Review

Chirality Induction in Bioorganometallic Conjugates

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Abstract: Considerable attention has been given to the research field of bioorganometallic chemistry, which is a hybrid chemistry field between biology and organometallic chemistry. The introduction of biomolecules, which have hydrogen bonding sites and chiral centers, into organometallic compounds is a promising strategy to construct chirality-organized bioorganometallic conjugates. This feature paper sketches an outline of induction of helical chirality into bioorganometallic conjugates by the control of a torsional twist of the organometallic moiety. Topics covered included control of the helical chirality of $1,n'$-disubstituted ferrocene moieties in ferrocene-dipeptide conjugates, and the chirality induction of the Au(I)–Au(I) axis in the dinuclear organogold(I)-uracil conjugates.

Keywords: chirality induction; helical chirality; bioorganometallic conjugate; dipeptide; nucleobase; ferrocene; organogold(I); self-assembly; hydrogen bond; Au(I)–Au(I) interaction

1. Introduction

Highly-organized structures as observed in proteins, enzymes, and DNA are created by self-assembling of biomolecules such as amino acids, peptides, and nucleobases, wherein hydrogen bonding [1] plays a crucial role in regulating and modulating the organized structures and functional properties. α-Helices, β-sheets, and β-turns, which are formed by complementary hydrogen bonding, are important secondary structures in protein folding [2,3]. The double helical DNA is formed by adenine-thymine and guanine-cytosine complementary base pairing based on hydrogen bonds [4]. In the last two decades, the research field of bioorganometallic chemistry, which is a hybrid chemistry between biology and organometallic chemistry, has been drawing much attention. A great deal of effort has been made on conjugation of organometallic compounds with biomolecules, such as amino acids, peptides, and nucleobases [5–15]. Ferrocene (Fc) is an organometallic compound with reversible redox properties and two rotatory coplanar cyclopentadienyl (Cp) rings (Figure 1) [16]. The inter-ring distance of about 3.3 Å in ferrocene is appropriate for hydrogen bonding between attached peptide strands on two Cp rings. In the $1,n'$-disubstituted ferrocene, *P*- and *M*-helical conformations, which are interconvertible, based on the presence of a torsional twist about the Cp(centroid)–Fe–Cp(centroid) axis are possible as shown in Figure 2 [17]. The introduction of peptide strands, which have hydrogen bonding sites and chiral centers, into a ferrocene unit as an organometallic scaffold is envisioned to be a potential approach to study the hydrogen bonding ability of introduced peptide strands and construct chirality-organized bioorganometallic conjugates. On the other hand, a d^{10}–d^{10} closed shell aurophilic bonding interaction are known to induce the aggregation of gold(I) compounds [18–20]. The presence of a torsional twist about the Au(I)–Au(I)

axis allows for the existence of the conformational enantiomers in the dinuclear gold(I) compounds with bridging diphosphine ligands as depicted in Figure 3. Rational arrangement of nucleobases by using Au(I)–Au(I) interaction is a convenient approach to control the organized structure of molecular assemblies based on the directionality and specificity of hydrogen bonds.
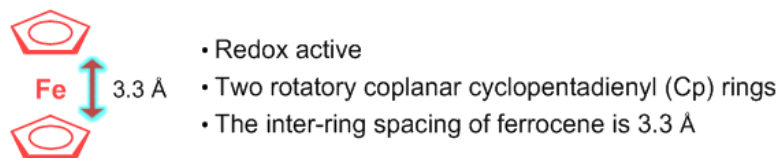

· Redox active
· Two rotatory coplanar cyclopentadienyl (Cp) rings
· The inter-ring spacing of ferrocene is 3.3 Å

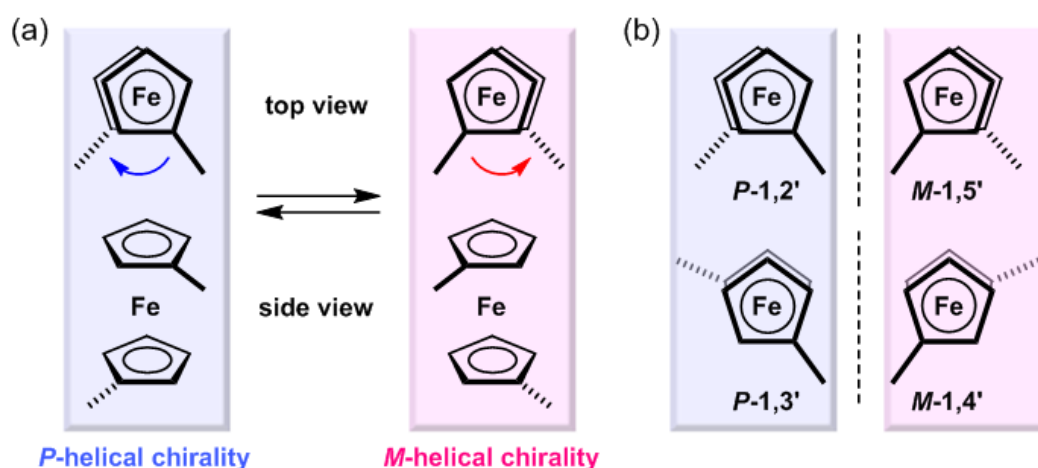**Figure 1.** Characteristic properties of ferrocene.

Figure 2. (**a**) Top and side views of *P*- and *M*-helical chirality and (**b**) stereoisomers of the axial chirality of 1,*n*′-disubstituted ferrocenes. The broken line is the mirror plane.
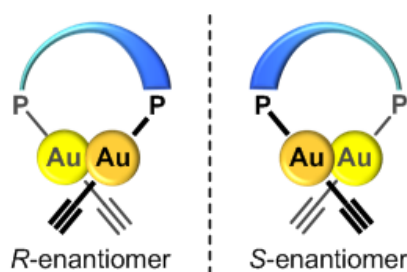

Figure 3. *R*- and *S*-enantiomers of the dinuclear organogold(I) compounds with bridging diphosphine ligands. The broken line is the mirror plane.

In this feature paper, recent advances in induction of helical chirality into the organometallic moiety of bioorganometallic conjugates by the control of a torsional twist of the organometallic moiety are highlighted. Specifically, we focus on control of helical chirality of the 1,*n*′-disubstituted ferrocene moiety in the ferrocene-dipeptide conjugates. In addition, the chirality induction of the Au(I)–Au(I) axis in the dinuclear organogold(I)-uracil conjugates is briefly described.

