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Helical Aromatic Oligoamide Macrocycle Incorporated with a Ferrocene Unit for Encapsulation and Chirality Signaling of Zwitterionic Proline

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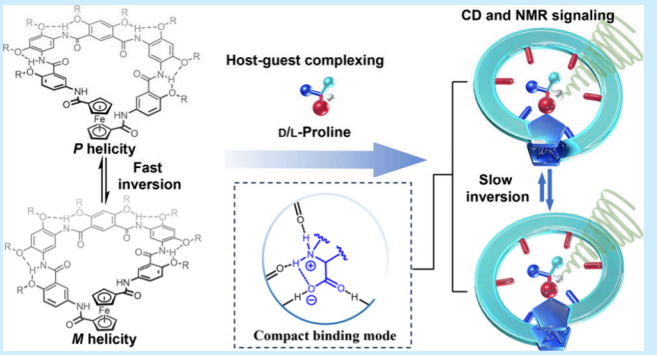
ABSTRACT: A strategy for developing ferrocene-incorporated heteroditopic macrocycles for the recognition of zwitterionic proline is presented. The receptor features a well-defined helical cavity, and diastereomeric conformers result upon encapsulation of D/L-proline as indicated by X-ray crystallography. Incorporation of a ferrocene unit allows efficient chirality signaling, which is clearly manifested by circular dichroism and NMR spectroscopy upon guest binding. This work demonstrates a viable approach for constructing ditopic hydrogen-bonded aromatic oligoamide macrocycles capable of sensing zwitterionic amino acids.



Zwitterions,[1] defined as molecules that contain both positive and negative charges, are present in many biological processes. Among them, amino acids[2] are one of the most typical types of zwitterions,[3] which are found to be involved in proteins and cell membranes.[4] Apart from their essential roles played in living organisms, the intrinsic chirality of amino acids also makes them indispensable synthons in asymmetric synthesis. Consequently, artificial receptors that recognize and signal zwitterionic amino acids[5] are in greater demand. Much of the effort in the context of design in this field has focused on creating ditopic receptors[6] with a marriage of cation recognition motifs such as crown ether[7] and calixarenes[8] and anion binding units such as ammonium,[9] guanidinium,[10] and urea[11] functionalities. Most of these receptor systems feature the separation of two distinct binding sites and exhibit complementary characteristics. Such separation, however, allows receptors to self-associate through electrostatically ion-paired patches,[12] which compete with the designed receptor or even prevent it from associating with the intended guest.[13] An ideal solution is to encapsulate both charges of a zwitterionic guest inside the same macrocyclic cavity consisting of two complementary sites. This approach would attenuate undesired intra- or intermolecular interactions and simplify complexation modes.[14] Nevertheless, integrating two types of binding sites in macrocyclic receptors with opposite electron distributions into a single cavity for synergistic recognition and chirality signaling of native amino acids remains a challenge.

The hydrogen-bonded (H-bonded) aromatic oligoamide macrocycles[15] featuring a hydrophilic cavity have attracted a considerable amount of attention for their ability to bind ionic guests. Our previous work showed that H-bonded macrocycles form ion pair complexes with secondary alkylammonium halides and alkaline metal halides.[16] However, they showed no detectable interaction with native amino acids, likely due to the D_2-symmetric backbone. With this in mind, a rational design of using H-bonded macrocycles to recognize zwitterionic amino acids is to desymmetrize the host framework by incorporating a ferrocene unit into the backbone. Herein, we report helical H-bonded aromatic oligoamide macrocycle **1**, which is capable of compactly binding an amino acid as a zwitterion in its cavity (Figure 1). The key point for achieving this lies in the use of a ferrocene unit in the designed receptor, which not only produces a cryptochiral molecule with a helical cavity but also makes the amide hydrogen atoms of the macrocycle hydrogen bond complementarily to the negatively charged carboxylate of an amino acid. Such a design places the other binding site (amide oxygen atoms) in a well-matched orientation for the ammonium group of an amino acid. Interestingly, the receptor

