

## Chiral, Metal Templated Self-Assembly

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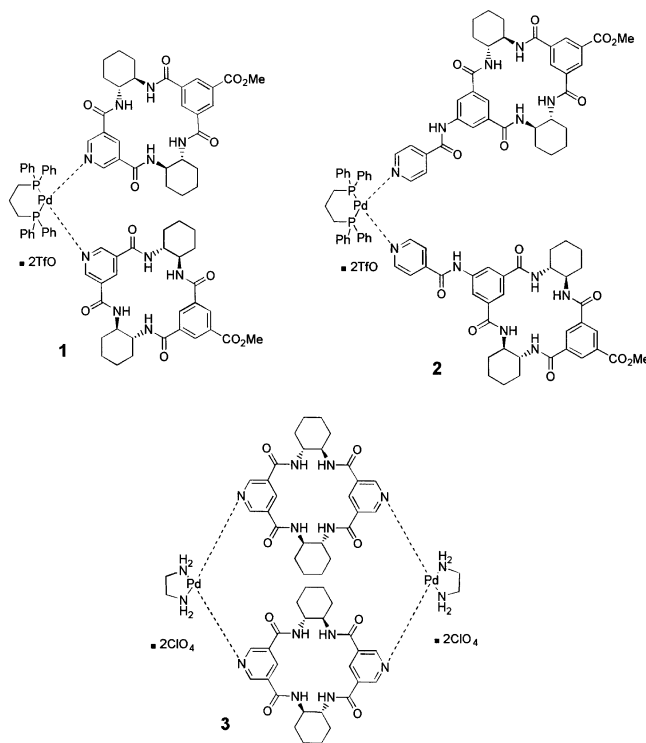
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The development of synthetic receptors having the selective binding property with the various substrates is of great importance for the simulation of specific functions of biological receptors, such as enzymes and antibodies. Furthermore, practical applications stemming from this study include the development of improved chromatographic separation techniques, novel catalysts, and chemical sensor systems.<sup>1</sup>

Thus the last decade has witnessed an explosion in the field of molecular recognition. Since the pioneering work<sup>2</sup> of Pederson, Cram and Lehn, many molecular receptors capable of interacting selectively with various substrates have been described.<sup>3</sup> To construct these receptors, chemists have used multi-step synthetic methods to create such binding sites that have the proper binding groups and shape to complement to those of the intended substrates.

Recently, an alternative method in which a receptor self-assembles from smaller constituents is recognized as an efficient method to construct molecular receptors.<sup>4</sup> The elegant strategies of self-assembly by exploiting hydrogen-bond, electrostatic interaction and metal-ligand coordinate bond have been developed. Over past few years, Fujita *et al.* and Stang *et al.* have reported a variety of Pd(II) templated self-assembling molecular boxes.<sup>5</sup> Of great challenge yet importance is to construct more biologically relevant, self-assembling receptors with chirality and functionalities as seen in biological receptors such as enzymes and antibodies.<sup>6</sup> Here, we describe Pd(II) templated self-assembling, chiral receptors with binding sites having convergent hydrogen bonding donor/acceptor functionalities, as well as hydrophobic surface.

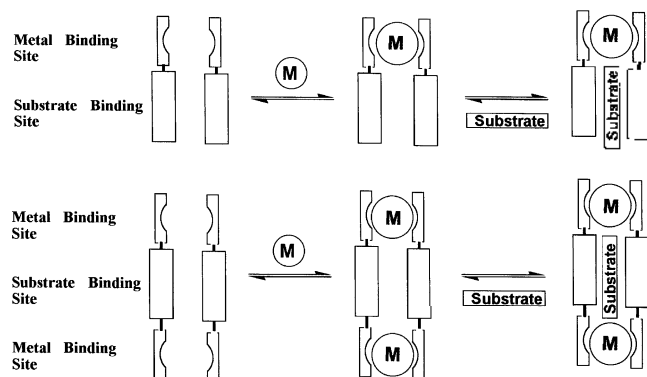
Self-assembling receptors have a large nonpolar, conformationally rigidified binding cavity surrounded by polar functionalities. Previous studies on cyclooligomeric recep-



**Scheme 1.** Structure of Metal Templated Self-Assembling, Chiral Receptors (1-3).

tors derived from 1,2-diamine and trimesic acid<sup>7</sup> revealed that these bound certain peptidic substrates highly selectively. Thus self-assembling receptors is reasonably expected to bind certain peptidic substrates selectively by hydrogen bondings and hydrophobic interactions.