2. Induction of Helical Chirality into Bioorganometallic Conjugates

2.1. Control of Helical Chirality of Ferrocene Moieties in Ferrocene-Dipeptide Conjugates

Ferrocenylalanine, which is the first example of the introduction of amino acid into a ferrocene unit, was synthesized in 1957 [21–23]. After its first example of a ferrocene-amino acid conjugate, much attention has been devoted to the design of ferrocene-amino acid or peptide conjugates to shed light on the factors affecting the formation of protein secondary structures and to construct highly-organized

molecular assemblies [24–30]. Ferrocene-1,1′-dicarboxylic acid (Fc-cc), 1′-aminoferrocene-1-carboxylic acid (Fc-ac), and 1,1′-diaminoferrocene (Fc-aa) scaffold are utilized as an organometallic scaffold with a central reverse-turn unit as pictured in Figure 4. The ferrocene-amino acid conjugate **1** composed of a valine unit was reported to reveal the capability of ferrocene-1,1′-dicarboxylic acid (Fc-cc) as a molecular scaffold for a regulated conformation through intramolecular antiparallel β-sheet-like hydrogen bonding ("Herrick" pattern) as depicted in Figure 5 [31]. The introduction of the L-Ala-L-Pro homochiral dipeptide chains into the Fc-cc scaffold induces *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety by restriction of a torsional twist about the Cp(centroid)-Fe-Cp(centroid) axis based on the chirality organization, through the formation of interchain intramolecular antiparallel β-sheet-like hydrogen bonds as observed in the ferrocene-dipeptide conjugate **2** composed of the L-Ala-L-Pro-OEt dipeptide chains (Figure 6) [32–35]. As expected, *M*-helical chirality with *M*-1,5′ helical conformation of the ferrocenoyl moiety is formed in the ferrocene-dipeptide conjugate **3** composed of the D-Ala-D-Pro-OEt dipeptide chains. Consequently, helical chirality of the ferrocenoyl moiety is easily controlled by changing the chirality of the introduced dipeptide chains (Figure 6). The ferrocene-dipeptide conjugate **2** shows a positive Cotton effect at the absorbance region of the ferrocenoyl moiety based on *P*-helical chirality in the CD spectrum in acetonitrile and a negative Cotton effect is observed in the CD spectrum of the ferrocene-dipeptide conjugate **3** with *M*-helical chirality as shown in Figure 7.
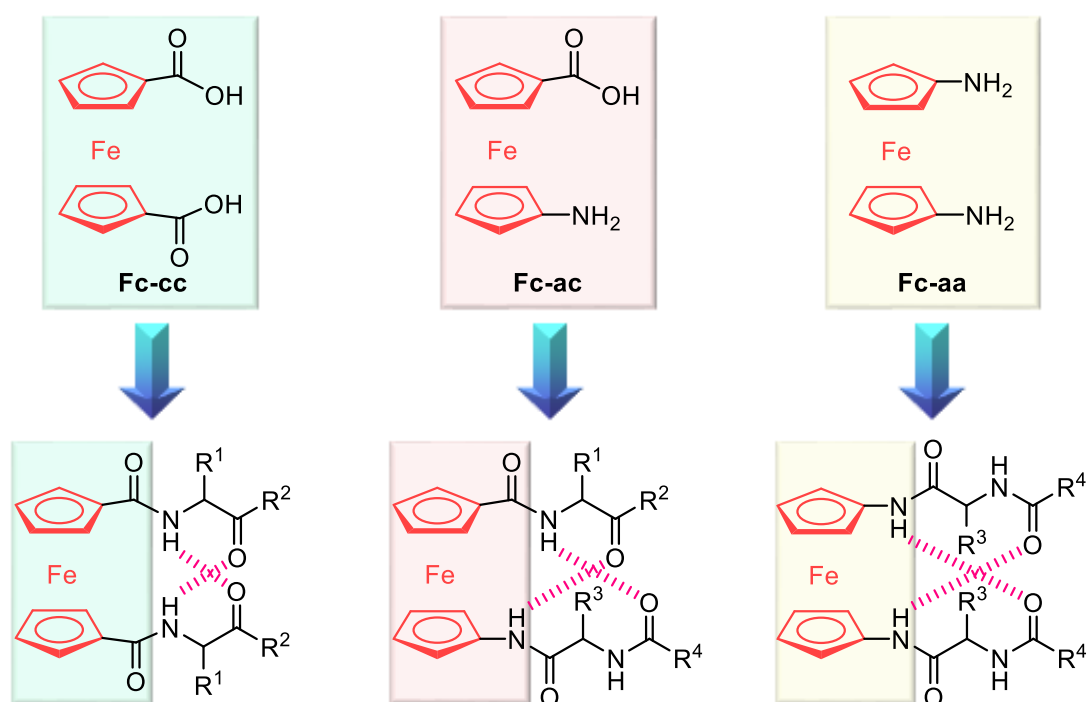