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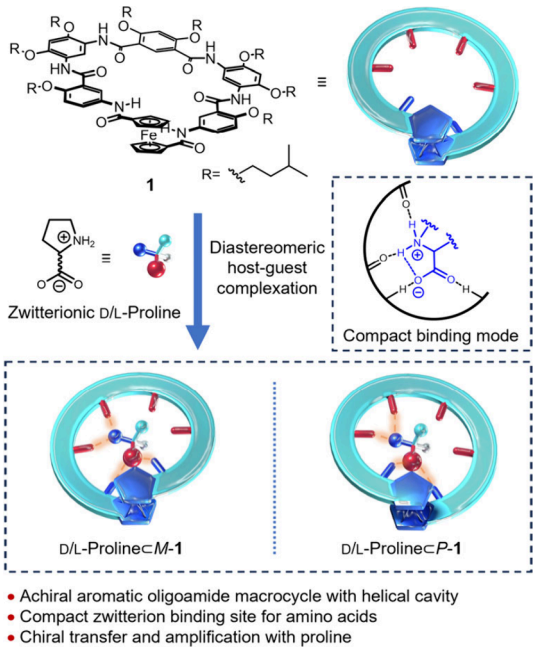

Figure 1. Chemical structure of macrocycle **1** and cartoon representation of the formation of diastereomers with proline. Hydrogen bonds are shown as dashed lines. Note that the *P* and *M* chiral helicity of free macrocycle **1** may be inverted by flipping.

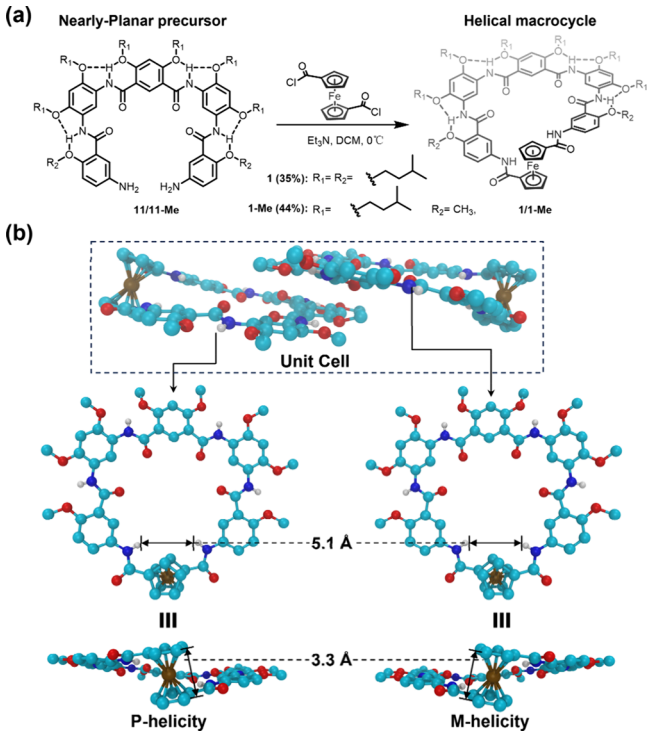

Figure 2. (a) Synthesis of macrocycle **1**/**1-Me**. (b) Single-crystal X-ray structure of macrocycle **1** with side chains and solvents omitted for the sake of clarity.

demonstrates NMR and circular dichroism (CD) signaling toward proline, which is suggestive of the potential of such macrocycles for determination of the enantiomeric excess of natural amino acids.

Macrocycle **1** was synthesized through bimolecular [5+1] condensation reactions (Figure 2a and Scheme S1) between 1,1′-ferrocenedicarbonyl dichloride and H-bonded pentamer diamine in 35% yield (Figures S1−S9). Additionally, derivative macrocycle **1-Me**, bearing a shorter side chain, was prepared in 44% yield to facilitate crystal growth. In addition, macrocycle **1** shows no intermolecular self-assembly in a variable-concentration NMR experiment (Figure S10). Single crystals of **1** were obtained by slow diffusion of diethyl ether into a 1,2-dichloroethane solution of the macrocycle over the course of 24 h. A geometry of the macrocycle with a helical cavity was confirmed by X-ray crystallography (Figure 2b). The helical macrocyclic cavity was decorated by four carbonyl oxygens and two amide N−H hydrogens to serve as zwitterionic guest binding sites. The left-handed helical (*M*) and right-handed helical (*P*) macrocycles coexist as racemates in the crystal structure with a helical pitch of 3.3 Å. Consistent with the energy-minimized model (Figure S11a), the crystal structure shows a distance of 5.1 Å between the inward-pointing amide H atoms, which is longer than the distance of 3.9 Å in the prior ditopic receptor analogue.[16a] This implies that helical macrocycle **1** can accommodate larger anionic species in comparison to chloride anions. DFT calculations reveal that its cavity can accommodate amino acids, using glycine as the simplest representative example (Figure S11b).

