalents of amine are required. To achieve the formation of T-shaped **D(*S*)4–7[Au]** (Scheme 3) by avoiding the removal of the acetylene proton, we replaced triethylamine with a silver salt. Under these conditions, the formation of a new dimer was observed, see Figure S8 in the Supporting Information. Firstly, the CPs and gold were mixed and the formation of the three nonequivalent heterodimers was confirmed by NMR spectroscopy (see Figure S8d in the Supporting Information). One equivalent of silver hexafluoroantimonate was then added and a precipitate was formed and a dramatic change was observed in the NMR spectrum of the mixture (Figure S8e in the Supporting Information). The NH region of the newly formed complex is very simple, with only one set of signals corresponding to three amide protons of a single peptide. None of the signals corresponding to **CP7** appear in the NMR spectrum, which must precipitate as a silver acetylide, whereas the phosphine-bearing CP (**CP4**) apparently forms a single isomer, to which we have attributed the structure **D(*S*)4[Au]** (Scheme 3). Mass spectrometry (*m*/*z*: 1186.0242 $[M+H]^{2+}$) supports the formation of **D(*S*)4[Au]** and this was confirmed by mixing **CP4** with gold chloride followed by treatment with $AgSbF_6$, a process that gave rise to the same complex (see Figure S9 in the Supporting Information). The silver derivative (**D(*S*)4[Ag]**) was discarded because the treatment of **CP4** with the silver salt did not give a compound with the same characteristics as those from the previous experiments (Figure S9b in the Supporting Information). The behavior of CP with phosphine-derived Lys (**CP6**) is quite different with respect to silver salt addition. Under similar conditions, the treatment of **CP7** and **CP6** (gold chloride followed by addition of $AgSbF_6$) led to the formation of a complex mixture of compounds that could not be characterized.



Scheme 3. Structure of the expected T-shaped gold complex (T-shaped **D(*S*)4–7[Au]**) and the observed homodimer **D(*S*)4[Au]** resulting of mixing **CP4** and **CP7** with gold(I) followed by addition of silver hexafluoroantimonate.

To further assess the relative stability of homo- and heterodimer complexes, the homodimer **D(*S*)7[Au]dppe** was treated with one equivalent of **CP6** and the formation of heterodimer **D(*S*)6–7[Au]** as a single product was observed immediately. Thus, the heterodimer between the CPs **CP6** and **CP7** make the interaction between the gold acetylide and phosphine moiety more stable than the homodimer in which two gold acetylide phosphine interactions are present. On the other hand, when this heterodimer was treated with an excess of the dppe ligand (see Figure S10 in the Supporting Information), a shift in the equilibrium towards the corresponding homodimer did not occur. Similarly, the addition of dppe to the Ser-derived heterodimer (**D(*S*)4–7[Au]**) drove the equilibrium towards the homodimer **D(*S*)7[Au]dppe**. These experiments again confirm the higher stability of the Lys-derived heterodimer in comparison to **D(*S*)4–7[Au]**, which is even less stable than the dppe homodimer.

Finally, these complexes can also be used for carbon–carbon bond-forming processes. For example, a Sonogashira-type reaction occurred when gold complex **D(*S*)6–7[Au]** was treated with 4-iodoanisole in boiling chloroform for 24 h. This reaction gave **CP8** although the yield was not high (15%).[24] Better results were obtained when catalytic amounts (1.2%) of palladium dibenzylideneacetone ($[Pd_2(dba)_3]\cdot CHCl_3$) were also added, in which case the cross-coupling process gave a higher yield (35%) in a shorter reaction time. The reaction was also carried out with derivative **D(*S*)7[Au]dppe** and **CP8** was also obtained in 45% yield. Finally, the process can be carried out by using catalytic amounts of gold chloride, palladium, and phosphine (**CP6**) in the presence of base (Et_3N) to give **CP8** in similar yields (Scheme 4).