Figure 4. Ferrocene-1,1′-dicarboxylic acid (Fc-cc), 1′-aminoferrocene-1-carboxylic acid (Fc-ac), and 1,1′-diaminoferrocene (Fc-aa) scaffold for the design of chirality-organized ferrocene-peptide conjugates.
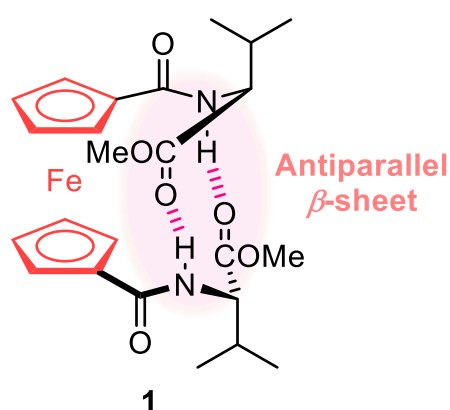
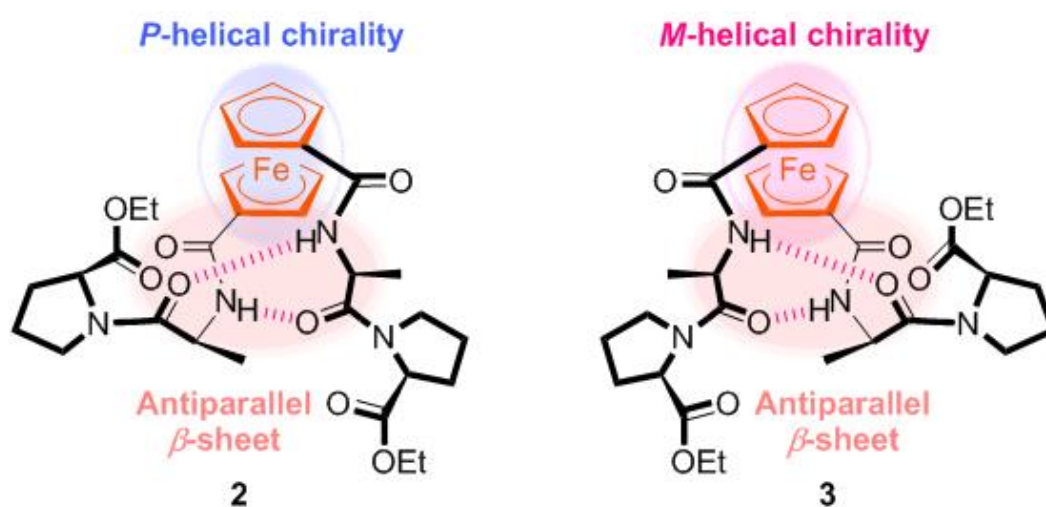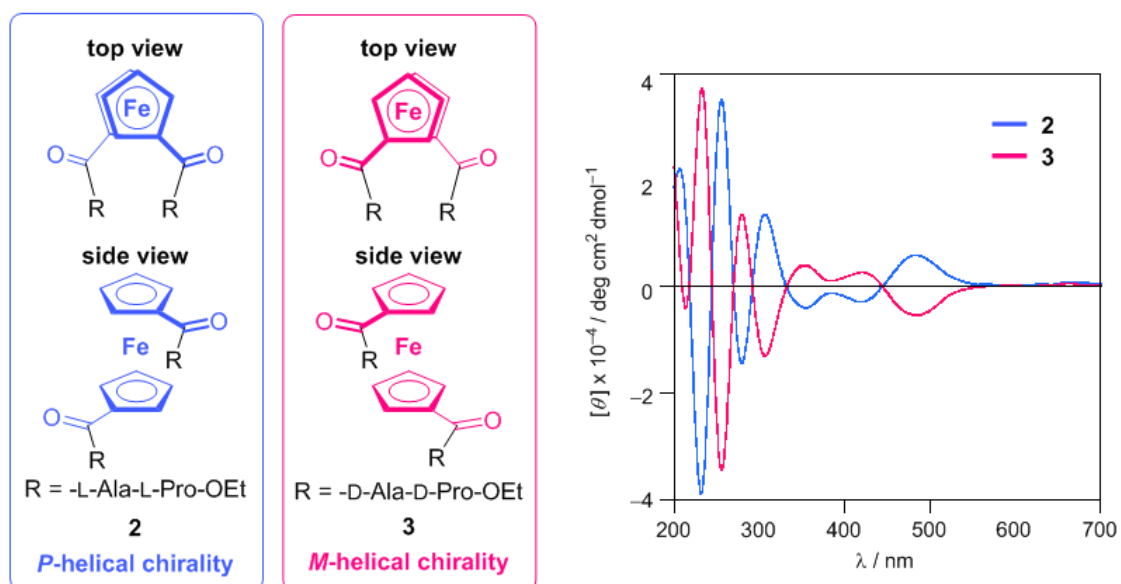**Figure 5.** Ferrocene-amino acid conjugate **1**.

Figure 6. Ferrocene-dipeptide conjugates **2** and **3**.

Figure 7. CD spectra of **2** and **3** in acetonitrile (1.0×10^{-4} M).

The ferrocene-dipeptide conjugate **4** composed of the L-Ala-L-Phe-OMe dipeptide chains also forms the chirality-organized structure through the formation of interchain intramolecular antiparallel β-sheet-like hydrogen bonds to lead *P*-helical chirality with *P*-1,2′ helical conformation of the

ferrocenoyl moiety as shown in Figure 8 [36]. *P*-Helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety can be induced in the ferrocene-dipeptide conjugate **5** composed of the Gly-L-Leu-OMe dipeptide chains even though Gly, which is achiral, is used as the adjacent amino acid (Figure 8) [34]. The Gly-L-Pro-OEt dipeptide chains also allow the induction of *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety in the ferrocene-dipeptide conjugate **6** composed of the Gly-L-Pro-OEt dipeptide chains (Figure 8) [37].
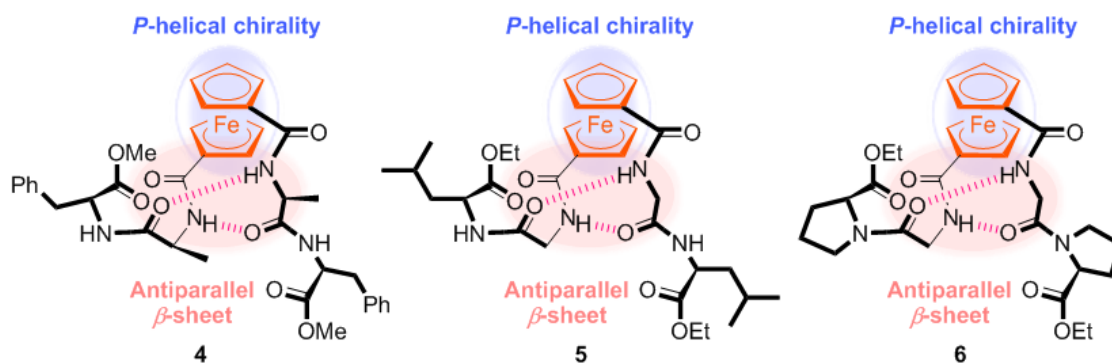

Figure 8. Ferrocene-dipeptide conjugates **4–6**.