In principle, macrocycle **1** can exist as a mixture of *P* and *M* conformers in solution. Only two diagnostic NMR signals from protons *k*/*l* and *m*/*n* of the ferrocene units are observed at room temperature, indicating fast interconversion between these two conformers on the NMR time scale. This is supported by the results of variable-temperature (VT) NMR experiments (Figure 3a). Protons *k*/*l* and *m*/*n* present identical signals at room temperature, which are progressively split into four inequivalent resonances with a decrease in temperature, demonstrating that the helical chirality of the two conformers is stabilized at a lower temperature. Analysis of the VT ^{1}H NMR coalescence behavior (Figure S12) reveals that the free energy barrier ($\Delta G^{\ddagger}$) for *P* and *M* interconversion is approximately 11.5 kcal mol^{-1} using the Eyring equation,[17] confirming rapid racemization at room temperature.[18] Such a dynamic transformation of a macrocycle with opposite chirality likely involves amide bond rotation and ferrocene moiety flipping. Inspection of two crystal structures of macrocycle **1-Me** (grown under two different conditions) suggests the possibility of amide bond rotation in solution. This rotation produces species with the amide NH group pointing in different directions relative to the molecular cavity (Figure 3b).

Next, we examined the binding of zwitterionic amino acids with macrocycle **1** in chloroform. Organic solvents play an essential role in the applications of amino acids and their derivatives, including peptide synthesis,[19] asymmetric catalysis,[20] and industrial separation.[21] L-Phenylalanine (L-Phe), L-lysine (L-Lys), and L-proline (L-Pro) were selected as three representative examples to evaluate the binding affinity of macrocycle **1** for natural amino acids. The host−guest ^{1}H NMR spectra with a $CDCl_3$ solution show significant downfield shifts of protons such as *g* and *k* in the macrocycle of the complex compared to free host **1**, which clearly indicate their strong intermolecular host−guest interactions as a consequence of hydrogen bonding-induced deshielding effects (Figure 4). Notably, only a simple set of signals of protons *k*/*l* and *m*/*n* is observed for the free macrocycle (Figure 4a), while the corresponding protons are split into four signals when amino acids are bound to the macrocycle (Figure 4b−d),

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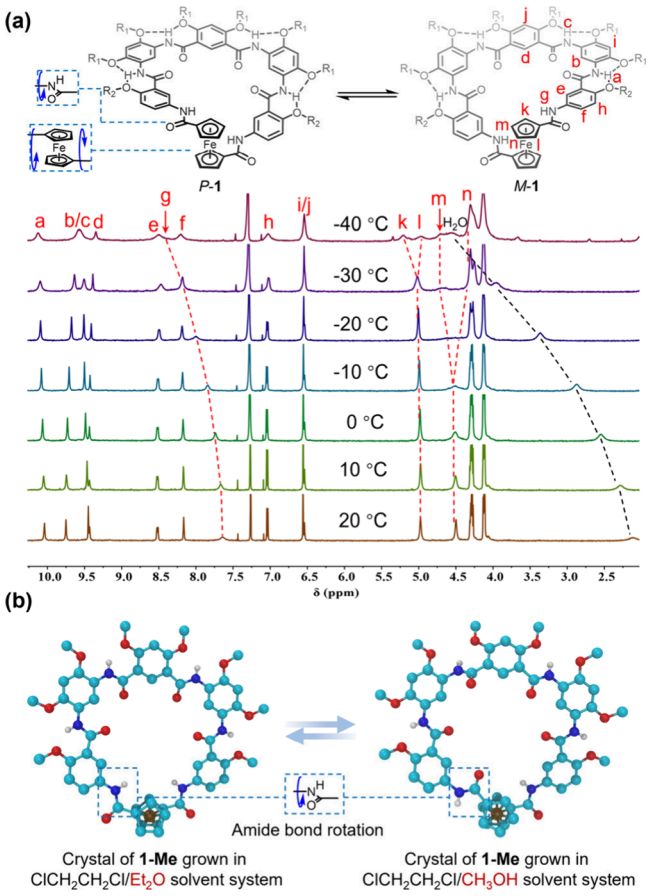

Figure 3. (a) Variable-temperature ^{1}H NMR spectra (600 MHz, $CDCl_3$, 5.0 mM) of macrocycle **1**. (b) Single-crystal X-ray structures of macrocycle **1-Me** grown in different solutions with side chains and solvents omitted for the sake of clarity.

