ACCOUNTS
of chemical research

Design of Ferrocene-Dipeptide Bioorganometallic Conjugates To Induce Chirality-Organized Structures

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RECEIVED ON FEBRUARY 4, 2010

CONSPECTUS

The highly ordered molecular assemblies in proteins can have a variety of functions, as observed in enzymes, receptors, and the like. Synthetic scientists are constructing bioinspired systems by harnessing the self-assembling properties of short peptides. Secondary structures such as α-helices, β-sheets, and β-turns are important in protein folding, which is mostly directed and stabilized by hydrogen bonding and the hydrophobic interactions of side chains. The design of secondary structure mimics that are composed of short peptides has attracted much attention, both for gaining fundamental insight into the factors affecting protein folding and for developing pharmacologically useful compounds, artificial receptors, asymmetric catalysts, and new materials.

Ferrocenes are an organometallic scaffold with a central reverse-turn unit based on the inter-ring spacing of about 3.3 Å, which is a suitable distance for hydrogen bonding between attached peptide strands. The conjugation of organometallic compounds with biomolecules such as amino acids, peptides, and DNA should provide novel systems that reflect properties of both the ferrocene and the biologically derived moieties. In this Account, we focus on recent advances in the design of ferrocene−peptide bioconjugates, which help illustrate the peptidomimetic basis for protein folding and the means of constructing highly ordered molecular assemblies.

Ferrocene−peptide bioconjugates are constructed to form chirality-organized structures in both solid and solution states. The ferrocene serves as a reliable organometallic scaffold for the construction of protein secondary structures via intramolecular hydrogen bonding: the attached dipeptide strands are constrained within the appropriate dimensions. The introduction of the chiral dipeptide chains into the ferrocene scaffold induces the conformational enantiomerization of the ferrocenyl moiety; the chirality-organized structure results from intramolecular hydrogen bonding. The configuration and sequence of the amino acids are instrumental in the process.

Regulation of the directionality and specificity of hydrogen bonding is a key component in the design of various molecular assemblies. Ferrocene−peptide bioconjugates also have a strong tendency to self-assemble through the contributions of available hydrogen-bonding donors in the solid state. Some ferrocene−peptide bioconjugates bearing only one dipeptide chain exhibit a helically ordered molecular assembly through a network of intermolecular (rather than intramolecular) hydrogen bonds. The propensity to form the chiral helicity appears to be controlled by the chirality of the dipeptide chains.

Organization of host molecules is a useful strategy for forming artificial receptors. The conformationally regulated ferrocene−peptide bioconjugate provides the chirality-organized binding site for size-selective and chiral recognition of dicarboxylic acids through multipoint hydrogen bonds.

Metal ions serve a variety of purposes in proteins, including structural stabilization for biological function. The complexation of ferrocene−peptide bioconjugates with palladium(II) compounds not only stabilizes the chirality conformational regulation but also induces conformational regulation of the dipeptide chain through complexation and intramolecular chirality organization. Construction of the chirality-organized ferrocene−peptide bioconjugates is also achieved by metal-directed assembly.

These varied examples amply demonstrate the value of ferrocene−peptide bioconjugates in asserting architectural control over highly ordered molecular assemblies.

Published on the Web 04/08/2010 www.pubs.acs.org/acr
10.1021/ar100022n

Introduction

Architectural control of molecular self-organization is important for the development of functional materials.[1] Regulation of hydrogen bonding[2] is a key factor in the design of various molecular assemblies by virtue of its directionality and specificity.[3] The reversibility and tuneability of hydrogen bonding is also of fundamental importance in the chemical or physical properties of molecular assemblies. The utilization of self-assembling properties of short peptides, which possess chiral centers and hydrogen bonding sites, is considered to be a relevant approach to highly ordered molecular assemblies. Hydrogen bonding regulates three-dimensional structures and functions of biological systems. Highly ordered molecular assemblies are constructed in proteins to fulfill unique functions as observed in enzymes, receptors, etc. Secondary structures such as α-helices, β-sheets, and β-turns play an important role in protein folding, which is mostly stabilized by hydrogen bonding and hydrophobic interactions of side chains.[4] Highly specific patterns of complementary intra- and intermolecular hydrogen bonds are created in such secondary structures. Although β-sheets are the key structural elements in a three-dimensional structure to fulfill the biological activity of proteins, the structure and stability of β-sheets are less understood compared with those of α-helices. A series of 12-membered hydrogen-bonded rings are formed in parallel β-sheets, while an alternating series of 10- and 14-membered hydrogen-bonded rings are organized in antiparallel β-sheets. It is difficult to predict the pattern of protein folding from the sequence of amino acids. Considerable efforts have focused on designing secondary structure mimics composed of short peptides to gain fundamental insight into the factors affecting the protein structure and stability and to facilitate the rational design of pharmacologically useful compounds. Generally, preparation of chemical models of β-sheets is difficult due to the complexity of their folding and their propensity for self-association. The utilization of molecular scaffolds is a potential strategy for organization of peptide structures, which allows the control of intramolecular interaction of peptides or peptidomimetic strands. Therefore, various molecular scaffolds such as a rigid aromatic,[5] an epindolidion,[6] a dibenzofuran,[7] an oligourea,[8] and an *endo-cis*-(2*S*,3*R*)-norbornene[9] scaffold have been employed to create the β-sheet-like structure of attached peptide chains and serve as substitutes for the β-turn in the chemical models of protein secondary structures.

Recently, the research field of bioorganometallic chemistry, which is a hybrid area between biochemistry and organometallic chemistry, has drawn much attention. Conjugation of organometallic compounds with biomolecules such as DNA, amino acids, and peptides is envisioned to provide novel systems depending on both properties. In these bioconjugates, the organometallic moiety can serve as a molecular scaffold, a sensitive probe, a chromophore, a biological marker, a redox-active site, a catalytic active site, etc. Considerable effort has been devoted to designing bioconjugates composed of organometallic compounds and biomolecules.[10] Ferrocene, which is one of the most stable organometallic compounds and a most useful one among metallocenes, has attracted much attention in application to materials due to a reversible redox couple and two rotatory coplanar cyclopentadienyl (Cp) rings.[11] The inter-ring spacing of ferrocene is appropriate for hydrogen bonding of the attached peptide strands. The utilization of a ferrocene unit as an organometallic scaffold with a central reverse-turn unit is considered to be one strategy to study the hydrogen bonding ability of various peptide strands. Ferrocenylalanine, which is the first example of a ferrocene−amino acid bioconjugate, was synthesized in 1957.[12] After its discovery, a variety of ferrocene−amino acid or −peptide bioconjugates have been designed to obtain a peptidomimetic basis for protein folding and to construct highly ordered molecular assemblies.[13]

In this Account, we summarize our ongoing research on the design of ferrocene−peptide bioconjugates to obtain peptidomimetic basis for protein folding and to construct highly ordered molecular assemblies. Especially, the hydrogen bonding properties of ferrocene−peptide bioconjugates to create chirality-organized structures are focused on. In addition, complexation-induced chirality organization of the chirality-organized ferrocene−peptide bioconjugates is described.

Chirality Organization of 1,1′-Disubstituted Ferrocene−Peptide Bioconjugates

Our design is based on symmetrical introduction of two dipeptide chains of alanyl-proline or prolyl-alanine sequence into the ferrocene scaffold as a central reverse-turn unit (Figure 1). An advantage in the use of the dipeptide chain depends on a hydrogen bonding site and a sterically constrained proline as a well-known turn inducer in proteins. The 1,1′-disubstituted ferrocene−peptide bioconjugates were synthesized from 1,1′-bis(chlorocarbonyl)ferrocene and the corresponding dipeptide derivatives.

X-ray crystallographic analyses clarified the ordered structures of the ferrocene−peptide bioconjugates. The single-crystal X-ray structure of the ferrocene−peptide bioconjugate **1** bearing the L-dipeptide chains (L-Ala-L-Pro-OEt) confirmed the interchain intramolecular antiparallel β-sheet-like hydrogen

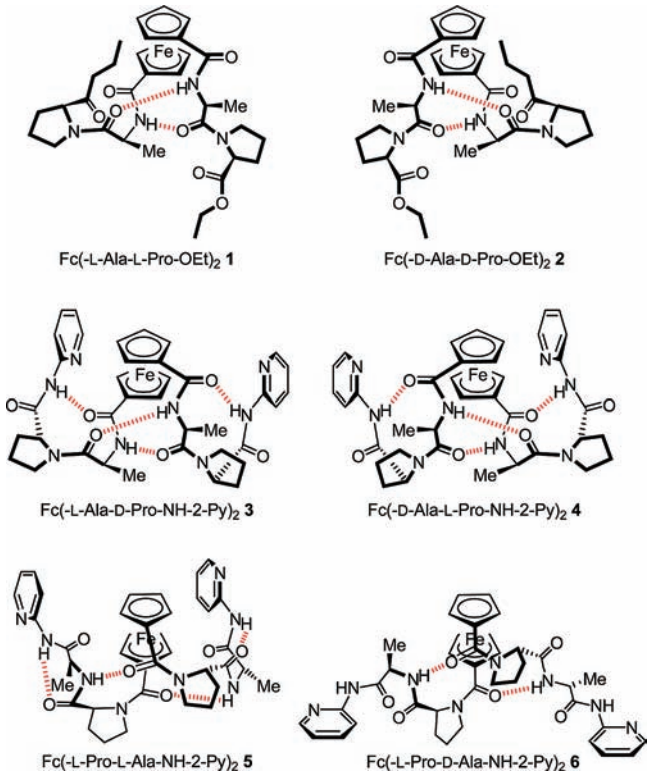


FIGURE 1. Ferrocene−peptide bioconjugates bearing the dipeptide chains.