The formation of protein secondary structures can be controlled by changing the absolute configuration and sequence of amino acids. The simultaneous formation of an antiparallel β-sheet-like structure and a type II β-turn-like structure is achieved by conjugation of the Fc-cc scaffold as a central reverse-turn unit with the L-Ala-D-Pro heterochiral dipeptide sequence to induce *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety in the ferrocene-dipeptide conjugates **7** as depicted in Figure 9 [38]. The helical chirality of the ferrocenoyl moiety is likely to be induced depending on the absolute configuration of the α-carbon atom of an amino acid adjacent to the ferrocenoyl moiety [39,40]. On the other hand, the introduction of the L-Pro-L-Ala homochiral dipeptide chains into the Fc-cc scaffold induces the chirality-organized structure based on the formation of an antiparallel β-sheet-like structure with a concomitant formation of an inverse γ-turn-like structure as observed in the ferrocene-dipeptide conjugate **8** (Figure 9) [41].
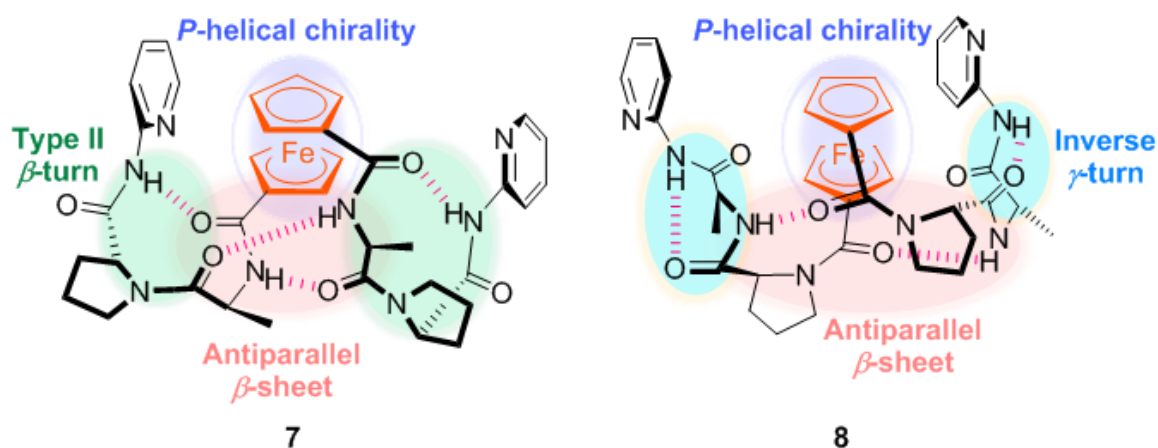

Figure 9. Ferrocene-dipeptide conjugates **7** and **8**.

Cyclization of ferrocene-dipeptide conjugates to lead to the close proximity of the two peptide strands is a convenient approach to form a β-sheet structure. The cyclic ferrocene-dipeptide conjugate **9** composed of the cyclic peptide (-Gly-L-Val-cystamine-L-Val-Gly-) forms intramolecular antiparallel β-sheet-like hydrogen bonds to induce *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety (Figure 10) [42].
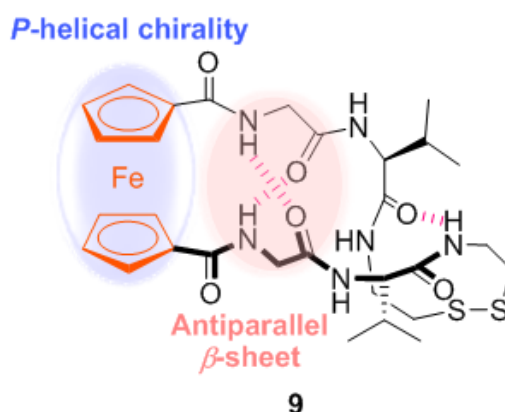
Figure 10. Ferrocene-dipeptide conjugate **9**.