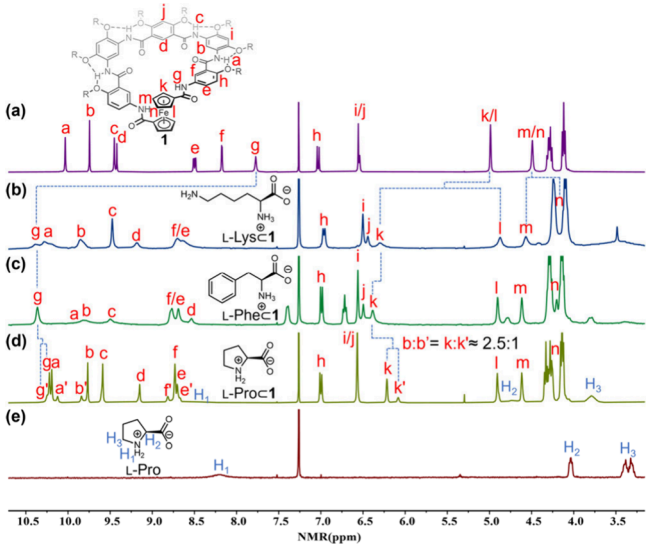

Figure 4. Excerpts of the 400 MHz ^{1}H NMR spectra of a 10.0 mM $CDCl_3$ solution of (a) macrocycle **1**, (b) a 1:1.5 macrocycle **1**/L-lysine mixture, (c) a 1:1.5 macrocycle **1**/L-phenylalanine mixture, (d) a 1:1.5 macrocycle **1**/L-proline mixture, and (e) L-proline at 298 K.

reflecting a change in the slowed inversion of the macrocyclic helix to a varying extent upon the addition of different types of amino acids at room temperature. Correspondingly, with L-Pro for example, all of the ^{1}H NMR signals of L-Pro shift downfield after binding to macrocycle **1** (Figure 4d,e). The 1:1 L-Pro⊂**1** complex is formed, as supported by ESI-MS and Job plot experiments (Figures S13 and S14). The NMR titration experiment revealed that the binding between the free macrocycle and amino acids is characteristic of slow host−guest exchanges on the NMR time scale (Figures S15−S17). Since the binding affinity is beyond the limitation of the NMR titration technique, competitive NMR experiments were carried out with excess TBAB (200 equiv). The results reveal that only L-Pro shows a binding constant (KL-Pro) of 1.77×10^6 M^{-1}, while the other two fail to bind the macrocycle under this condition (Figures S18−S20), which is indicative of the selectivity of macrocycle **1** toward L-Pro compared with L-Lys and L-Phe. In addition, the ^{1}H NMR spectrum of **1** with 1.5 equiv of L-Pro reveals two sets of well-resolved new resonances (Figure 3d) with a signal integration ratio of 2.5:1 (proton b to b' and proton k to k'), suggesting the formation of diastereomeric complexes and a diastereoselectivity of the P-helical macrocycle and the M-helical macrocycle toward L-Pro. Attempts to probe the spatial arrangement of the guest within the host cavity by 2D ROESY spectroscopy at 298 K did not reveal any discernible intermolecular ROE cross-peaks (Figure S21). This is likely due to the highly dynamic complexation equilibrium and rapid tumbling of L-Pro within the cavity of the macrocycle, which effectively suppress intermolecular ROE correlations. Similar observations have been reported for other dynamic host−guest systems.[22,23] As expected for a racemic host, the ^{1}H NMR spectra of complexes with L-Pro and D-Pro were identical (Figure S22), confirming the equivalent binding behavior in solution. To pinpoint the binding position (positive or negative charge) on the amino acid, control guests, including proline methyl ester, 2-tetrahydrofuroic acid, and prolinol, were tested in the host−guest ^{1}H NMR experiments (Figure S23). Since all of them show no or weak binding ability with respect to the macrocycle, we conclude that macrocyclic receptor **1** interacts exclusively with the zwitterionic proline rather than isolated amino or carboxyl groups.