bonding between NH (alanine) and CO (alanine of another chain) of each dipeptide chain to induce the chirality-organized structure (Figure 2a).[14] The conformational enantiomers based on the torsional twist about the Cp(centroid)−Fe−Cp(centroid) axis are possible with the 1,1′-disubstituted ferrocene as shown in Figure 3.[11,15] The ferrocenoyl moiety of **1** adopted the *P*-helical arrangement. The incorporation of the dipeptide chains into the ferrocene scaffold achieved the chirality-organized structure based on two rigid interchain intramolecular hydrogen bonds, although a wide range of relative orientations are possible depending on

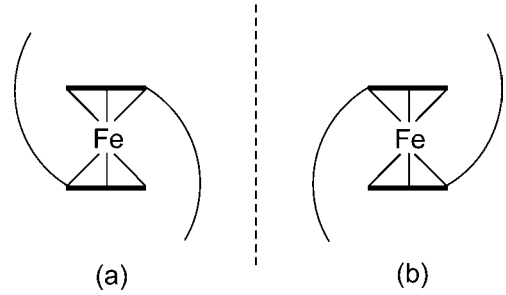


FIGURE 3. Enantiomorphous conformations of the 1,1′-disubstituted ferrocene. The enantiomorphs are related by the mirror plane.

two rotatory Cp rings. The crystal structure of **2** composed of the corresponding D-dipeptide chains (D-Ala-D-Pro-OEt) revealed the *M*-helical arrangement of the ferrocenoyl moiety (Figure 2b). The molecular structures of **1** and **2** are in an excellent mirror image relationship as shown in Figure 2, indicating conformational enantiomers present (Figure 3). As a result, the introduction of the chiral dipeptide chains into the ferrocene was found to induce the chirality organization by restriction of the torsional twist through the interchain intramolecular hydrogen bonds.[14c]

Circular dichroism (CD) spectrometry is a useful tool to determine an ordered structure in solution. The ferrocene−peptide bioconjugate **1** exhibited a positive Cotton effect at the absorbance region of the ferrocenoyl moiety in acetonitrile, which indicates the *P*-helical arrangement of the ferrocenoyl moiety (Figure 4). The mirror image of the signals was obtained in the CD spectrum of **2**, indicating that the chiral molecular arrangement based on an ordered structure via interchain intramolecular hydrogen bondings was formed even in solution.[14c] Furthermore, two identical intramolecular hydrogen bonds between the dipeptide chains were supported by ^{1}H NMR ($CDCl_3$) and FT-IR (CH_2Cl_2) analyses.

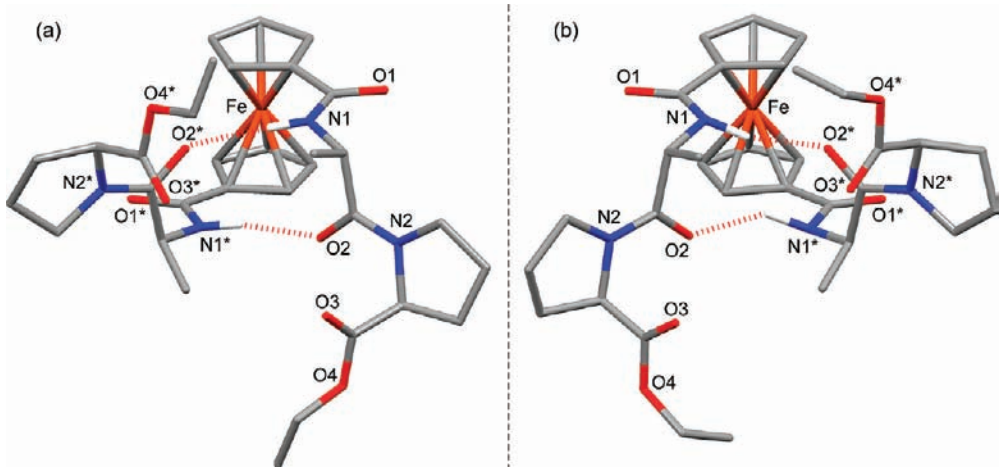


FIGURE 2. Molecular structures of (a) **1** and (b) **2**.

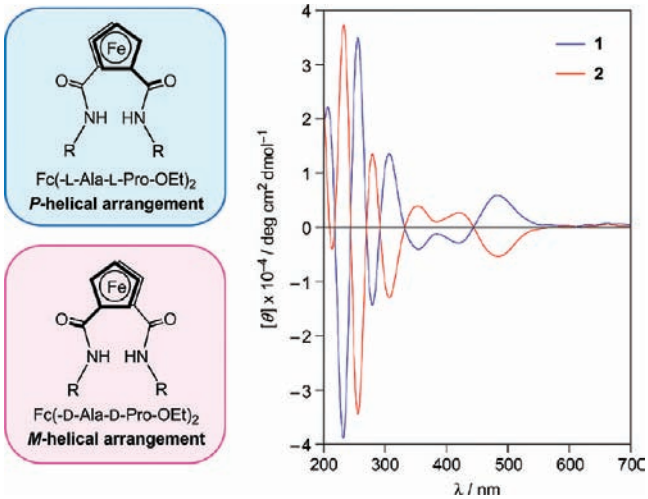


FIGURE 4. CD spectra of **1** and **2** in MeCN (1.0×10^{-4} M).

Chirality choice and sequence of amino acids are considered to be a key factor for constructing chirality-organized bioinspired systems with highly ordered structures. The effect of the configuration and sequence of the dipeptide chains on the organization of the template structure was examined. The single-crystal X-ray structure determination of the ferrocene−peptide bioconjugate **3** bearing the dipeptide chains of the heterochiral sequence L-Ala-D-Pro-NH-2-Py revealed the interchain intramolecular antiparallel β-sheet-like hydrogen bonding between NH (alanine) and CO (alanine of another chain) of each dipeptide chain to induce the chirality-organized structure in which the *P*-helical arrangement of the ferrocenoyl moiety was formed (Figure 5a).[16] The *P*-helical arrangement of the ferrocenoyl moiety appears to be controlled by the configuration of the alanyl α-carbon atom,[17] because a similar type of chiral molecular conformation was also observed with the ferrocene−dipeptide bioconjugate **1** bearing the L-Ala-L-Pro-OEt dipeptide chains. Another remarkable feature of the structure is that the NH adjacent to the pyridyl moiety participates in intramolecular hydrogen bonding with the CO adjacent to the ferrocene unit of the same peptide chain to nucleate a type II β-turn-like structure in each dipeptide chain. The combination of the ferrocene scaffold as a central reverse-turn unit with the L-alanyl-D-proline heterochiral dipeptide sequence permits the artificially regulated antiparallel β-sheet-like and type II β-turn-like structures simultaneously. The molecular structure of **4** composed of the D-Ala-L-Pro-NH-2-Py dipeptide chains, in which the *M* helical arrangement of the ferrocenoyl moiety is formed (Figure 5b), is in a mirror image relationship with **3**.[16]

A positive Cotton effect at the absorbance region of the ferrocenoyl moiety was detected in a CD spectrum of the ferrocene−peptide bioconjugate **3** in dichloromethane, indicating the *P*-helical arrangement of the ferrocenoyl moiety.[16] Proton magnetic resonance nuclear Overhauser effect (NOE) of **3** in $CDCl_3$ at 25 °C additionally provided diagnostic evidence for the chirality-organized structure. Irradiation of the Cp proton at the α position also enhanced the alanine NH, NH adjacent to the pyridyl moiety, and pyridyl proton at the 3-position. A type II β-turn-like structure was found to be achieved in solution.

The crystal structure of the ferrocene−peptide bioconjugate **5** bearing the dipeptide chains of the homochiral sequence L-Pro-L-Ala-NH-2-Py was characterized by the presence of the NH adjacent to the pyridyl moiety participating in an intramolecular hydrogen bond with the proline CO of the same peptide chain, nucleating an inverse γ-turn-like structure in each dipeptide chain, where the interchain intramolecular antiparallel β-sheet-like hydrogen bondings between the NH of the alanine and the CO of the ferrocene unit attached to the opposite peptide chain were formed (Figure 6a).[18] The combination of the ferrocene scaffold with the L-prolyl-L-alanine homochiral sequence permits the simultaneous formation of the artificial inverse γ-turn-like and antiparallel β-sheet-like structures.