In general, the helical chirality of the ferrocenoyl moiety in the ferrocene-dipeptide conjugates composed of the Fc-cc scaffold, depends on the absolute configuration of the α-carbon atom of an amino acid adjacent to the Fc-cc scaffold as described above. The helical chirality and protein secondary structures in ferrocene-dipeptide conjugates can be controlled by the regulation of the conformational flexibility of the dipeptide chains through cyclization of the dipeptide chains. Interestingly, the cyclic ferrocene-dipeptide conjugate **10** composed of the heterochiral dipeptides (-L-Ala-D-Pro-cystamine-D-Pro-L-Ala-) shows *M*-helical chirality with *M*-1,4′ helical conformation of the ferrocenoyl moiety by the creation of a type II β-turn-like structure as pictured in Figure 11 [43]. On the contrary, *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety through the formation of an antiparallel β-sheet-like structure with a concomitant formation of an inverse γ-turn-like structure is observed in the cyclic ferrocene-dipeptide conjugate **11** composed of the homochiral dipeptides (-L-Ala-L-Pro-cystamine-L-Pro-L-Ala-) (Figure 11) [43]. From these results, both *P*- and *M*-helical chirality can be induced by control of the absolute configuration of the remote amino acid without changing the absolute configuration of the adjacent amino acid in the cyclic ferrocene-dipeptide conjugates. Moreover, the conversion of *M*-helical chirality into *P*-helical chirality of the ferrocenoyl moiety can be controlld by the conversion of a type II β-turn-like structure to an antiparallel β-sheet-like structure. *P*-Helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety based on the chirality organization through the formation of an antiparallel β-sheet-like structure is observed in the acyclic ferrocene-dipeptide conjugate **12** composed of the L-Ala-D-Pro-NHCH$_2$CH$_2$SH dipeptide chains, which is synthesized by the reductive cleavage of disulfide bonds in cyclic conjugate **10** as shown in Figure 11 [43]. The acyclic ferrocene-dipeptide conjugate **13** composed of the L-Ala-L-Pro-NHCH$_2$CH$_2$SH dipeptide chains displays *P*-helical chirality with *P*-1,2′ helical conformation of the ferrocenoyl moiety, based on the chirality organization through the formation of an antiparallel β-sheet-like structure (Figure 11) [43].
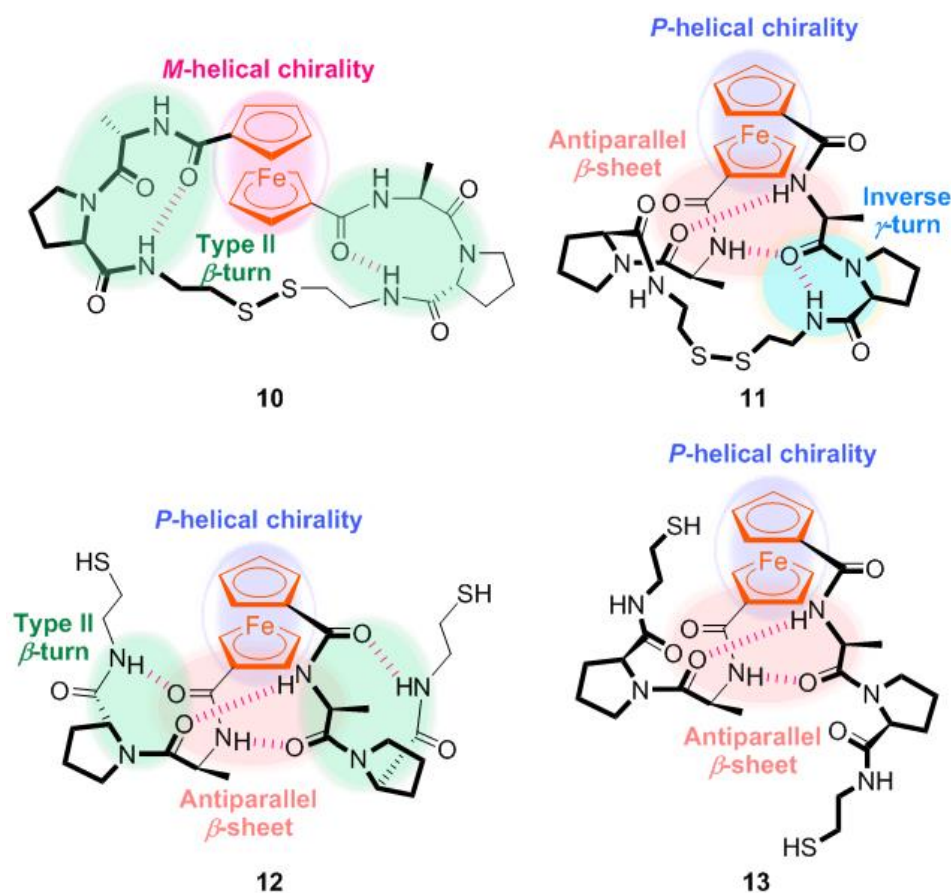
Figure 11. Ferrocene-dipeptide conjugates **10–13**.

The organometallic amino acid, 1′-aminoferrocene-1-carboxylic acid (Fc-ac), can be also utilized as a reliable molecular scaffold to allow the chirality-organized structure. *P*-Helical chirality with *P*-1,2′ helical conformation of the Fc-ac moiety through the formation of a 12-membered hydrogen-bonded ring is induced in the ferrocene-amino acid conjugate **14** (Boc-L-Ala-Fc-ac-L-Ala-L-Ala-OMe) as illustrated in Figure 12 [44]. The attachment of amino acids to 1,1′-diaminoferrocene (Fc-aa) as a molecular scaffold induces the chirality organization. An intramolecular 14-membered hydrogen-bonded ring is formed in the ferrocene-amino acid conjugate **15** composed of the L-Ala-Boc amino acids, resulting in *P*-helical chirality of the Fc-aa moiety (Figure 12) [45]. The ferrocene-amino acid conjugate **16** composed of only one L-Ala-Boc amino acid also forms the chirality-organized structure through intramolecular hydrogen bonds (Figure 12) [46]. The DFT studies accompanied with the data of CD measurements of the ferrocene-dipeptide conjugate **17** (Ac-L-Ala-L-Pro-NH-Fc-NH-L-Pro-L-Ala-Boc) indicate *P*-helical chirality of the Fc-aa moiety (Figure 12) [47]. The formation of intramolecular 10-membered and 13-membered hydrogen-bonded rings induces *P*-helical chirality of the Fc-aa moiety in the ferrocene-dipeptide conjugate **18** (Ac-D-Ala-L-Pro-NH-Fc-NH-L-Pro-D-Ala-Boc) (Figure 12) [47].