Fortunately, single crystals of the macrocycle−proline racemate complexes were obtained by crystallization from THF with slow diffusion of diethyl ether. Their solid-state structures unambiguously reveal that proline is indeed encapsulated within the helical cavity in its zwitterionic form (Figure 5a,b). The proline guest is disordered over two positions, which produces four species (D-Pro⊂P-**1**, L-Pro⊂P-**1**, D-Pro⊂M-**1**, and L-Pro⊂M-**1**) in the single-crystal structure.[22] In these helical complexes, quadruple intermolecular [N−H···O] hydrogen bonds are observed. Two of four inward-pointing carbonyl oxygen atoms of the macrocycle interact with the ammonium group of proline, while the inward-pointing amide hydrogens form dual intermolecular hydrogen bonds with carboxylate anions. It is noteworthy that the major components, D-Pro⊂P-**1**/L-Pro⊂M-**1**, have a site occupancy factor of 80.2% while the minor components, L-Pro⊂P-**1**/D-Pro⊂M-**1**, exhibit an occupancy of 19.8%. Compared with the minor species, the major component displays a shorter intermolecular [N−H···O] hydrogen bond distance (highlighted by the red dashed line in Figure 4), which may contribute to the preferential formation of D-Pro⊂P-**1**/L-Pro⊂M-**1**. The preference (80.2:19.8) observed in the crystal structure is consistent with the diastereomeric ratio (2.5:1) based on the ^{1}H NMR spectra.

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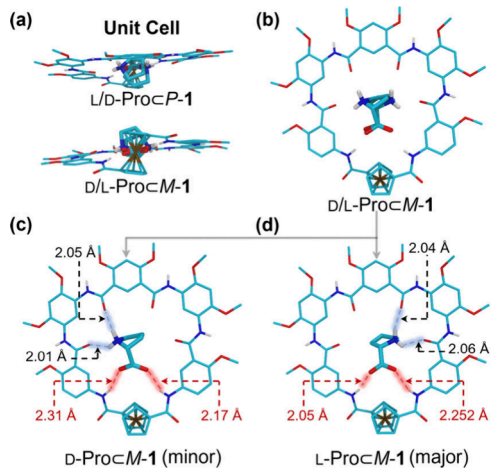

Figure 5. X-ray crystal structures of the complex of macrocycle **1** and racemic proline: (a) front view of the unit cell containing enantiomeric complexes, (b) top view of the D/L-Pro⊂*M*-**1** complex with a disordered position of the guest, (c) minor D-Pro⊂*M*-**1** complex with a site occupancy factor of 19.8%, and (d) major L-Pro⊂*M*-**1** complex with a site occupancy factor of 80.2%. Hydrogen bonds are shown as red and blue dashed lines. Solvent molecules and CH protons have been omitted for the sake of clarity.