To evaluate the effect of the diastereomeric dipeptide configurations, the ferrocene−peptide bioconjugate **6** bear-

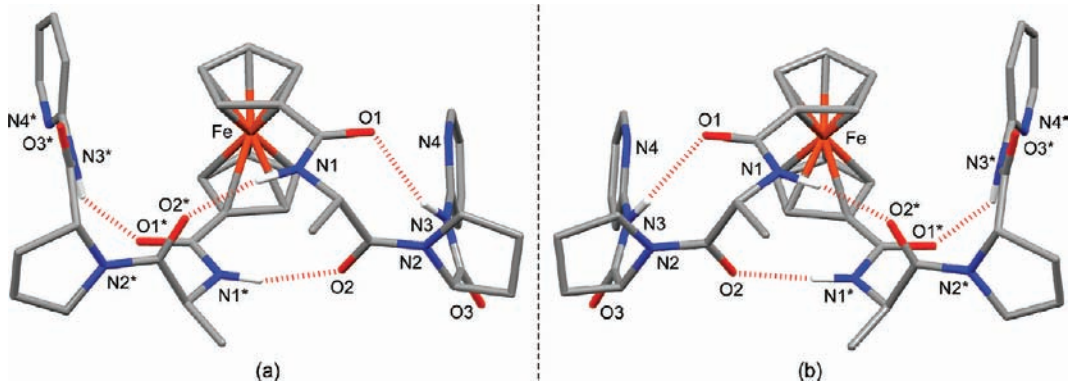


FIGURE 5. Molecular structures of (a) **3** and (b) **4**.

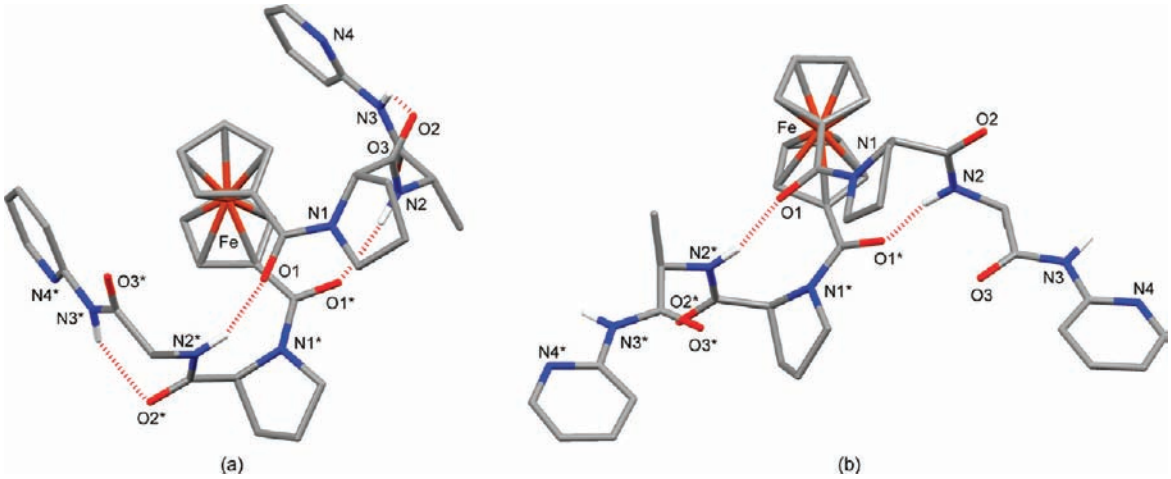


FIGURE 6. Molecular structures of (a) **5** and (b) **6**.

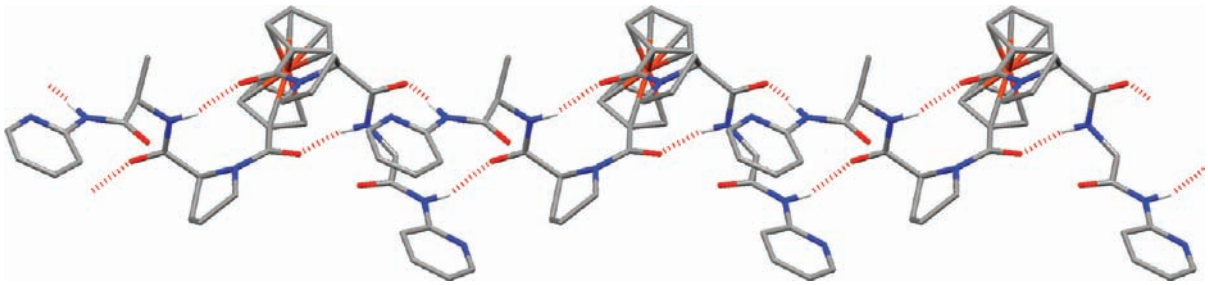


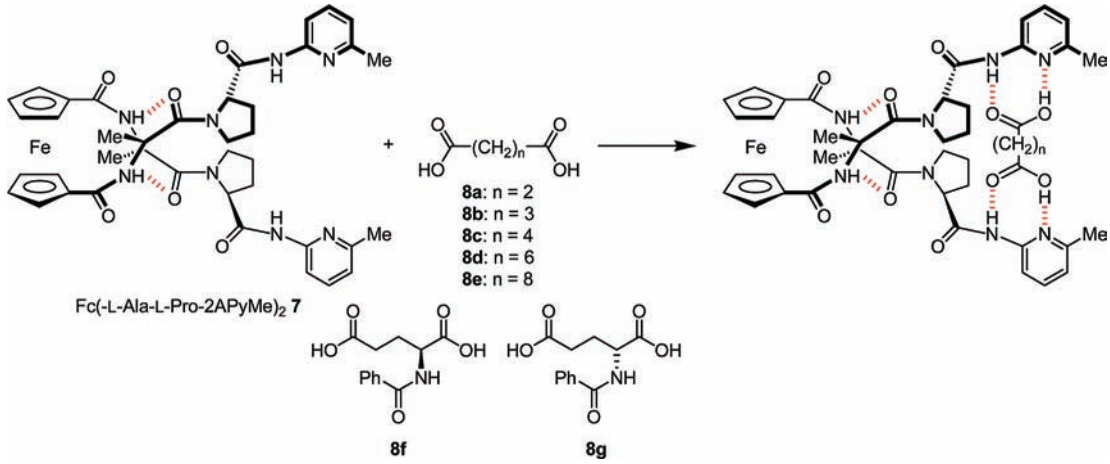
FIGURE 7. A self-assembly of **6** via the formation of a 14-membered intermolecularly hydrogen-bonded ring in the crystal packing.

ing the L-Pro-D-Ala-NH-2-Py dipeptide chains was produced. In the X-ray structure of **6**, the interchain intramolecular antiparallel β-sheet-like hydrogen bonds were observed between the NH of the alanine and the CO of the ferrocene unit attached to the opposite peptide chain (Figure 6b).[18] In contrast to **5**, the NH adjacent to the pyridyl moiety participated in an intermolecular hydrogen bond with the CO of the proline of the neighboring molecule to form a 14-membered intermolecularly hydrogen-bonded ring. In the crystal packing, each molecule is connected to two neighboring molecules (Figure 7).

The organization of host molecules by self-assembly is a useful strategy to form active receptors.[19] Metal-templated organization has been exploited to provide oriented binding sites, resulting in the construction of artificial receptors for molecular recognition.[20] Utilization of self-assembling properties of amino acids as observed in proteins, which are organized into well-defined three-dimensional structures, is considered to be a convenient approach to the desired receptors. On the other hand, ferrocenes have been focused on as an organometallic scaffold for molecular receptors.[21] Ferrocene−peptide bioconjugates have been demonstrated to recognize anions[22] and biomolecules.[23]

In the ferrocene−peptide bioconjugate **7** bearing the dipeptide chains L-Ala-L-Pro-NH-2-PyMe, the two amido pyridyl moieties as hydrogen bonding sites are well arranged for dicarboxylic acids by the chirality organization through two intramolecular hydrogen bondings.[24] In fact, the ferrocene−peptide bioconjugate **7** formed a 1:1 complex with a series of dicarboxylic acids **8**, wherein the highest association constant was observed with adipic acid (**8c**, $K_a = 2.1 \times 10^4$ M^{-1}) (Scheme 1). The binding space size of **7** can discriminate the size of dicarboxylic acids. Since an induced CD around the absorbance of the ferrocene function of **7** hardly changed upon addition of five molar equivalents of **8c**, the chirality organization through two intramolecular hydrogen bondings appears to be maintained in the recognition process to afford a rigid binding site for the selective recognition. Noteworthy is that benzoyl-L-glutamic acid (**8f**, $K_a = 5.5 \times 10^3$ M^{-1}) was bound approximately 15 times more tightly to **7** than benzoyl-D-glutamic acid (**8g**, $K_a = 3.7 \times 10^2$ M^{-1}). The chirality-organized binding site of **7** is capable of discriminating the chirality of guest molecules. The size-selective and chiral recognition of dicarboxylic acids was achieved by multipoint hydrogen bondings of the binding sites.