Scheme 4. Sonogashira cross-coupling studies carried out with peptide–gold complexes to form **CP8**.

Conclusion

We have described how the use of metal coordination can allow the selective formation of a single dimer. The peptides designed for this purpose self-assemble through β-sheet-type interactions and contain phosphine moieties attached to an amino acid side chain. In the presence of metals, such as Pd or Au, the dimers behaved as chelating ligands to coordinate with the metal. This coordination restricted the interdimer equilibria to the form in which the amino acids that contain the phosphine moieties in each CP are hydrogen-bonded. In addition, selective heterodimer formation can be achieved by forming gold acetylide complexes. These complexes can form stable homodimers by coordination with bidentate phosphines (dppe) or heterodimers by addition of a phosphine-containing CP. In all of these examples, metal coordination restricts the β-sheet register to allow the metal to coordinate to both peptides. The length of the spacer between the CP skeleton and the phosphine moiety modifies the stability of the complexes.

Experimental Section

Materials and methods: See the Supporting Information

Peptide synthesis: Synthesis of amino acids (Acp and Ach) and hexapeptides were prepared by following a similar synthetic strategy previously described elsewhere.[11,17]

***c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$]**: A solution of Boc-(L-Phe-D-^{Me}N-γ-Ach-)$_2$L-Ser(Bn)-D-^{Me}N-γ-Ach-OFm (*tert*-butoxycarbonyl, 332 mg, 0.28 mmol) in 20% piperidine in CH_2Cl_2 (2.8 mL) was stirred at RT for 30 min. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (40 mL) and washed with HCl (5%), dried over Na_2SO_4, filtered, and concentrated. The resulting material was dissolved in TFA/CH_2Cl_2 (1:1, 2.5 mL) and stirred at RT for 10 min. The solvent was removed and the residue was dried under high vacuum for 3 h and used without further purification. The linear peptide was dissolved in CH_2Cl_2 (280 mL) and treated with TBTU (1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium tetrafluoroborate 3-oxide) (99 mg, 0.31 mmol), followed by dropwise addition of DIEA (290 μL, 1.70 mmol). After 12 h, the solvent was removed under reduced pressure, and the crude was purified by flash chromatography (0–7% MeOH/CH_2Cl_2) to afford 204 mg of *c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] as a white solid (82%, R_f = 0.60 (5% MeOH/CH_2Cl_2)). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.82 (d, ^3J(H,H) = 9.2 Hz, 0.36H; NH_{Phe}), 8.78 (d, ^3J(H,H) = 8.3 Hz, 0.38H; NH_{Phe}), 8.76 (d, ^3J(H,H) = 8.0 Hz, 0.34H; NH_{Phe}), 8.71 (d, ^3J(H,H) = 9.3 Hz, 0.30H; NH_{Phe}), 8.63 (d, ^3J(H,H) = 8.9 Hz, 0.30H; NH_{Phe}), 8.59 (d, ^3J(H,H) = 8.9 Hz, 0.32H; NH_{Phe}), 8.54 (d, ^3J(H,H) = 9.4 Hz, 0.35H; NH_{Ser}), 8.50 (d, ^3J(H,H) = 9.4 Hz, 0.35H; NH_{Ser}), 8.31 (d, ^3J(H,H) = 9.3 Hz, 0.30H; NH_{Ser}), 7.25 (m, 15H; Ar), 5.54 (m, 1H; $H\alpha_{Ser}$), 5.36 (m, 2H; $H\alpha_{Phe}$), 4.79–4.30 (m, 5H; $H\gamma_{Ach}$, $CH\beta_{Bn}$), 3.86–3.33 (m, 2H; $H\beta_{Ser}$), 3.24–2.75 (m, 7H; $H\beta_{Phe}$, $H\alpha_{Ach}$), 3.10 (s, 2H; Me-N), 3.07 (s, 1H; Me-N), 2.58 ppm (s, 6H; Me-N); FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$ = 3303 (amide A), 2932, 2861, 1671 (amide I_{II}), 1625 (amide I), 1525 cm^{-1} (amide II); MS (ESI): *m*/*z* (%): 912 (58) $[M+Na]^+$, 890 (100) $[M+H]^+$; HRMS (ESI): *m*/*z*: calcd for $C_{52}H_{69}N_6O_7$: 889.5222; found: 889.5218.