The ferrocene-dipeptide conjugate **19** composed of the L-Ala-L-Pro-NH-2-PyMe dipeptide chains forms the chirality-organized structure with *P*-helical chirality of the ferrocenoyl moiety, through the formation of interchain intramolecular antiparallel β-sheet-like hydrogen bonds, wherein two C-terminal amido pyridyl moieties are well arranged for binding of dicarboxylic acids through hydrogen bonding (Figure 13) [48]. As a matter of fact, the ferrocene-dipeptide conjugate **19** can form the 1:1 complex **20** with a series of dicarboxylic acids and serve as a receptor for the size-selective and chiral recognition of dicarboxylic acids (Figure 13) [48].
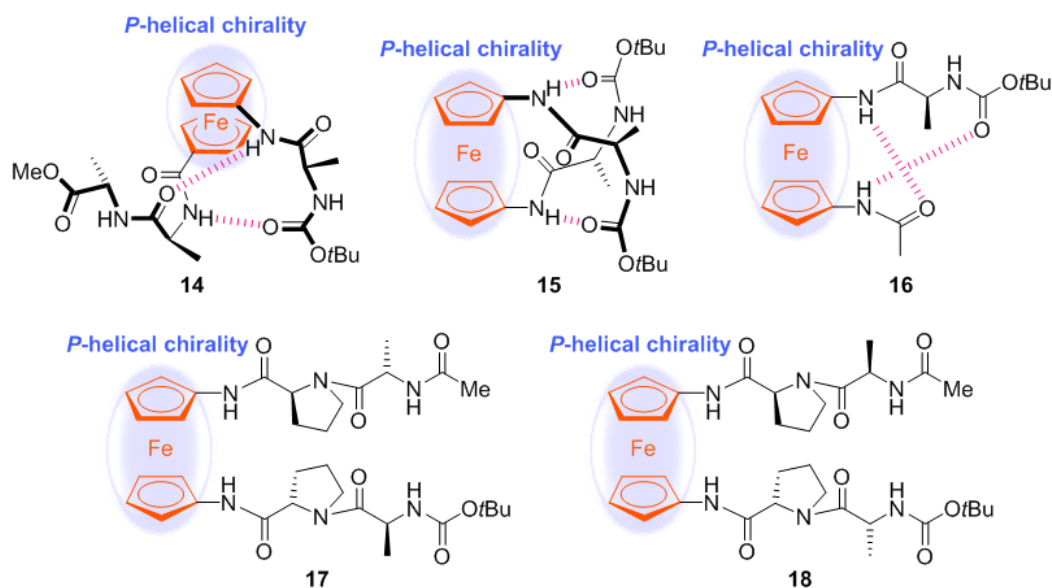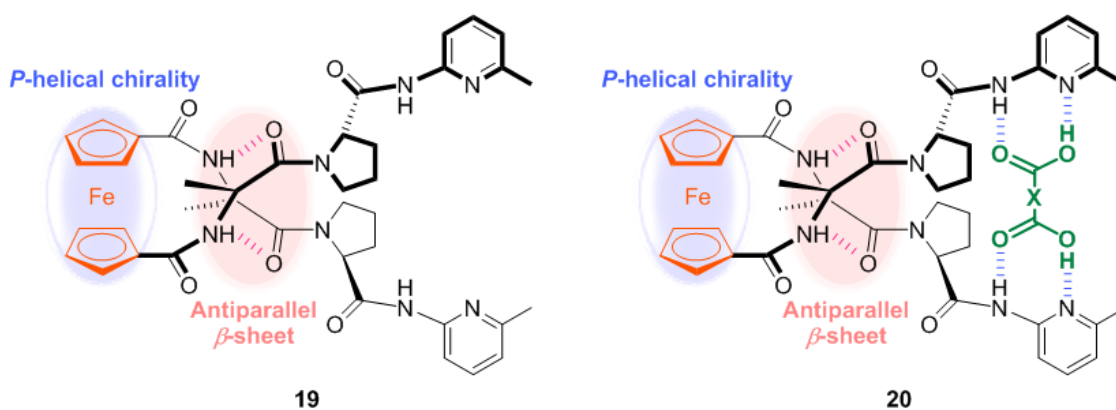
Figure 12. Ferrocene-dipeptide conjugates **14**–**18**.

Figure 13. Ferrocene-dipeptide conjugate **19** and the 1:1 complex **20** with dicarboxylic acid.

The reaction of the ferrocene-dipeptide conjugate **21** composed of the L-Ala-L-Pro-NH-2-Py dipeptide chains with PdCl$_2$(MeCN)$_2$ affords the 1:1 *trans*-palladium complex **22**, wherein the chirality-organized structure through the formation of an antiparallel β-sheet-like structure is stabilized in both solution and solid states (Figure 14) [49].
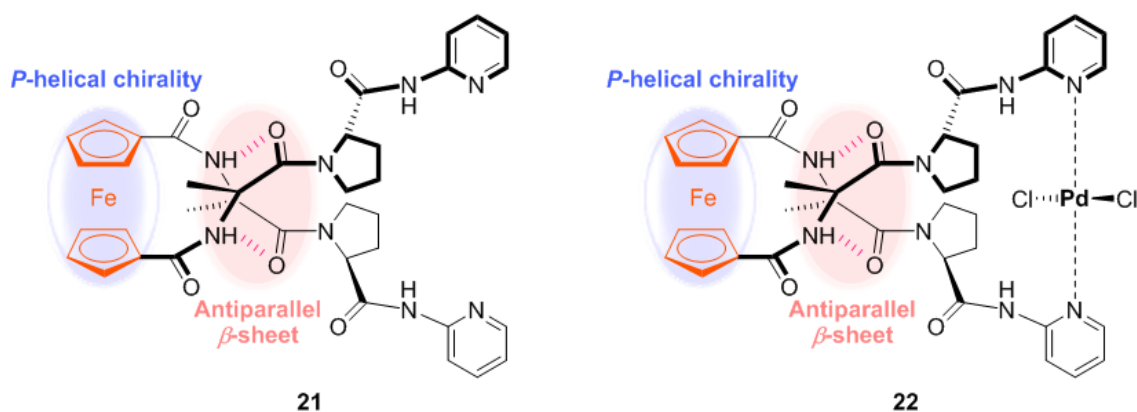

Figure 14. Ferrocene-dipeptide conjugate **21** and the 1:1 *trans*-palladium complex **22**.