Self-assembling receptors were prepared by exploiting Pd(II)-pyridine coordinate bond.<sup>8</sup> Synthesis of receptors (1-3)<sup>9-11</sup> began with the preparation of monocyclic ligands as shown in Scheme 2. Ligands for receptors 1 and 2 were prepared by macrolactamization reactions between bis-pentafluorophenyl ester of trimesic acid mono methylester and the corresponding diamine diTFA salts in high dilution conditions. The Pd(II) complex 1 and 2 were prepared as white solids with 75% and 77% yield by mixing 0.5 eq. of 1,3-bis(diphenylphosphino)propyl palladium bistriflate, Pd(dppp) (OTf)<sub>2</sub>, and the corresponding ligands in CH<sub>2</sub>Cl<sub>2</sub>, stirring for 3 hrs at room temperature, then adding diethyl ether. The products, Pd(II) complex 1 and 2 are air-stable, moisture-insensitive, and soluble in various organic solvents including dichloromethane, chloroform, acetone, and dimethyl sulfoxide. Macrolactamization reaction between (1R,2R)-1,2-diaminocyclohexane-diTFA salts and bis pentafluorophenyl



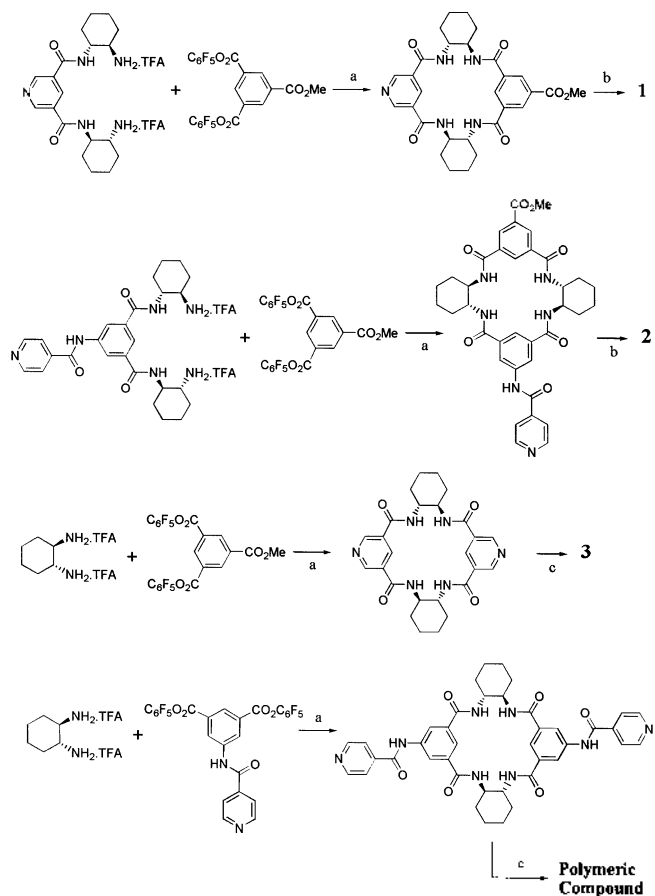
**Figure 1.** Schematic representation of metal templated self-assembly.

ester of pyridine 3,5-dicarboxylic acid in high dilution condition provided ligand for receptor **3** with 39% yield. Ligand for receptor **3** is sparingly soluble in chloroform and dichloromethane. Therefore, Pd(II) complexation reaction using ethylenediaminopalladium dinitrate, Pd(en)(NO<sub>3</sub>)<sub>2</sub>, instead of Pd(dppp)(OTf)<sub>2</sub> was performed. The Pd(II) complex **3** was prepared as white solid with 45% yield by mixing 1 eq. of Pd(en)(NO<sub>3</sub>)<sub>2</sub> and the corresponding ligand in methanol, stirring for 3 hrs at room temperature, then adding AgClO<sub>4</sub>. The products, Pd(II) complex **3** is air-stable, moisture-insensitive, and soluble in various organic solvents including 1/1 - methanol/chloroform and dimethyl sulfoxide. To obtain Pd(II) templated self-assembling receptor with the extended binding cavity, monocyclic ligand was prepared by macro-lactamization reaction with bis pentafluorophenyl ester of isonicotinyl amide of 5-amino-isophthalic acid with 35% yield. However, we could not obtain the discrete Pd(II) complex such as **3**. In the similar condition for **3**, only unidentified polymeric solid was obtained.