***c*-[L-Lys(*Z*)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$]**: The mentioned cyclic peptide was prepared from Boc-(L-Phe-D-^{Me}N-γ-Ach-)$_2$L-Lys(*Z*)-D-^{Me}N-γ-Ach-OFm (180 mg, 0.14 mmol) by following a similar procedure described for *c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] to afford, after purification by flash chromatography (2–7% MeOH/CH_2Cl_2), 67 mg of expected CP as a white solid (48%, R_f = 0.60 (5% MeOH/CH_2Cl_2)). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.76 (d, ^3J(H,H) = 9.1 Hz, 0.33H; NH_{Phe}), 8.75 (d, ^3J(H,H) = 9.2 Hz, 0.33H; NH_{Phe}), 8.68 (d, ^3J(H,H) = 8.6 Hz, 0.33H; NH_{Phe}), 8.67 (d, ^3J(H,H) = 8.6 Hz, 0.33H; NH_{Phe}), 8.60 (d, ^3J(H,H) = 9.0 Hz, 0.33H; NH_{Phe}), 8.59 (d, ^3J(H,H) = 9.0 Hz, 0.33H; NH_{Phe}), 8.42 (d, ^3J(H,H) = 9.4 Hz, 0.33H; NH_{Lys}), 8.37 (d, ^3J(H,H) = 9.4 Hz, 0.33H; NH_{Lys}), 8.24 (d, ^3J(H,H) = 9.4 Hz, 0.33H; NH_{Lys}), 7.23 (m, 15H; Ar), 5.28 (m, 2H; $H\alpha_{Phe}$), 5.16–4.81 (m, 3H; $H\alpha_{Lys}$, CH_{2Bn}), 4.54 (m, 3H; $H\gamma_{Ach}$), 3.14–2.70 (m, 9H; $H\alpha_{Ach}$, $H\beta_{Phe}$, $H\delta_{Lys}$), 2.99 (m, 3H; Me-N), 2.54, 2.51, 2.50, 2.49, 2.48 ppm (5 s, 6H; Me-N); FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$ = 3302 (amide A), 3001, 2931, 2860, 1716, 1666

(amide I_{II}), 1624 (amide I), 1525 cm^{-1} (amide II); MS (ESI): *m/z* (%): 997 (100) $[M+Na]^+$, 975 (43) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{56}H_{75}N_7NaO_8$: 996.5569; found: 996.5576.