In the case of the ferrocene-dipeptide conjugate **23** composed of only one L-Ala-L-Pro-OEt homochiral dipeptide chain, a left-handed helically ordered molecular arrangement, wherein two independent molecules are connected alternately to form an intermolecular hydrogen bonding network, is observed in the crystal packing as depicted in Figure 15a [33]. A left-handed helically ordered molecular arrangement through a network of intermolecular hydrogen bonds is also created in the ferrocene-dipeptide conjugate **24** composed of only one L-Ala-D-Pro-NH-2-Py heterochiral dipeptide chain (Figure 15b) [38]. The utilization of the D-Ala-L-Pro-NH-2-Py heterochiral dipeptide chain leads to the formation of an opposite helically ordered molecular assembly; a right-handed helically ordered molecular arrangement in the crystal packing of the ferrocene-dipeptide conjugate **25** composed of only one D-Ala-L-Pro-NH-2-Py heterochiral dipeptide chain as shown in Figure 15c [38].
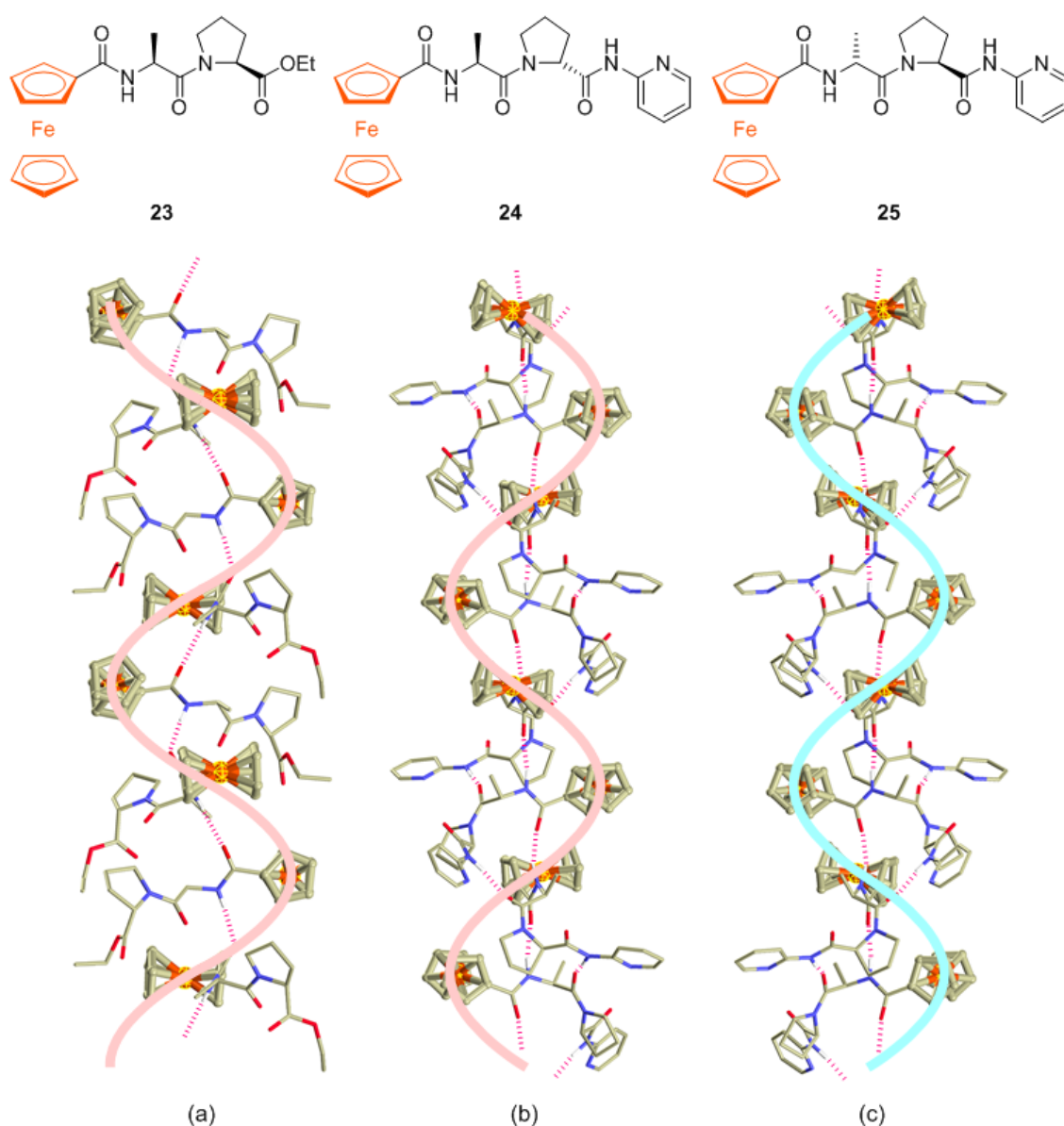

Figure 15. A portion of a layer containing the helical assembly of crystal packing of the ferrocene-dipeptide conjugates (**a**) **23**, (**b**) **24**, and (**c**) **25** (hydrogen atoms, which are not involved in hydrogen bonding, are omitted for clarity).

The chirality-organized structure depends on the position of the pyridyl nitrogen of the C-terminal pyridyl moiety. In contrast to assembling properties of **24**, an intramolecular type

II β-turn-like hydrogen bond is created in the ferrocene-dipeptide conjugate **26** composed of only one L-Ala-D-Pro-NH-4-Py heterochiral dipeptide chain (Figure 16) [50]. Assembling of the chirality-organized ferrocene-dipeptide conjugate **26** with a β-turn-like structure is demonstrated by the reaction of **26** with 0.25 molar equivalent amount of [Pd(MeCN)$_4$](BF$_4$)$_2$, giving the 4:1 palladium complex **27**, where the four chirality-organized ferrocene-dipeptide conjugates are arranged in the same direction to form a chiral pocket as pictured in Figure 16 [50].
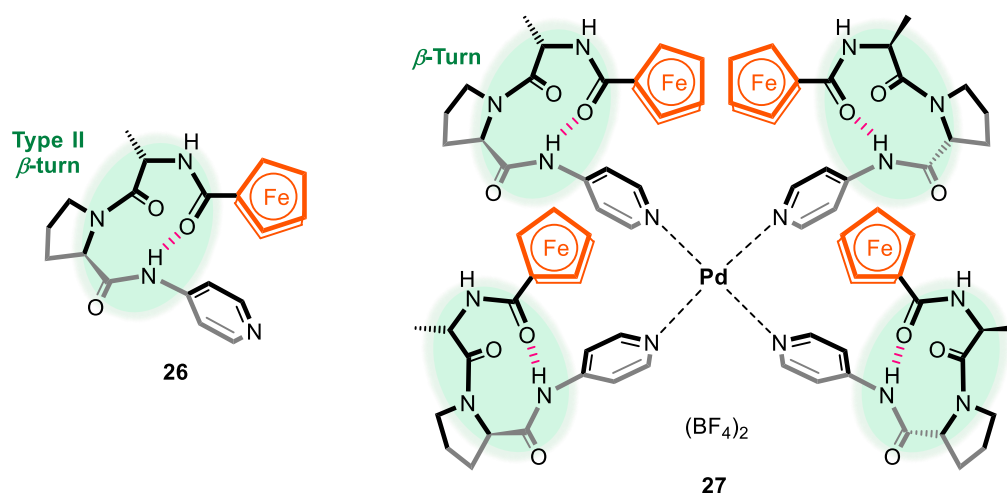

Figure 16. Ferrocene-dipeptide conjugate **26** and the 4:1 palladium complex **27**.