SCHEME 1. Binding of Dicarboxylic Acid to Ferrocene−Peptide Bioconjugate **7**



Hydrogen Bonding Properties of Monosubstituted Ferrocene−Peptide Bioconjugates

The utilization of self-assembling properties of short peptides, which possess chiral centers and hydrogen bonding sites, is considered to be a convenient strategy to construct molecular assemblies. Generally, an organized structure based on intramolecular interchain hydrogen bonding is not formed in the case of ferrocenes bearing only one peptide chain (Figure 8), but a network of intermolecular hydrogen bonds is expected to be formed in a solid state. The ferrocene−peptide bioconjugate **9** bearing one dipeptide chain of the homochiral sequence L-Ala-L-Pro-OEt exhibited intermolecular hydrogen bonding between the CO of the ferrocene unit and the NH of the alanine attached to another molecule, wherein two independent molecules exist in an asymmetric unit and are connected alternately to form an intermolecular hydrogen-bonding network, resulting in a left-handed helically ordered arrangement with one turn of 17.86 Å pitch height and 7.50 Å separation (Fe−Fe) between the closest ferrocene units (Figure 9).[14b]

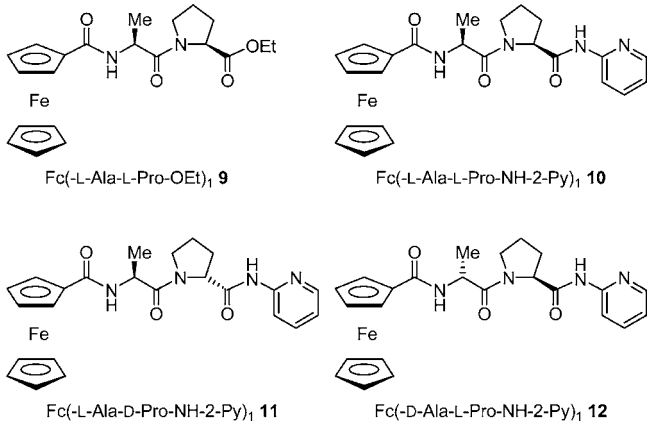


FIGURE 8. Ferrocene−peptide bioconjugates bearing one dipeptide chain.

Instead of intramolecular hydrogen bonding, an antiparallel hydrogen-bonded network was formed in a solid state of the ferrocene−peptide bioconjugate **10** bearing one dipeptide chain of the homochiral sequence L-Ala-L-Pro-NH-2-Py to create a highly organized assembly, wherein each molecule is connected to two neighboring molecules through NH (Ala)/N (pyridine of another molecule) and NH

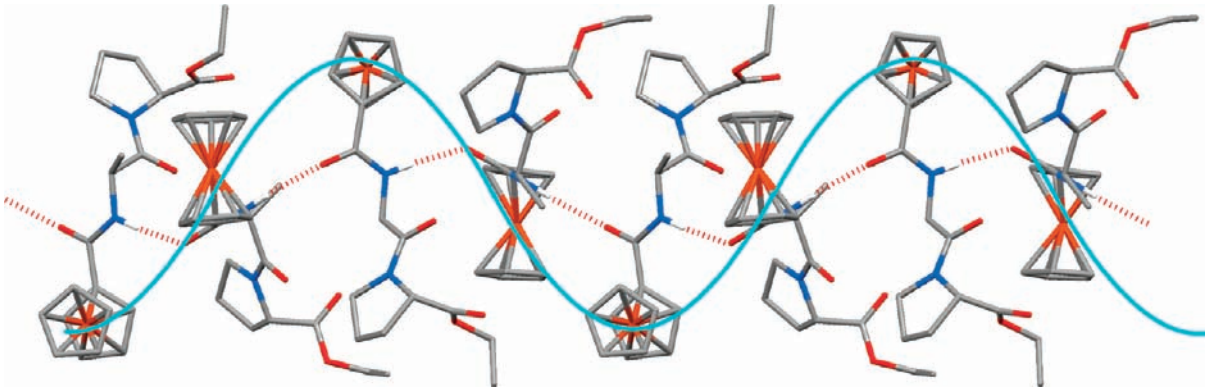


FIGURE 9. A portion of a layer containing the helical assembly of crystal packing of **9**.

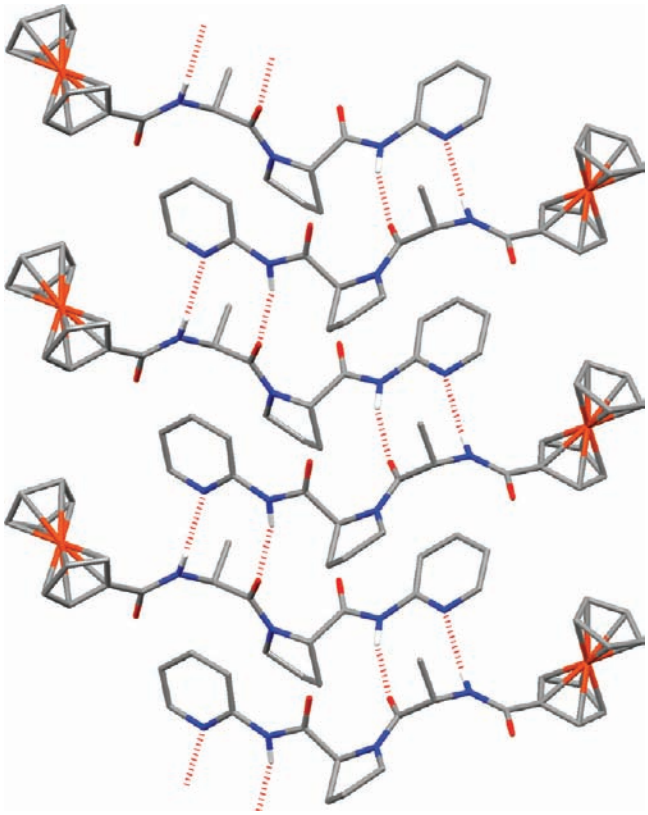


FIGURE 10. A portion of a layer containing the antiparallel arrangement of crystal packing of **10**.

(adjacent to pyridine unit of another molecule)/O (Ala) intermolecular hydrogen bonds forming a nine-membered intermolecularly hydrogen-bonded ring (Figure 10).[25] In contrast, the ferrocene−peptide bioconjugate **11** bearing one dipeptide chain of the heterochiral sequence L-Ala-D-Pro-NH-2-Py exhibited intermolecular hydrogen bonds, wherein two independent molecules exist in the asymmetric unit and are connected alternately to be packed in a left-handed helically ordered arrangement with one turn of 19.44 Å pitch height through a network of intermolecular hydrogen bonds, within which the distance between the closest ferrocene units is 6.95 Å (Fe−Fe) (Figure 11a).[16] Noteworthy is that an opposite helically ordered molecular assembly, a right-handed helically ordered arrangement, was formed in the crystal packing of the ferrocene−peptide bioconjugate **12** bearing one dipeptide chain of the heterochiral sequence D-Ala-L-Pro-NH-2-Py (Figure 11b).

The single-crystal X-ray structure determination of the ferrocene−peptide bioconjugate **13** bearing one dipeptide chain of the heterochiral sequence L-Ala-D-Pro-NH-4-Py revealed that the NH adjacent to the pyridyl moiety participates in an intramolecular hydrogen bonding with the CO adjacent to the ferrocene unit of the same peptide chain to nucleate a type II β-turn-like structure (Figure 12).[26] The creation of the β-turn mimic was achieved by utilizing the minimum-sized peptide chain. This chirality-organized structure is in sharp contrast to the crystal structure of **11**. The position of the pyridyl nitrogen is found to regulate the self-organization.

Stabilization of Chirality-Organized Ferrocene−Peptide Bioconjugates by Complexation

Metal ions have been known to exhibit a variety of properties in proteins, one of which is structural stabilization for biological function.[27] Metal ions also play a crucial role in the redox processes of proteins.[27] The incorporation of metal coordination sites into peptides has been investigated on the stabilization of secondary structures[28] and catalytic activities.[29] Phosphine-containing β-turn ligands are used in asymmetric catalysis.[29b,c]

The complexation with metal ions is envisioned to stabilize or regulate secondary structures of peptide chains. The ferrocene−peptide bioconjugate **14** bearing the dipeptide chains of the homochiral sequence L-Pro-L-Ala-NH-2-Py, which is characterized by chirality organization through two intramolecular interchain hydrogen bondings as observed with **1**, formed the 1:1 *trans* palladium complex **15** with $PdCl_2(MeCN)_2$ to stabilize the chirality conformational regulation in both solution and solid states (Figure 13).[30] The greater downfield shifting of the alanine N−H resonance was observed in the ^{1}H NMR spectrum of **15** in $CDCl_3$ as compared with that of **14**, indicating that complexation strengthens the intramolecular hydrogen bonding. The single-crystal X-ray structure determination of **15** confirmed the pseudohelical conformation through palladium coordination and chirality organization based on the preservation of the intramolecular interchain hydrogen bonds as depicted in Figure 14.[30]

Complexation of the ferrocene−peptide bioconjugate **10** bearing one dipeptide chain of the homochiral sequence L-Ala-L-Pro-NH-2-Py with 0.5 equiv of $PdCl_2(MeCN)_2$ afforded the 2:1 *trans* palladium complex **16**.[25] Two ferrocenoyl dipeptide strands of the palladium complex **16** are able to rotate with respect to each other about the palladium center by the ball-bearing motion of two pyridyl rings (Scheme 2). The rotational barrier of the two pyridyl rings in the palladium(II) complex **16** was obtained as 10.1 kcal mol^{-1}.