***c*-[L-Ser(2-DPPBA)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (CP4)**: A solution of *c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (50 mg, 56 μmol) in $Pd(OH)_2$ (10 mg, 20% wt.) in EtOH (630 μL) was stirred at RT for 5 h under a hydrogen atmosphere (balloon pressure). The resulting mixture was filtered through a Celite pad, the residue was washed with ethanol, and the combined filtrates and washings were concentrated under reduced pressure. The resulting material was dissolved in CH_2Cl_2 (270 μL) and treated with 2-(diphenylphosphino)benzoic acid (2-DPPBA, 12.6 mg, 41 μmol), HOBt (8.4 mg, 60 μmol), EDC·HCl (12 mg, 60 μmol), and DMAP (7.6 mg, 60 μmol). After 3 h the solvent was removed under reduced pressure. The residue was purified by flash chromatography (2–6% MeOH/CH_2Cl_2) to afford 31 mg of **CP4** as a white solid (69%, R_f= 0.50 (5% MeOH/CH_2Cl_2)). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ= 8.76 (d, ^3J(H,H)=9.2 Hz, 0.40 H; NH_{Phe}), 8.73 (d, ^3J(H,H)=9.3 Hz, 0.30 H; NH_{Phe}), 8.69 (d, ^3J(H,H)=8.8 Hz, 0.40 H; NH_{Phe}), 8.65 (d, ^3J(H,H)=8.8 Hz, 0.35 H; NH_{Phe}), 8.64 (d, ^3J(H,H)=7.4 Hz, 0.40 H; NH_{Phe}), 8.36 (d, ^3J(H,H)=9.4 Hz, 0.35 H; NH_{Ser}), 8.30 (d, ^3J(H,H)= 9.4 Hz, 0.35 H; NH_{Ser}), 8.24 (d, ^3J(H,H)=9.3 Hz, 0.30 H; NH_{Ser}), 7.94 (brs, 1 H; $Ar_{2\text{-}DPPBA}$), 7.22 (m, 22 H; Ar_{Phe}, $Ar_{2\text{-}DPPBA}$), 6.89 (brs, 1 H; $Ar_{2\text{-}DPPBA}$), 5.51 (brs, 1 H; $H\alpha_{Ser}$), 5.33 (m, 2 H; $H\alpha_{Phe}$), 4.53 (m, 3.75 H; 3 $H\gamma_{Ach}$, 0.75 $H\beta_{Ser}$), 4.38 (dd, ^3J(H,H)=10.8, 7.1 Hz, 0.25 H; $H\beta_{Ser}$), 4.22 (m, 0.75 H; $H\beta_{Ser}$), 4.11 (dd, ^3J(H,H)=10.8, 7.5 Hz, 0.25 H; $H\beta_{Ser}$), 2.98, 2.97 (2 s, 2.30 H; Me-N), 2.90 (s, 0.70 H; Me-N), 2.54, 2.53, 2.51, 2.50, 2.49 ppm (5 s, 6 H; Me-N); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ= −6.0 ppm; FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$=3307 (amide A), 3001, 2931, 2860, 1718, 1670 (amide I_{II}), 1626 (amide I), 1523 cm^{-1} (amide II); MS (ESI): *m/z* (%): 1088 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{64}H_{76}N_6O_8P$: 1087.5457; found: 1087.5453.

***c*-[L-Ser(4-DPPBA)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (CP5)**: Prepared from *c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (21.7 mg, 24 μmol) in the same way as **CP4** to yield, after HPLC purification (R_t= 17.3 min, 1–15% MeOH/CH_2Cl_2, Phenomenex, 5 μ, 250×10.0 mm, 5 micron), 18.5 mg of **CP5** as a white solid (71%, R_f=0.50 (5% MeOH/CH_2Cl_2)). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=8.76 (d, ^3J(H,H)=9.1 Hz, 0.60 H; NH_{Phe}), 8.72 (d, ^3J(H,H)=10.5 Hz, 0.6 H; NH_{Phe}), 8.68 (d, ^3J(H,H)=9.6 Hz, 0.60 H; NH_{Phe}), 8.64 (d, ^3J(H,H)= 8.6 Hz, 0.35 H; NH_{Phe}), 8.36 (d, ^3J(H,H)=9.0 Hz, 0.35 H; NH_{Ser}), 8.32 (d, ^3J(H,H)=7.9 Hz, 0.30 H; NH_{Ser}), 8.31 (d, ^3J(H,H)=8.4 Hz, 0.35 H; NH_{Ser}), 7.83 (d, ^3J(H,H)=7.7 Hz, 2 H; CH-$Ar_{2\text{-}DPPBA}$), 7.25 (m, 22 H; CH-Ar_{Phe}, CH-$Ar_{2\text{-}DPPBA}$), 5.61 (m, 1 H; $H\alpha_{Ser}$), 5.31 (m, 2 H; $H\alpha_{Phe}$), 4.70–4.24 (m, 5 H; $H\gamma_{Ach}$, $H\beta_{Ser}$), 3.13–2.75 (m, 7 H; $H\beta_{Phe}$, $H\alpha_{Ach}$), 3.10, 3.09, 3.08 (3 s, 3 H; Me-N), 2.53, 2.52, 2.51, 2.50 ppm (4 s, 6 H; Me-N); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ= −7.5 ppm; FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$=3307 (amide A), 2929, 2858, 1730, 1670 (amide I_{II}), 1624 (amide I), 1522 cm^{-1} (amide II); MS (ESI): *m/z* (%): 1110 (64) $[M+Na]^+$, 1088 (79) $[M+H]^+$, 544 (100) $[M+H]^{2+}$; HRMS (ESI): *m/z*: calcd for $C_{64}H_{76}N_6O_8P$: 1087.5457; found: 1087.5449.