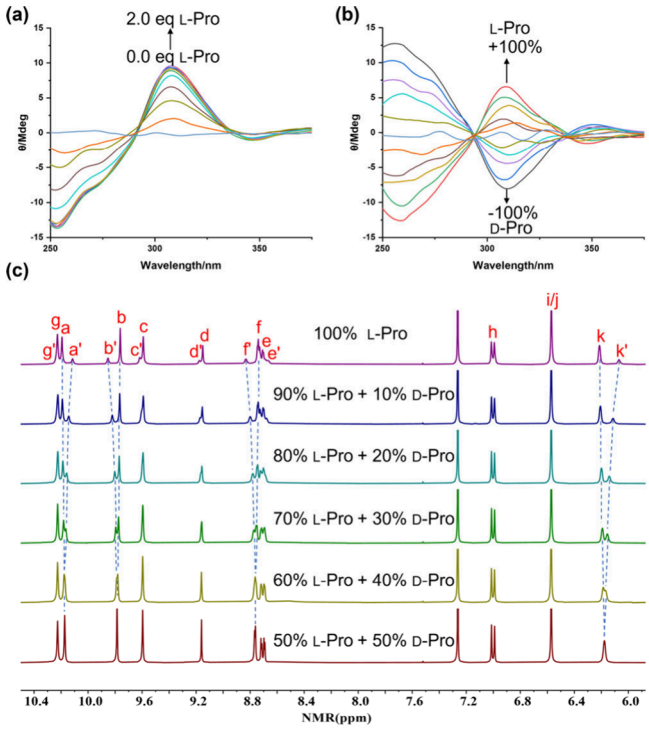

Figure 6. (a) Host–guest CD titration spectra ($CHCl_3$, 298 K) of macrocycle **1** (0.2 mM) upon addition of different numbers of equivalents of L-Pro (0–2.0 equiv). (b) CD spectra of the complexes formed by macrocycle **1** (0.2 mM) and 1.2 equiv of proline with ee values varying from −100% to 100% ($CHCl_3$, 298 K). (c) Partially stacked ^{1}H NMR spectra (400 MHz) of macrocycle **1** (5.0 mM) with 1.2 equiv of mixtures of D-Pro and L-Pro in various chiral ratios in $CDCl_3$ at 298 K.

Given the importance of chirality analysis of amino acids by CD spectroscopy,[24] we examined the CD spectra of proline before and after binding to the macrocycle. Proline is known to be a typical cryptochiral compound. Its UV–vis absorption and chiral signals are difficult to detect in CD. However, the CD signals are observed with a mixture of macrocycle **1** and L-Pro, suggesting that the helical chirality of macrocycle **1** is induced and stabilized in the presence of the amino acid (Figure 6a). In addition, the CD signals are dependent on the chiral ratio of the proline guest (Figure 6b). NMR spectroscopic detection of chirality with the assistance of chiral auxiliaries plays a crucial role in the determination of enantiomeric purities.[25] Therefore, a mixture of macrocycle **1** and proline was examined by ^{1}H NMR spectroscopy to probe diastereomer formation. Upon addition of a 1:1 mixture of L-Pro and D-Pro (1.2 equiv total) to a solution of compound **1** in $CDCl_3$ (5.0 mM) at room temperature, a single set of signals is observed. However, when the L/D-Pro ratio deviates from 1:1, the proton signals start to split into two distinct sets with varying shifts going upfield (e.g., protons *a*′ and *k*′) or downfield (e.g., protons *a* and *k*) (Figure 6c). This observation suggests a rapid exchange between L-Pro⊂**1** and D-Pro⊂**1**; i.e., a proline exchange between diastereomeric complexes occurs faster than racemization of the helix. Such nonequivalency ensures the unique potential of macrocycle **1** as a prochiral solvating agent (Pro-CSA),[26] which makes it an alternative option for NMR-based determination of the ee values of proline. So far, among all other achiral macrocyclic systems, only porphyrin analogues have provided access to Pro-CSA for sensing chiral hydroxyl acid and alcohols.[27]

In conclusion, we have demonstrated that the incorporation of a ferrocene unit into the backbone of a H-bonded aromatic oligoamide macrocycle can result in a ditopic receptor with a helical cavity for effectively recognizing native amino acids in a zwitterionic fashion. The study with proline as an example reveals that helical chirality is induced by the stereochemistry of L/D-proline within the host molecule as shown by a significant chiral amplification effect in CD spectra. Furthermore, the macrocyclic receptor exhibits a chiral ratio-dependent behavior for proline, showing its potential of using macrocycle **1** for NMR-based determination of enantiomeric purities of amino acids. The crystal structures of diastereomers of the host–guest complex are informative in helping to understand the stereoselectivity of the macrocycle toward proline observed in NMR and CD spectra. This work provides a viable approach for constructing ditopic H-bonded macrocycles capable of encapsulating zwitterionic amino acids and can serve as guidance for the design of helical H-bonded macrocyclic receptors for other zwitterionic species.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c05193.

Details of the synthesis and structural characterizations of compounds, MS spectrum, NMR spectra, UV–vis spectrum, crystallographic data, and Cartesian coordinates (Scheme S1, Figures S1–S27, and Tables S1 and S2) (PDF)

Accession Codes

Deposition Numbers 2497426–2497429 contain the supplementary crystallographic data for this paper. These data can be

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obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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