The ferrocene−peptide bioconjugate **11** bearing one dipeptide chain of the heterochiral sequence L-Ala-D-Pro-NH-2-Py also formed the 2:1 *trans* palladium complex **17**.[31] The chirality-organized structure of the palladium complex **17** is present in a pseudohelical conformation through coordina-

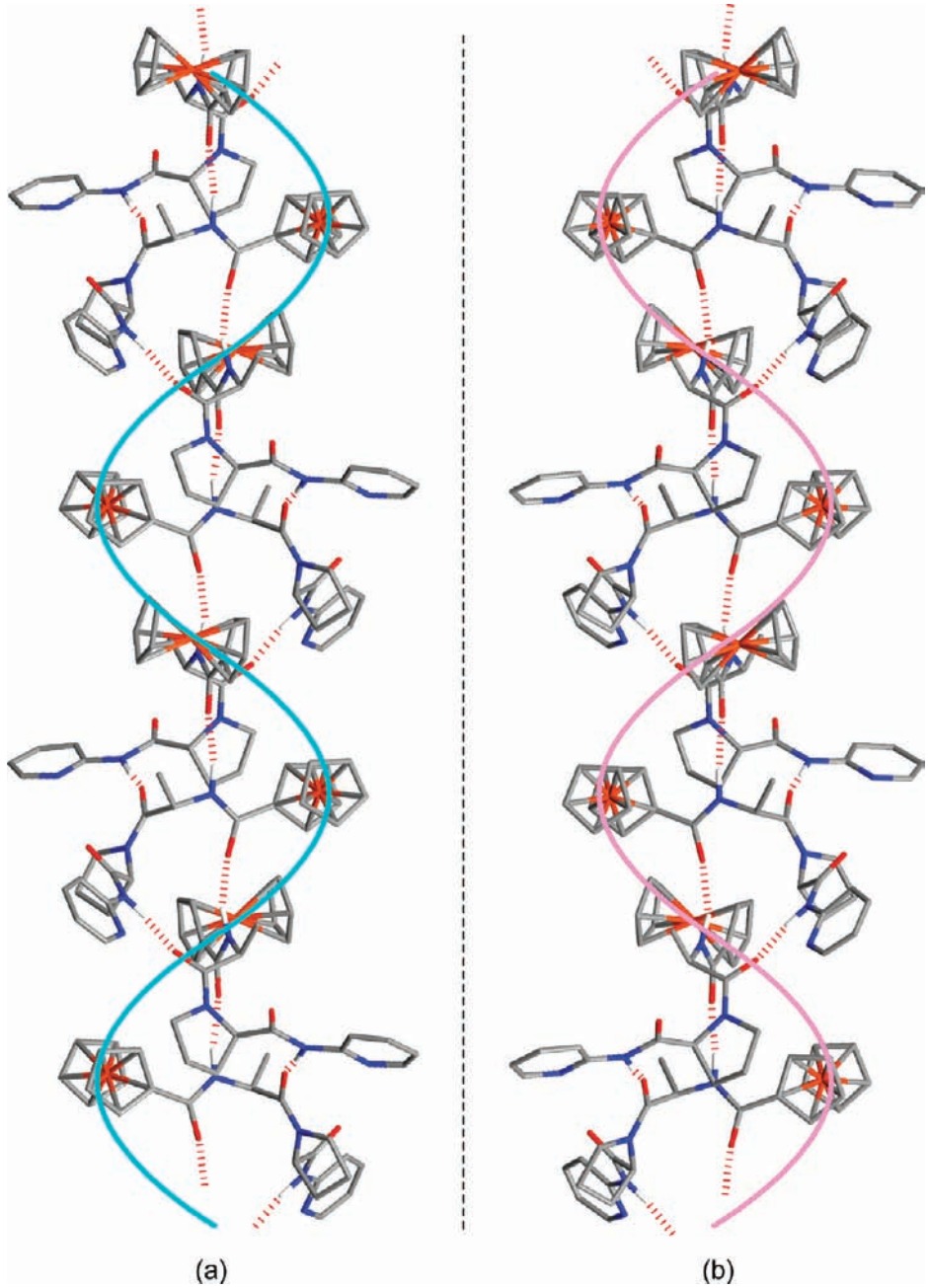


FIGURE 11. A portion of a layer containing the helical assembly of crystal packing of (a) **11** and (b) **12**.

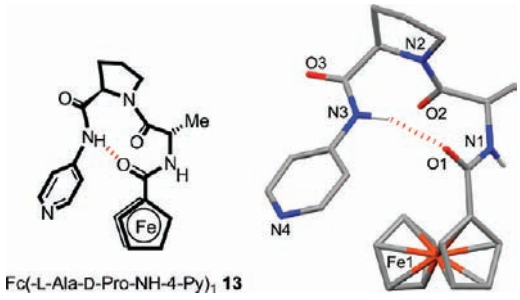


FIGURE 12. Molecular structure of **13**.

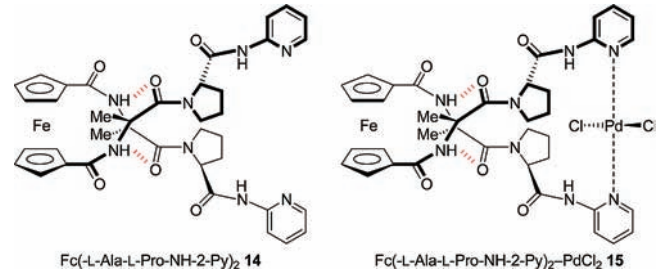


FIGURE 13. Ferrocene–peptide bioconjugate **14** and the 1:1 *trans* palladium complex **15**.

tion to palladium and chirality organization through NH (Ala)/Cl, NH (adjacent to pyridine unit)/O (Ala), and NH (adjacent to pyridine unit of another molecule)/O (Ala) intramolecular hydrogen bonds, in which two ferrocene–dipeptide conju-

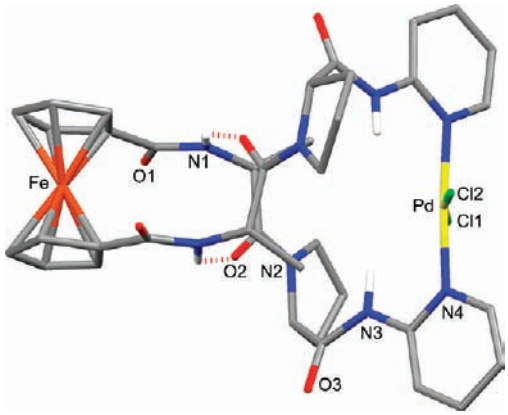
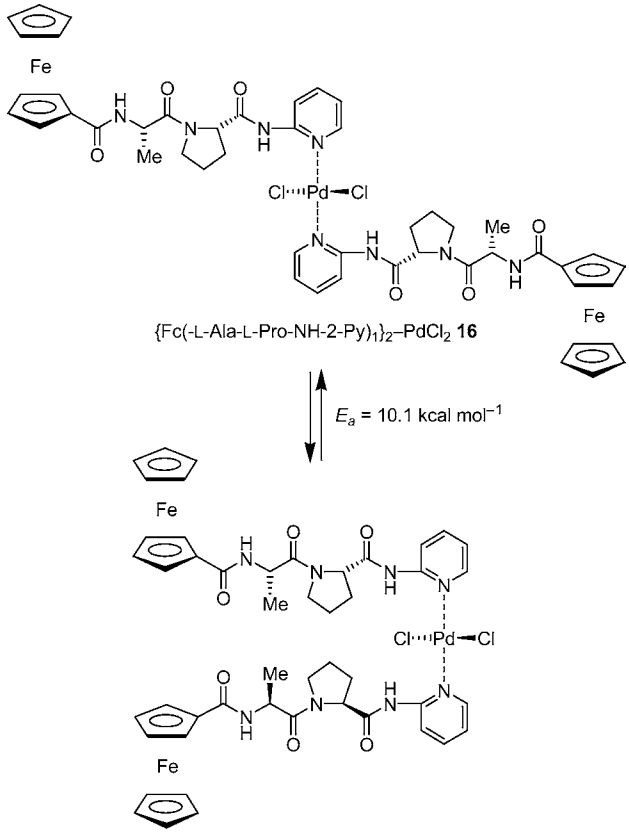


FIGURE 14. Molecular structure of **15**.

SCHEME 2. Rotation of the 2:1 *trans* Palladium Complex **16** about the Palladium Center

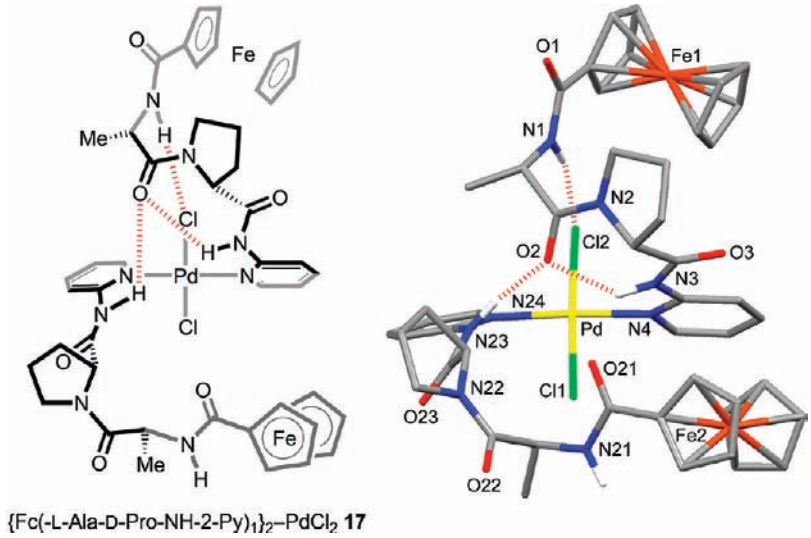


gates coordinate to the palladium center unsymmetrically (Figure 15). It should be noted that the NH adjacent to the pyridyl moiety of one peptide chain participates in intramolecular hydrogen bonding with the CO of the alanine of the same peptide chain to nucleate a γ-turn-like structure. This chirality-organized structure is in sharp contrast to the crystal structure of **11**, in which an intermolecular hydrogen bonding network is observed instead of the intramolecular hydrogen bonds to induce a helically ordered molecular assembly (Figure 11a).[16] These findings suggest that the complexation with $PdCl_2(MeCN)_2$ induces the γ-turn-like structural regulation of the dipeptide chain through intramolecular hydrogen bonding in the crystal structure.