***c*-[L-Lys(2-DPPBA)-L-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (CP6)**: A solution of *c*-[L-Lys(*Z*)-L-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] (33.3 mg, 34 μmol) in Pd/C (6.7 mg, 10% in wt.) in MeOH (2.2 mL) was stirred at RT for 5 h under hydrogen atmosphere (balloon pressure). The resulting mixture was filtered through a Celite pad, the residue was washed with methanol, and the combined filtrates and washings were concentrated under reduced pressure. The resulting material was dissolved in CH_2Cl_2 (340 μL) and treated with 2-DPPBA (10.5 mg, 34 μmol) and HATU (14.2 mg, 37 μmol), followed by the dropwise addition of DIEA (35 μL, 0.204 mmol). After 3 h the solvent was removed under reduced pressure. The crude was purified by flash chromatography (0–6% MeOH/CH_2Cl_2) to afford 19.0 mg of **CP6** as a white solid (50%, R_f=0.50 (5% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=8.77 (d, ^3J(H,H)= 9.4 Hz, 0.35 H; NH_{Phe}), 8.75 (d, ^3J(H,H)=9.4 Hz, 0.35 H; NH_{Phe}), 8.69 (d, ^3J(H,H)=8.8 Hz, 0.35 H; NH_{Phe}), 8.67 (d, ^3J(H,H)=8.8 Hz, 0.35 H; NH_{Phe}), 8.61 (d, ^3J(H,H)=8.4 Hz, 0.35 H; NH_{Phe}), 8.59 (d, ^3J(H,H)= 8.4 Hz, 0.35 H; NH_{Phe}), 8.45 (d, ^3J(H,H)=9.3 Hz, 0.30 H; NH_{Lys}), 8.40 (d, ^3J(H,H)=9.6 Hz, 0.30 H; NH_{Lys}), 8.26 (d, ^3J(H,H)=9.4 Hz, 0.36 H; NH_{Lys}), 7.55 (brs, 0.6 H; $Ar_{2\text{-}DPPBA}$), 7.44 (brs, 0.35 H; $Ar_{2\text{-}DPPBA}$), 7.36–7.10 (m, 22 H; Ar_{Phe}, $Ar_{2-DPPBA}$), 6.91 (s, 1 H; $Ar_{2-DPPBA}$), 6.48 (s, 0.35 H; $NH\omega_{Lys}$), 6.05 (s, 0.30 H; $NH\omega_{Lys}$), 5.30 (m, 2 H; $H\alpha_{Phe}$), 5.11 (m, 0.60 H; $H\alpha_{Lys}$), 5.04 (m, 0.40 H; $H\alpha_{Lys}$), 4.54 (m, 3 H; $H\gamma_{Ach}$), 3.19–2.73 (m, 9 H; $H\alpha_{Ach}$, $H\beta_{Phe}$, $H\delta_{Lys}$), 2.99 (s, 3 H; Me-N), 2.55, 2.53, 2.52, 2.51, 2.50, 2.48 ppm (6 s, 6 H; Me-N); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ= −11.4 ppm; FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$=3303 (amide A), 3002, 2932, 2861, 1657 (amida I_{II}), 1624 (amide I), 1528 cm^{-1} (amide II); MS (ESI): *m/z* (%): 1151 (6) $[M+Na]^+$, 1129 (100) $[M+H]^+$, 565 (92) $[M+H]^{2+}$; HRMS (ESI): *m/z*: calcd for $C_{67}H_{83}N_7O_7P$: 1128.6086; found: 1128.6061.