2.2. Chirality Induction of the Au(I)–Au(I) Axis in Dinuclear Organogold(I)-Uracil Conjugates

Gold(I) compounds can aggregate through a d^{10}–d^{10} closed shell aurophilic bonding interaction, where the strength is comparable to the strength of a hydrogen bonding [18–20]. G-octamer formation of the organogold(I)-guanosine conjugates [51,52] and self-organization of the organogold(I)-uracil conjugate [53] were demonstrated to induce Au(I)–Au(I) interaction. Conversely, the utilization of Au(I)–Au(I) interaction is a promising strategy for preorganization of the self-assembling nucleobase moieties. The dinuclear organogold(I)-uracil conjugate **28** shows an intramolecular aurophilic Au(I)–Au(I) interaction by using Xantphos as a bridging diphosphine ligand for the arrangement of the phosphorus coordination site on the same side to induce intramolecular Au(I)–Au(I) interaction as shown in Figure 17 [54]. *R*- and *S*-enantiomers based on the presence of a torsional twist about the Au(I)–Au(I) axis are present in the crystal structure of **28** (Figure 17), wherein the hydrogen-bonded assembly through intermolecular hydrogen bonding between the uracil moieties is observed [54].
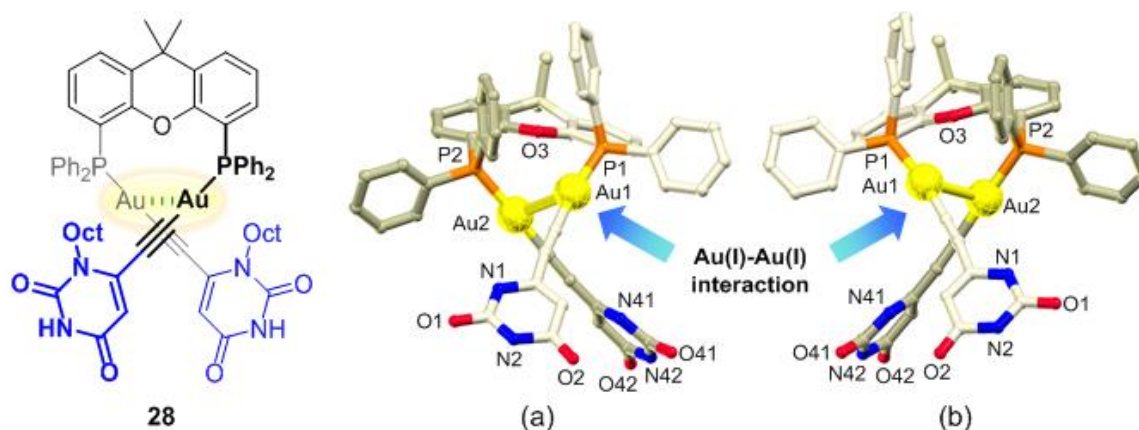

Figure 17. Crystal structures of the (**a**) *R*- and (**b**) *S*-enantiomers of the dinuclear organogold(I)-uracil conjugate **28** (hydrogen atoms and octyl moieties are omitted for clarity).

The utilization of the bridging diphosphine ligand with axial chirality induces chirality induction in the Au(I)–Au(I) axis. An intramolecular aurophilic Au(I)–Au(I) interaction is observed in the crystal structure of the dinuclear organogold(I)-uracil conjugate **29** with (*R*)-BINAP as a bridging diphosphine ligand, wherein **29** adopts a *R*,*R*-configuration through the chirality induction of the Au(I)–Au(I) axis as illustrated in Figure 18a [54]. In the crystal packing, a helical molecular assembly is formed by self-assembling through intermolecular hydrogen bonds between the uracil moieties (Figure 18b) [54].
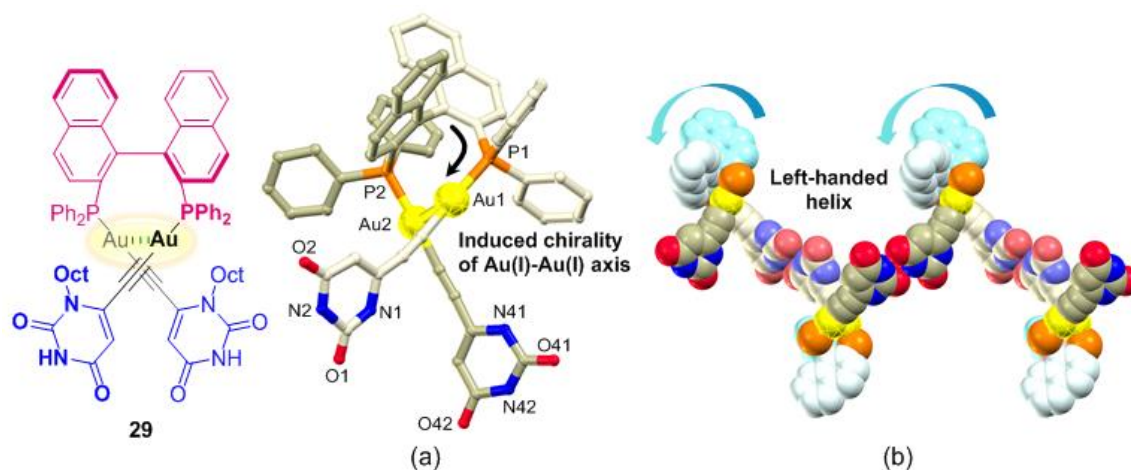

Figure 18. (**a**) Crystal structure of the *R*-enantiomer and (**b**) the helical molecular assembly through intermolecular hydrogen bonds between the uracil moieties of the dinuclear organogold(I)-uracil conjugate **29** (hydrogen atoms and octyl moieties are omitted for clarity).

3. Conclusions

In the bioorganemetallic ferrocene-dipeptide conjugates, the formation of protein secondary structures through intramolecular hydrogen bonding induces helical chirality of the 1,*n*′-disubstituted ferrocene moiety, wherein the formation of protein secondary structures can be altered by changing the absolute configuration and sequence of amino acids. The helical chirality of the ferrocenoyl moiety is also controlled by adjusting the conformational flexibility of the dipeptide chains through cyclization of the dipeptide chains. Chirality induction in the Au(I)–Au(I) axis of the dinuclear organogold(I)-uracil conjugate is demonstrated by using (*R*)-BINAP as a bridging diphosphine ligand for the arrangement of the phosphorus coordination site on the same side, to induce intramolecular Au(I)–Au(I) interaction. Directionality and specificity of hydrogen bonding play a crucial role in the construction of chirality-organized structures. In this sense, amino acids and peptides, which have hydrogen bonding sites and chiral centers, are promising to serve as chirality induction units through the formation of hydrogen bonds.

Conflicts of Interest: The authors declare no conflict of interest.

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