Transition metal-directed assembly is regarded as a useful approach to a highly ordered molecular assembly. To assemble the ferrocene−peptide bioconjugates, a metal-directed strategy is embarked upon by using $[Pd(MeCN)_4](BF_4)_2$, which has four binding sites, as a metal binder. The complexation of the ferrocene−peptide bioconjugate **13** with 0.25 equiv of $[Pd(MeCN)_4](BF_4)_2$ in acetonitrile led to a quantitative formation of the 4:1 palladium complex **18**.[26] The molecular structure of **18** confirmed that the four ferrocene−peptide bioconjugates are assembled around a palladium center in the same direction to form a chiral pocket surrounded by the dipeptide chains, wherein one BF_4^- counteranion is accommodated (Figure 16). The binding of anions has been of considerable interest because ion pairing effects are known to play an important role in the reactivity and catalytic properties of metal complexes.[32] Another noteworthy feature of the palladium complex **18** is that a β-turn-like structure through intramolecular hydrogen bonding is preserved in each ferrocene−dipeptide conjugate despite complexation, in which a type II β-turn-like structure of one ferrocene−dipeptide conjugate changes to an intermediate between a type I′ and type III′ β-turn-like structures.

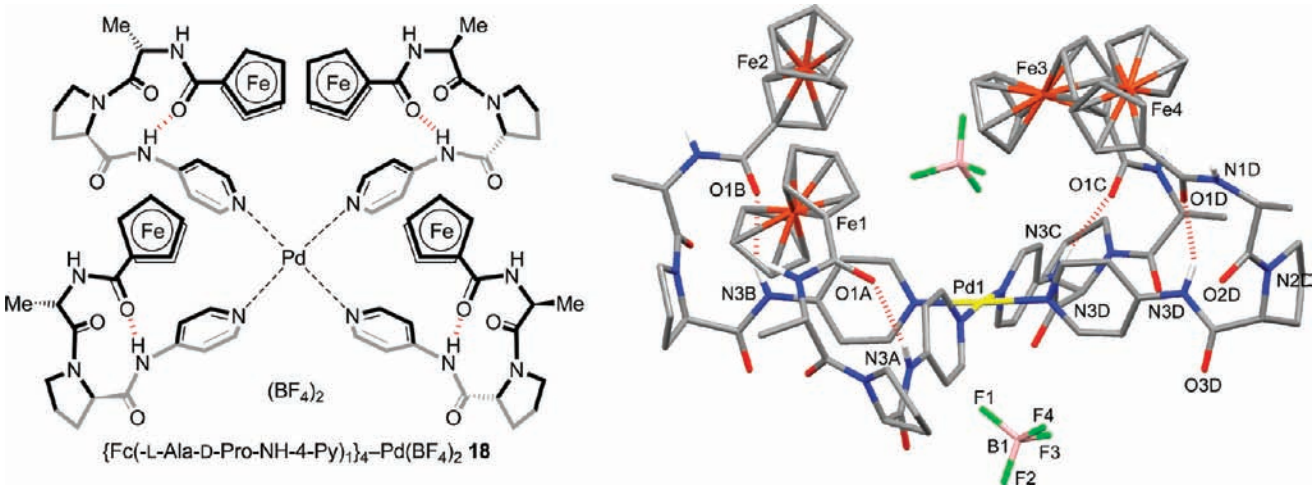
Summary and Outlook

Ferrocenes are recognized as a potential organometallic scaffold that is appropriate for hydrogen bonding of the attached peptide strands as observed in β-sheets. A variety of ferrocene−peptide bioconjugates have been designed to induce highly ordered structures of peptides. The ferrocene serves as a reliable organometallic scaffold for the construction of a chirality-organized structure via intramolecular hydrogen bonding, wherein the attached peptide strands are regulated in the appropriate dimensions. Conformational enantiomerization, through chirality organization, has been achieved by restricting the torsional twist around the Cp(centroid)−Fe−Cp(centroid) axis and the C(ipso)−CO bond through the intramolecular hydrogen bonds between the dipeptide chains. The configuration and sequence of the amino acids were found to play an important role in the construction of the chirality-organized bioinspired systems under controlled hydrogen bonds. The combination of the ferrocene scaffold as a central reverse-turn unit with the L-alanyl-D-proline heterochiral sequence as a dipeptide unit has been performed to induce the antiparallel β-sheet-like and type II β-turn-like structures simultaneously. In contrast, the combi-



{Fc(-L-Ala-D-Pro-NH-2-Py)$_1$}$_2$–PdCl$_2$ **17**

FIGURE 15. Molecular structure of **17**.



{Fc(-L-Ala-D-Pro-NH-4-Py)$_1$}$_4$–Pd(BF$_4$)$_2$ **18**

FIGURE 16. Molecular structure of **18**.

nation with the L-prolyl-L-alanine homochiral sequence as a dipeptide unit has been found to induce the simultaneous formation of the inverse γ-turn-like and antiparallel β-sheet-like structures. The complexation of the ferrocene–peptide bioconjugates with palladium(II) compounds has been demonstrated not only to stabilize the chirality conformational regulation and but also to induce conformational regulation of the dipeptide chain through complexation and chirality organization based on intramolecular hydrogen bonding. These chemical models of protein secondary structures afford fundamental insight into the factors affecting protein structure and stability. A further noteworthy feature of the ferrocene–peptide bioconjugates is their strong tendency to self-assemble through contribution of all available hydrogen bonding donors in a solid state. An assembling of the chirality-organized ferrocene–peptide bioconjugates has also been achieved by metal-directed assembly. The architectural control of molecular assemblies utilizing peptide chains, which possess chiral centers and hydrogen bonding sites, is envisioned to be a useful approach to artificial highly ordered systems.

This bioorganometallic chemistry is envisioned to provide not only a peptidomimetic basis for protein folding but also pharmacologically useful compounds, artificial receptors, asymmetric catalysts, and new materials with functional properties.

We thank all of our talented co-workers for their great contributions reported in this Account. Financial support from Japan Science and Technology Agency and the Japan Society for the Promotion of Science is gratefully appreciated.

BIOGRAPHICAL INFORMATION

Toshiyuki Moriuchi received his bachelor's degree in 1991 and his doctoral degree in 1995, both from Osaka University. He

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Toshikazu Hirao was graduated from Kyoto University in 1973, where he obtained his doctorate in 1978. He became Assistant Professor at Osaka University and was a postdoctoral fellow at the University of Wisconsin with Professor Barry M. Trost (1981−1982). Dr. Hirao was promoted to Associate Professor in 1992 and Professor in 1994. He has been involved in the development of synthetic methodology and received the Chemical Society of Japan Award for Young Chemists in 1984. Dr. Hirao's current research interests lie in the area of the construction of an efficient system for electron transfer, which allows the development of new methods in organic synthesis including radical reactions, and novel redox-active systems consisting of transition metal complexes or π-conjugated polymers or oligomers. These areas of research are correlated to the development of artificial biochemical systems. He received the Vanadius Award and the Award for Outstanding Achievements in Bioorganometallic Chemistry in 2008. He was a director and is a vice-president of the Chemical Society of Japan. He served as a head of the research project entitled "Construction of Dynamic Redox Systems Based on Nano-Space Control", Grant-in Aid for Scientific Research on Priority Areas, supported by the Ministry of Education, Science, Sports and Culture, Japan (2001−2003).

FOOTNOTES

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REFERENCES

1 (a) Braga, D.; Grepioni, F.; Desiraju, G. R. Crystal Engineering and Organometallic Architecture. *Chem. Rev.* **1998**, *98*, 1375–1406. (b) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. Artificial Molecular Machines. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348–3391. (c) Swiegers, G. F.; Malefetse, T. J. New Self-Assembled Structural Motifs in Coordination Chemistry. *Chem. Rev.* **2000**, *100*, 3483–3538.

2 Jeffrey, G. A. *An Introduction to Hydrogen Bonding*, 1st ed.; Oxford University Press: New York, 1997.

3 (a) Conn, M. M.; Rebek, J., Jr. Self-Assembling Capsules. *Chem. Rev.* **1997**, *97*, 1647–1668. (b) Archer, E. A.; Gong, H.; Krische, M. J. Hydrogen Bonding in Noncovalent Synthesis: Selectivity and the Directed Organization of Molecular Strands. *Tetrahedron* **2001**, *57*, 1139–1159. (c) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. Noncovalent Synthesis Using Hydrogen Bonding. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426.

4 (a) Kyte, J. *Structure in Protein Chemistry*; Garland: New York, 1995. (b) Branden, C.; Tooze, J. *Introduction to Protein Structure*, 2nd ed.; Garland: New York, 1998.

5 (a) Feigel, M. J. 2,8-Dimethyl-4-(carboxymethyl)-6-(aminomethyl)phenoxathiin S-Dioxide: An Organic Substitute for the β-Turn in Peptides. *J. Am. Chem. Soc.* **1986**, *108*, 181–182. (b) Brandmeier, V.; Feigel, M.; Bremer, M. 2′-Aminomethylbiphenyl-2-carboxylic Acid as Component of a Cyclopeptide; Crystal Structure and Conformation in Solution. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 486–488.