***c*-[L-Prg-D-^{Me}N-γ-Acp-(L-Leu-D-^{Me}N-γ-Acp-)$_2$] (CP7)**: The mentioned cyclic peptide was prepared from Boc-(L-Leu-D-^{Me}N-γ-Acp-)$_2$L-Prg-D-^{Me}N-γ-Acp-OFm (188 mg, 0.19 mmol) by following a similar procedure described for *c*-[L-Ser(Bn)-D-^{Me}N-γ-Ach-(L-Phe-D-^{Me}N-γ-Ach-)$_2$] to afford, after purification by flash chromatography (2–7% MeOH/CH_2Cl_2), 110 mg of CP7 as a white solid (84%, R_f=0.6 (5% MeOH/CH_2Cl_2)). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=8.35 (d, ^3J(H,H)=12.2 Hz, 0.35 H; NH_{Prg}), 8.33 (d, ^3J(H,H)=11.1 Hz, 0.35 H; NH_{Prg}), 8.22 (d, ^3J(H,H)=8.1 Hz, 1.8 H; NH_{Leu}, NH_{Prg}), 8.11 (d, ^3J(H,H)=8.3 Hz, 0.50 H; NH_{Leu}), 5.35 (q, ^3J(H,H)=9.3 Hz, 1 H; $H\alpha_{Prg}$), 5.17 (m, 2 H; $H\alpha_{Leu}$), 4.94–4.69 (m, 3 H; $H\gamma_{Acp}$), 3.10 (s, 3 H; Me-N), 3.07 (s, 6 H; Me-N), 2.92 ppm (m, 3 H; $H\alpha_{Acp}$); FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$= 3300 (amide A), 2956, 1672 (amide I_{II}), 1618 (amide I), 1533 cm^{-1} (amide II); MS (ESI): *m/z* (%): 719 (78) $[M+Na]^+$, 698 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{38}H_{61}N_6O_6$: 697.4647; found: 697.4637.

***c*-[L-Prg(4-methoxyphenyl)-D-^{Me}N-γ-Acp-(L-Leu-D-^{Me}N-γ-Acp-)$_2$] (CP8)**: In a screw-cap sealed tube a mixture of **CP7** (5.0 mg, 6.95 nmol), 4-iodoanisole (3.4 mg, 14.5 nmol), AuCl·SMe_2 (2.1 mg, 71.3 nmol), **CP6** (8.1 mg, 71.9 nmol), and Et_3N (6 μL) were dissolved in $CHCl_3$ (2.5 mL) and $[Pd_2(dba)_3]\cdot CHCl_3$ (1.2 mol%, 0.76 mg, 0.083 nmol) was added. The tube was sealed and heated at 40 °C for 24 h. After cooling down, the mixture was purified by HPLC (R_t=15.0 min, 5–15% MeOH/CH_2Cl_2, Phenomenex, 5 μ, 250×10.00 mm, 5 micron) to afford 2 mg of **CP8** as a yellow oil (35%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=8.38 (d, ^3J(H,H)= 6.4 Hz, 1 H; NH_{Prg}), 8.23 (d, ^3J(H,H)=8.2 Hz, 2 H; NH_{Leu}), 7.26 (s, 2 H; Ar), 6.80 (d, ^3J(H,H)=8.2 Hz, 2 H; Ar), 5.44 (q, ^3J(H,H)=9.1 Hz, 1 H; $H\alpha_{Prg}$), 5.17 (s, 2 H; $H\alpha_{Leu}$), 4.95–4.72 (m, 3 H; $H\gamma_{Acp}$), 3.79 (s, 3 H; Me-O), 3.13 (s, 3 H; Me-N), 3.08 (s, 6 H; Me-N), 2.95 ppm (m, 3 H; $H\alpha_{Acp}$); FTIR (293 K, CaF_2 Pellet): $\tilde{\nu}$=3300 (amide A), 2957, 2872, 1672 (amide I_{II}), 1622 (amide I), 1531 cm^{-1} (amide II); MS (ESI): *m/z* (%): 1607 (10) $[M+H]^{2+}$, 826 (54) $[M+Na]^+$, 804 (100) $[M+H]^+$; HRMS (ESI): *m/z*: calcd for $C_{45}H_{67}N_6O_7$: 803.5066; found: 803.5078.