The structures of **1**, **2** and **3** were established by mass spectrum and <sup>1</sup>H NMR spectroscopy. In <sup>1</sup>H NMR spectrum of **1**, **2** and **3**, upon complexation with Pd the resonance peaks of arising from the aromatic protons of pyridine moiety of ligands showed the characteristic downfield shifts about 0.1 ppm. Also <sup>1</sup>H NMR spectrum of **1** and **2** showed the resonance peaks arising from both monocyclic ligands and 1,3-bis(diphenylphosphino)propyl group with the ratio of 2 : 1, while <sup>1</sup>H NMR spectrum of **3** showed the resonance peaks arising from both monocyclic ligands and ethylenediamino group with the ratio of 1 : 1. These observations are well compatible with the proposed structures. In mass spectrum of **1** and **2**, the detection of peaks arising from (M-OTf)<sup>+</sup> at m/z 1763 and 2001 confirms the proposed structures. Also, in mass spectrum of **3**, the detection of peak arising from (M-ClO<sub>4</sub>)<sup>+</sup> at m/z 1610 confirms the proposed structure. Although the possibility of the existence of the other oligomeric structures such as trimer and tetramer can not be excluded, it is interesting that the formation of dimeric structure from monocyclic ligands and Pd(en) is highly efficient. This suggests that the conformation of monocyclic ligand derived 3,5-pyridine dicarboxylic acid and 1,2-diaminocyclohexane is ideal for the formation of the proposed dimeric structure. To confirm this idea, conformational study on monocycle derived 3,5-pyridine dicarboxylic acid and 1,2-diaminocyclohexane using CPK model was conducted. This study and the other computational studies<sup>12</sup> on the related monocyclic compounds revealed that the monocyclic compound exist in the bent structure in which two aromatic groups have about 90° angle, and thus monocyclic ligand is ideal for the formation of the proposed dimeric structure.

In conclusion, Pd(II) templated self-assembly with the well-defined binding cavity were successfully prepared from monocyclic pyridine ligands. The binding properties of these receptors are investigated in this laboratory and will be reported in due course.

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**Scheme 2.** Syntheses of Metal Templated Self-Assembling, Chiral Receptors (**1-3**): (a) slow addition to iPr<sub>2</sub>NEt/TfOH, (b) Pd(dppp)(OTf)<sub>2</sub>, (c) Pd(en)(NO<sub>3</sub>)<sub>2</sub>, then AgClO<sub>4</sub>.

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9. Spectroscopic data of **1**:  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  1.32 (m, 8H), 1.54 (m, 8H), 1.85 (m, 8H), 1.92 (m, 10H), 2.89 (bs, 4H), 3.87 (s, 6H), 3.93 (bs, 8H), 7.50 (m, 8H), 7.57 (m, 4H), 7.71 (m, 8H), 8.32 (s, 6H), 8.46 (s, 2H), 8.65 (m, 8H), 8.87 (s, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.9, 25.8, 31.4, 32.0, 32.9, 53.0, 53.6, 59.0, 59.7, 120.1, 122.6, 130.4, 130.7, 131.8, 132.7, 133.5, 135.0, 137.7, 150.6, 154.2, 162.1, 165.8, 170.1; IR (KBr) 3570-3340, 2938, 1723, 1666, 1543, 1263, 1164  $\text{cm}^{-1}$ ; MS (FAB)  $m/z = 1763$  ( $\text{M-OTf}^+$ ).
10. Spectroscopic data of **2**:  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  1.32 (m, 8H), 1.53 (m, 8H), 1.74 (m, 8H), 1.95 (m, 10H), 2.98 (bs, 4H), 3.88 (s, 6H), 3.91 (bs, 8H), 8.34 (s, 4H), 7.46 (m, 6H), 7.56 (m, 4H), 7.69 (m, 6H), 7.81 (m, 4H), 7.96 (s, 2H), 8.15 (bs, 4H), 8.42 (s, 6H), 8.62 (d, 4H,  $J = 7.0$  Hz), 8.81 (bs, 4H), 10.73 (bs, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.2, 22.1, 22.2, 25.4, 30.2, 32.5, 53.1, 53.2, 55.4, 123.0, 124.2, 124.8, 125.2, 125.4, 125.6, 130.3, 131.8, 133.5, 135.8, 136.0, 138.7, 144.3, 151.8, 163.0, 166.7, 168.1, 168.8; IR (KBr) 3418, 3344, 2938, 1723, 1651, 1540, 1278, 1261, 1165  $\text{cm}^{-1}$ ; MS (FAB)  $m/z = 2001$  ( $\text{M-OTf}^+$ ).
11. Spectroscopic data of **3**:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}+\text{DMSO-d}_6$ )  $\delta$  1.32 (m, 8H), 1.42 (m, 4H), 1.60 (m, 4H), 1.79 (m, 8H), 1.88 (m, 4H), 1.97 (m, 4H), 2.61 (s, 8H), 3.89 (m, 4H), 4.06 (m, 4H), 8.08 (s, 4H), 9.12 (s, 4H), 9.18 (s, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.9, 32.8, 32.9, 48.3, 48.4, 53.7, 55.6, 132.7, 133.4, 138.9, 151.6, 155.6, 163.0, 164.2; IR (KBr) 3430, 3248, 2939, 1655, 1544, 1385, 1145  $\text{cm}^{-1}$ ; MS (FAB)  $m/z = 1610$  ( $\text{M-ClO}_4^+$ ).
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