6 (a) Kemp, D. S.; Bowen, B. R. Synthesis of Peptide-Functionalized Diacylaminoepindolidiones as Templates for β-Sheet Formation. *Tetrahedron Lett.* **1988**, *29*, 5077–5080. (b) Kemp, D. S.; Bowen, B. R.; Muendel, C. C. Synthesis and Conformational Analysis of Epindolidione-Derived Peptide Models for β-Sheet Formation. *J. Org. Chem.* **1990**, *55*, 4650–4657.

7 (a) Díaz, H.; Kelly, J. W. The Synthesis of Dibenzofuran Based Diacids and Amino Acids Designed to Nucleate Parallel and Antiparallel β-Sheet Formation. *Tetrahedron Lett.* **1991**, *32*, 5725–5728. (b) Díaz, H.; Espina, J. R.; Kelly, J. W. A Dibenzofuran-Based Amino Acid Designed to Nucleate Antiparallel β-Sheet Structure: Evidence for Intramolecular Hydrogen-Bond Formation. *J. Am. Chem. Soc.* **1992**, *114*, 8316–8318. (c) Tsang, K. Y.; Díaz, H.; Graciani, N.; Kelly, J. W. Hydrophobic Cluster Formation is Necessary for Dibenzofuran-Based Amino Acids to Function as β-Sheet Nucleators. *J. Am. Chem. Soc.* **1994**, *116*, 3988–4005.

8 (a) Nowick, J. S.; Powell, N. A.; Martinez, E. J.; Smith, E. M.; Noronha, G. Molecular Scaffolds I: Intramolecular Hydrogen Bonding in a Family of Di- and Triureas. *J. Org. Chem.* **1992**, *57*, 3763–3765. (b) Nowick, J. S.; Holmes, D. L.; Mackin, G.; Noronha, G.; Shaka, A. J.; Smith, E. M. An Artificial β-Sheet Comprising a Molecular Scaffold, a β-Strand Mimic, and a Peptide Strand. *J. Am. Chem. Soc.* **1996**, *118*, 2764–2765. (c) Nowick, J. S.; Smith, E. M.; Pairish, M. Artificial β-Sheets. *Chem. Soc. Rev.* **1996**, *25*, 401–415. (d) Nowick, J. S. Chemical Models of Protein β-Sheets. *Acc. Chem. Res.* **1999**, *32*, 287–296. (e) Nowick, J. S.; Tsai, J. H.; Bui, Q.-C. D.; Maitra, S. A Chemical Model of a Protein β-Sheet Dimer. *J. Am. Chem. Soc.* **1999**, *121*, 8409–8410. (f) Moriuchi, T.; Tamura, T.; Hirao, T. Self-Assembly of Dipeptidyl Ureas: A New Class of Hydrogen-Bonded Molecular Duplexes. *J. Am. Chem. Soc.* **2002**, *124*, 9356–9357.

9 (a) Jones, I. G.; Jones, W.; North, M. Conformational Analysis of Peptides and Pseudopeptides Incorporating an *endo*-(2*S*,3*R*)-Norborn-5-ene Residue as a Turn Inducer. *J. Org. Chem.* **1998**, *63*, 1505–1513. (b) Ranganathan, D.; Haridas, V.; Kurur, S.; Thomas, A.; Madhusudanan, K. P.; Nagaraj, R.; Kunwar, A. C.; Sarma, A. V. S.; Karle, I. L. Demonstration of *endo-cis*-(2*S*,3*R*)-Bicyclo[2.2.1]hept-5-en-2,3-dicarbonyl Unit as a Reverse-Turn Scaffold and Nucleator of Two-Stranded Parallel β-Sheets: Design, Synthesis, Crystal Structure, and Self-Assembling Properties of Norborneno Peptide Analogues. *J. Am. Chem. Soc.* **1998**, *120*, 8448–8460. (c) Hackenberger, C. P. R.; Schiffers, I.; Runsink, J.; Bolm, C. General Synthesis of Unsymmetrical Norbornane Scaffolds as Inducers for Hydrogen Bond Interactions in Peptides. *J. Org. Chem.* **2004**, *69*, 739–743.

10 (a) Jaouen, G.; Vessiéres, A.; Butler, I. S. Bioorganometallic Chemistry: A Future Direction forTransition Metal Organometallic Chemistry. *Acc. Chem. Res.* **1993**, *26*, 361–369. (b) Severin, R.; Bergs, R.; Beck, W. Bioorganometallic Chemistry - Transition Metal Complexes with α-Amino Acids and Peptides. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634–1654. (c) Jaouen, G., Ed. Bioorganometallic Chemistry special issue. *J. Organomet. Chem.* **1999**, *589*, 1−126. (d) Fish, R. H.; Jaouen, G. Bioorganometallic Chemistry: Structural Diversity of Organometallic Complexes with Bioligands and Molecular Recognition Studies of Several Supramolecular Hosts with Biomolecules, Alkali-Metal Ions, and Organometallic Pharmaceuticals. *Organometallics* **2003**, *22*, 2166–2177. (e) Jaouen, G., Ed. *Bioorganometallics; Biomolecules, Labeling, Medicine*; Wiley-VCH, Weinheim, Germany, 2006 and references therein.

11 Togni, A.; Hayashi, T. *Ferrocenes*; Wiley-VCH, Weinheim, Germany, 1995.

12 (a) Schlögl, K. Über Ferrocen-Aminosäuren und verwandte Verbindungen. *Monatsh. Chem.* **1957**, *88*, 601–621. (b) Hauser, C. R.; Lindsay, J. K. Certain Alkylations with the Methiodide of *N*,*N*-Dimethylaminomethylferrocene. Synthesis of an α-Amino Acid Having the Ferrocene Group. *J. Org. Chem.* **1957**, *22*, 1246–1247. (c) Osgerby, J. M.; Pauson, P. L. Ferrocene Derivatives. Part VI. DL-Ferrocenylalanine. *J. Chem. Soc.* **1958**, 656–660.

13 (a) Moriuchi, T.; Hirao, T. Highly Ordered Structures of Peptides by Using Molecular Scaffolds. *Chem. Soc. Rev.* **2004**, *33*, 294–301. (b) van Staveren, D. R.; Metzler-Nolte, N. Bioorganometallic Chemistry of Ferrocene. *Chem. Rev.* **2004**, *104*, 5931–5986. (c) Kirin, S. I.; Kraatz, H.-B.; Metzler-Nolte, N. Systematizing Structural Motifs and Nomenclature in 1,*n*′-Disubstituted Ferrocene Peptides. *Chem. Soc. Rev.* **2006**, *35*, 348–354. (d) Moriuchi, T.; Hirao, T. Ferrocene-Peptide Bioconjugates. In *Bioorganometallic Chemistry*; Simonneaux, G., Ed., Topics in Organometallic Chemistry, Vol. 17; Springer-Verlag: Berlin, 2006; pp 143−175. (e) Salmain, M.; Metzler-Nolte, N. Bioorganometallic Chemistry of Ferrocene. In *Ferrocenes*; Stepnicka, P., Ed.; John Wiley & Sons: Chichester, U.K., 2008; pp 499−639. (f) Lataifeh, A.; Beheshti, S.; Kraatz, H.-B. Designer Peptides: Attempt to Control Peptide Structure by Exploiting Ferrocene as a Scaffold. *Eur. J. Inorg. Chem.* **2009**, 3205–3218, and references threrein.

14 (a) Nomoto, A.; Moriuchi, T.; Yamazaki, S.; Ogawa, A.; Hirao, T. A Highly Ordered Ferrocene System Regulated by Podand Peptide Chains. *Chem. Commun.* **1998**, 1963–1964. (b) Moriuchi, T.; Nomoto, A.; Yoshida, K.; Hirao, T. Characterization of Ferrocene Derivatives Bearing Podand Dipeptide Chains (-L-Ala-L-Pro-OR). *J. Organomet. Chem.* **1999**, *589*, 50–58. (c) Moriuchi, T.; Nomoto, A.; Yoshida, K.; Ogawa, A.; Hirao, T. Chirality Organization of Ferrocenes Bearing Podand Dipeptide Chains: Synthesis and Structural Characterization. *J. Am. Chem. Soc.* **2001**, *123*, 68–75.

15 Cerichelli, G.; Floris, B.; Ortaggi, G. Stereochemical Consequences of the Intramolecular Hydrogen Bond in 1′-Acetyl-1-α-hydroxyethyl- and 1,1′-Bis(α-hydroxyethyl)ferrocenes. *J. Organomet. Chem.* **1974**, *76*, 73–79.

16 Moriuchi, T.; Nagai, T.; Hirao, T. Chirality Organization of Ferrocenes Bearing Dipeptide Chains of Heterochiral Sequence. *Org. Lett.* **2005**, *7*, 5265–5268.

17 (a) Kirin, S. I.; Wissenbach, D.; Metzler-Nolte, N. Unsymmetrical 1,*n*′-Disubstituted Ferrocenoyl Peptides: Convenient One Pot Synthesis and Solution Structures by CD

and NMR Spectroscopy. *New J. Chem.* **2005**, *29*, 1168–1173. (b) Heinze, K.; Beckmann, M. Conformational Analysis of Chiral Ferrocene-Peptides. *Eur. J. Inorg. Chem.* **2005**, 3450–3457.