***c*-[L-Prg[Au]-D-^{Me}N-γ-Acp-(L-Leu-D-^{Me}N-γ-Acp-)$_2$] (CP7[Au])$_n$**: A solution of **CP7** (8.0 mg, 9.96 nmol) and Et_3N (10 μL, 71.9 nmol) in THF (750 μL) was added to a solution of AuCl·SMe_2 (3.4 mg, 11.54 nmol) in THF (750 μL) and MeOH (560 μL). After having been stirred at RT for 30 min the solid was isolated by filtration, washed successively with THF, MeOH, and Et_2O to afford, after high vacuum drying, 8.1 mg of **(CP7[Au])$_n$** (79%). The peptide was stored in the refrigerator and protected from light and used without further characterization.[18]

D(*S*)4–7[Au]: **Procedure A**: Peptide **CP4** (4.9 mg, 4.5 nmol) was dissolved in $CDCl_3$ (500 μL) in a NMR tube and portions (0.25, 0.50, 0.75, and 1.0 equiv) of **(CP7[Au])$_n$** (4.5 mg, 4.5 nmol) were added for heterodimer formation. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=8.73 (d, ^3J(H,H)=9.6 Hz, 1 H; NH_{Leu}), 8.65 (d, ^3J(H,H)=9.4 Hz, 1 H; NH_{Leu}), 8.46 (d, ^3J(H,H)=9.5 Hz, 1 H; NH_{Ser}), 8.43 (d, ^3J(H,H)=9.5 Hz, 1 H; NH_{Phe}), 8.42 (d, ^3J(H,H)=9.4 Hz, 1 H; NH_{Phe}), 8.04 (d, ^3J(H,H)=6.3 Hz, 1 H; NH_{Prg}), 7.82 (m, 1 H; $Ar_{2\text{-}DPPBA}$), 7.55–7.44 (m, 6 H; Ar), 7.43–7.34 (m, 6 H; Ar), 7.29–7.11 (m, 10 H; Ar_{Phe}), 6.86 (dd, ^3J(H,H)=10.3, 8.3 Hz, 1 H; $Ar_{2\text{-}DPPBA}$), 5.50 (m, 1 H; $H\alpha_{Ser}$), 5.24 (m, 2 H; $H\alpha_{Leu}$, $H\alpha_{Phe}$), 5.18 (m, 2 H; $H\alpha_{Leu}$, $H\alpha_{Phe}$), 5.00 (m, 3 H; $H\gamma_{Acp}$), 4.86 (brs, 1 H; $H\alpha_{Prg}$), 4.71 (dd, ^3J(H,H)=11.1, 3.1 Hz, 1 H; $H\beta_{Ser}$), 4.45 (t, ^3J(H,H)=11.1 Hz, 1 H; $H\beta_{Ser}$), 4.37 (m, 3 H; $H\gamma_{Ach}$), 3.25 (m, 2 H; $H\beta_{Prg}$, $H\alpha_{Acp}$), 3.11 (s, 3 H; Me-N), 3.09 (s, 3 H; Me-N), 2.98 (s, 3 H; Me-N), 2.98 (s, 3 H; Me-N), 2.81 (d, ^3J(H,H)=17.0 Hz, 1 H; $H\beta_{Prg}$), 2.72 (m, 2 H; $H\alpha_{Acp}$, $H\alpha_{Ach}$), 2.58 (s, 3 H; Me-N), 2.56 (s, 3 H; Me-N), 2.72 (m, 2 H; $H\alpha_{Ach}$), 2.34–2.03 (m, 2 H; $H\alpha_{Acp}$), 0.90 ppm (overlapped doublets, 12 H; Me_{Leu}); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ=40.9 ppm; FTIR (293 K, $CHCl_3$): $\tilde{\nu}$=3302