18 Moriuchi, T.; Nagai, T.; Hirao, T. Induction of γ-Turn-Like Structure in Ferrocene Bearing Dipeptide Chains via Conformational Control. *Org. Lett.* **2006**, *8*, 31–34.

19 Rebek, J., Jr. Simultaneous Encapsulation: Molecules Held at Close Range. *Angew. Chem., Int. Ed.* **2005**, *44*, 2068–2078.

20 (a) Linton, B.; Hamilton, A. D. Formation of Artificial Receptors by Metal-Templated Self-Assembly. *Chem. Rev.* **1997**, *97*, 1669–1680. (b) Leininger, S.; Olenyuk, B.; Stang, P. J. Self-Assembly of Discrete Cyclic Nanostructures Mediated by Transition Metals. *Chem. Rev.* **2000**, *100*, 853–908. (c) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. Selective Molecular Recognition, C−H Bond Activation, and Catalysis in Nanoscale Reaction Vessels. *Acc. Chem. Res.* **2005**, *38*, 351–360. (d) Kitagawa, S.; Matsuda, R. Chemistry of Coordination Space of Porous Coordination Polymers. *Coord. Chem. Rev.* **2007**, *251*, 2490–2509. (e) Dalgarno, S. J.; Power, N. P.; Atwood, J. L. Metallo-Supramolecular Capsules. *Coord. Chem. Rev.* **2008**, *252*, 825–841. (f) Kumar, A.; Sun, S.-S.; Lees, A. J. Directed Assembly Metallocyclic Supramolecular Systems for Molecular Recognition and Chemical Sensing. *Coord. Chem. Rev.* **2008**, *252*, 922–939. (g) Uemura, T.; Yanai, N.; Kitagawa, S. Polymerization Reactions in Porous Coordination Polymers. *Chem. Soc. Rev.* **2009**, *38*, 1228–1236. (h) Klosterman, J. K.; Yamauchi, Y.; Fujita, M. Engineering Discrete Stacks of Aromatic Molecules. *Chem. Soc. Rev.* **2009**, *38*, 1714–1725. (i) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. Functional Molecular Flasks: New Properties and Reactions within Discrete, Self-Assembled Hosts. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418–3438.

21 (a) Saji, T.; Kinoshita, I. Electrochemical Ion Transport with Ferrocene Functionalized Crown Ether. *J. Chem. Soc., Chem. Commun.* **1986**, 716–717. (b) Medina, J. C.; Li, C.; Bott, S. G.; Atwood, J. L.; Gokel, G. W. A Molecular Receptor Based on the Ferrocene System: Selective Complexation Using Atomic Ball Bearings. *J. Am. Chem. Soc.* **1991**, *113*, 366–367. (c) Medina, J. C.; Goodnow, T. T.; Rojas, M. T.; Atwood, J. L.; Lynn, B. C.; Kaifer, A. E.; Gokel, G. W. Ferrocenyl Iron as a Donor Group for Complexed Silver in Ferrocenyldimethyl[2.2]cryptand: A Redox-Switched Receptor Effective in Water. *J. Am. Chem. Soc.* **1992**, *114*, 10583–10595. (d) Beer, P. D. Anion Selective Recognition and Optical/Electrochemical Sensing by Novel Transition-Metal Receptor Systems. *Chem. Commun.* **1996**, 689–696. (e) Carr, J. D.; Lambert, L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A.; Tucker, J. H. R. Novel Electrochemical Sensors for Neutral Molecules. *Chem. Commun.* **1997**, 1649–1650.

22 (a) Gallagher, J. F.; Kenny, P. T. M.; Sheehy, M. J. Electrochemical Anion Recognition by Redox-Responsive Unnatural Amino Acid Derivatives; the X-ray Crystal Structure of N-ferrocenoyl Glycine Methyl Ester, (η^5-C_5H_5)Fe(η^5-C_5H_4)CONHCH$_2$COOMe. *Inorg. Chem. Commun.* **1999**, *2*, 200–202. (b) Gallagher, J. F.; Kenny, P. T. M.; Sheehy, M. J. Synthesis and Electrochemical Anion Recognition by Novel Redox-Responsive Ferrocenoyl Dipeptide Ester Derivatives; 1H NMR Anion Complexation Studies. *Inorg. Chem. Commun.* **1999**, *2*, 327–330.

23 (a) Georgopoulou, A. S.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J.; Horrocks, B. R.; Houlton, A. Bifunctional Ferrocene Derivatives for Molecular Recognition of DNA Duplexes. *J. Chem. Soc., Dalton Trans.* **2000**, 2969–2974. (b) Plumb, K.; Kraatz, H.-B. Interaction of a Ferrocenoyl-Modified Peptide with Papain: Toward Protein-Sensitive Electrochemical Probes. *Bioconjugate. Chem.* **2003**, *14*, 601–606. (c) Miklán, Z.; Szabó, R.; Zsoldos-Mády, V.; Reményi, J.; Bánóczi, Z.; Hudecz, F. New Ferrocene Containing Peptide Conjugates: Synthesis and Effect on Human Leukemia (HL-60) Cells. *Biopolymers* **2007**, *88*, 108–114. (d) Mahmoud, K. A.; Kraatz, H.-B. A Bioorganometallic Approach for the Electrochemical Detection of Proteins: A Study on the Interaction of Ferrocene-Peptide Conjugates with Papain in Solution and on Au Surfaces. *Chem.—Eur. J.* **2007**, *13*, 5885–5895. (e) Kerman, K.; Kraatz, H.-B. Electrochemical Probing of HIV Enzymes Using Ferrocene-Conjugated Peptides on Surfaces. *Analyst* **2009**, *134*, 2400–2404.

24 Moriuchi, T.; Yoshida, K.; Hirao, T. Chirality-Organized Ferrocene Receptor Bearing Podand Dipeptide Chains (-L-Ala-L-Pro-NHPyMe) for the Selective Recognition of Dicarboxylic Acids. *Org. Lett.* **2003**, *5*, 4285–4288.

25 Moriuchi, T.; Yoshida, K.; Hirao, T. Structural Characterization and Complexation Behavior of Ferrocene Bearing Dipeptide Chain (-L-Ala-L-Pro-NHPy). *J. Organomet. Chem.* **2001**, *637−639*, 75–79.

26 Moriuchi, T.; Fujiwara, T.; Hirao, T. β-Turn-Structure-Assembled Palladium Complexes by Complexation-Induced Self-Organization of Ferrocene-Dipeptide Conjugates. *Dalton Trans.* **2009**, 4286–4288.

27 (a) Anfinsen, C. B.; Edsall, J. T.; Richards, F. M.; Eisenberg, D. S. *Advances in Protein Chemistry*; Academic Press, New York, 1991. (b) Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*; Wiley, New York, 1994.

28 (a) Ghadiri, M. R.; Choi, C. Secondary Structure Nucleation in Peptides. Transition Metal Ion Stabilized α-Helices. *J. Am. Chem. Soc.* **1990**, *112*, 1630–1632. (b) Handel, T.; DeGrado, W. F. De Novo Design of a Zn^{2+}-Binding Protein. *J. Am. Chem. Soc.* **1990**, *112*, 6710–6711. (c) Ruan, F.; Chen, Y.; Hopkins, P. B. Metal Ion-Enhanced Helicity in Synthetic Peptides Containing Unnatural, Metal-Ligating Residues. *J. Am. Chem. Soc.* **1990**, *112*, 9403–9404. (d) Schneider, J. P.; Kelly, J. W. Synthesis and Efficacy of Square Planar Copper Complexes Designed to Nucleate β-Sheet Structure. *J. Am. Chem. Soc.* **1995**, *117*, 2533–2546. (e) Gilbertson, S. R.; Pawlick, R. V. Synthesis of Thiophosphoryl Derivatives of Proline: Building Blocks for Phosphanyl-Substituted Peptides with β-Turns. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 902–904.

29 (a) Merkle, D. L.; Schmidt, M. H.; Berg, J. M. Design and Characterization of a Ligand-Binding Metallopeptide. *J. Am. Chem. Soc.* **1991**, *113*, 5450–5451. (b) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. Asymmetric Catalysis with Libraries of Palladium β-Turn Phosphine Complexes. *J. Am. Chem. Soc.* **2000**, *122*, 6522–6523. (c) Agarkov, A.; Greenfield, S. J.; Ohishi, T.; Collibee, S. E.; Gilbertson, S. R. Catalysis with Phosphine-Containing Amino Acids in Various "Turn" Motifs. *J. Org. Chem.* **2004**, *69*, 8077–8085.

30 Moriuchi, T.; Yoshida, K.; Hirao, T. Complexation Stabilized Conformational Regulation of Ferrocene Bearing Podand Dipeptide Chains (-L-Ala-L-Pro-NHPy. *Organometallics* **2001**, *20*, 3101–3105.

31 Moriuchi, T.; Fujiwara, T.; Hirao, T. Complexation-Induced Conformational Regulation of Ferrocene-Dipeptide Conjugates to Nucleate γ-Turn-Like Structure. *J. Organomet. Chem.* **2007**, *692*, 1353–1357.

32 Macchioni, A. Ion Pairing in Transition-Metal Organometallic Chemistry. *Chem. Rev.* **2005**, *105*, 2039–2074.