(amide A), 2999, 2958, 2933, 2862, 1670 (amide I_{II}), 1624 (amide I), 1531 cm^{-1} (amide II); MS-MALDI-TOF: *m/z* (%): 2088 (100) $[M+Ag]^+$.

D(s)6–7[Au]: **Procedure B**: Peptide **CP6** (4.9 mg, 4.3 nmol), **CP7** (3.0 mg, 4.3 nmol), and $AuCl{\cdot}SMe_2$ (1.3 mg, 4.3 nmol) were dissolved in $CDCl_3$ (500 μL) in a NMR tube and portions (1.0, 2.0 and 3.0 equiv) of triethylamine (1.8 μL, 13.0 nmol) were added to form the mentioned heterodimeric gold complex. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 8.69 (d, ^3J(H,H) = 9.4 Hz, 1H; NH_{Leu}), 8.61 (d, ^3J(H,H) = 9.3 Hz, 1H; NH_{Leu}), 8.42 (m, 4H; NH_{Phe}, NH_{Lys}, NH_{Prg}), 7.63 (br s, 1H; $Ar_{2\text{-}DPPBA}$), 7.52–7.32 (m, 12H; Ar), 7.29–7.13 (m, 10H; Ar_{Phe}), 6.86 (dd, ^3J(H,H) = 10.4, 8.1 Hz, 1H; $Ar_{2\text{-}DPPBA}$), 6.28 (dd, ^3J(H,H) = 7.0, 3.4 Hz, 1H; $NH\omega_{Lys}$), 5.22 (m, 4H; $H\alpha_{Phe}$, $H\alpha_{Leu}$), 4.97 (m, 4H; $H\alpha_{Prg}$, $H\alpha_{Lys}$, $2H\gamma_{Acp}$), 4.81 (pentet, ^3J(H,H) = 8.6 Hz, 1H; $H\gamma_{Acp}$), 4.36 (m, 3H; $H\gamma_{Ach}$), 3.70 (m, 1H; $H\omega_{Lys}$), 3.09 (s, 9H; Me-N), 2.97 (s, 3H; Me-N), 2.76–2.60 (m, 3H; $H\alpha_{Ach}$), 2.58 (s, 3H; Me-N), 2.52 (s, 3H; Me-N), 0.96 (d, ^3J(H,H) = 5.4 Hz, 6H; Me_{Leu}), 0.90 (d, ^3J(H,H) = 6.2 Hz, 3H; Me_{Leu}), 0.89 ppm (d, ^3J(H,H) = 6.1 Hz, 3H; Me_{Leu}); ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): $\delta =$ 40.1 ppm; FTIR (293 K, $CHCl_3$): $\tilde{\nu} = 3300$ (amide A), 2999, 2956, 2931, 2870, 1664 (amide I_{II}), 1624 (amide I), 1531 cm^{-1} (amide II); MS-MALDI-TOF: *m/z* (%): 2129 (100) $[M+Ag]^+$.

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