

# Tripodal oxazoline-based homochiral coordination cages with internal binding sites†

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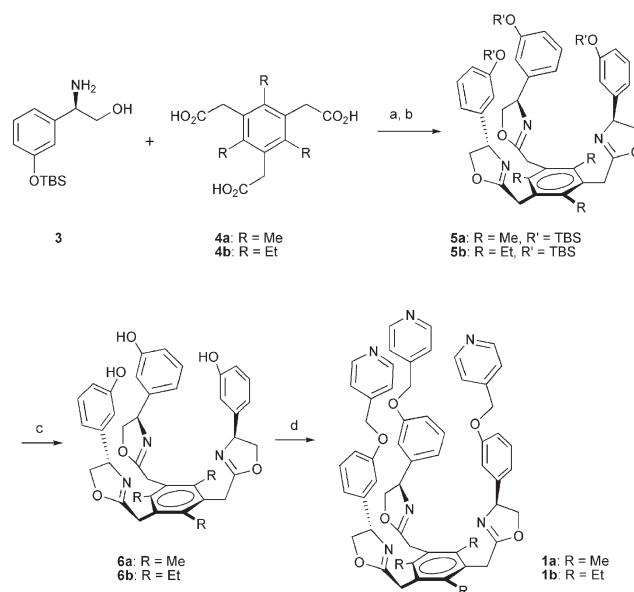
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Homochiral coordination cages, which have two well-defined internal binding sites for ammonium and organoammonium ions, have been constructed by Pd(II)-mediated self-assembly of preorganized tripodal oxazolines containing pyridine pendant groups.

Metal-directed self-assembly has been widely used to construct supramolecular container molecules because of its operational simplicity compared to syntheses based on non-coordinative covalent bond formation. Thus, a variety of so-called coordination cages or capsules have been constructed for potential applications such as molecular receptors, catalysts, delivery systems, and so on.<sup>1</sup> In spite of such efforts in the synthesis of coordination cages in recent years,<sup>2</sup> the construction of coordination cages that have homochirality and/or internal binding sites specific to certain guests has been rarely addressed and remains as a challenging task.<sup>3</sup> This may be due to the difficulty of incorporating chirality or guest binding sites in the cavity of coordination cages. Herein, we wish to report for the first time the construction of homochiral supramolecular cages by metal mediated self-assembly of chiral tripodal oxazolines containing pyridine pendant groups. The cages contain two well-defined internal binding sites suitable for ammonium and organoammonium ions, provided by the homochiral oxazoline ligands.

Based on our experience of molecular recognition using tripodal oxazoline receptors,<sup>4</sup> we envisioned that they might be used as new platforms for the construction of homochiral coordination cages because they readily provide screw-sense chiral pockets through preorganization. A molecular modelling study suggested that tripodal oxazolines based on (3-substituted-phenyl)glycinols, such as **1** in Scheme 1, would form dimeric supramolecular cages. Upon binding an ammonium ion through tripodal hydrogen bonds to three oxazoline nitrogens, the 3-substituted metal binding ligands point upwards, ready for metal binding to form dimeric cages. Thus, a protected (3-hydroxyphenyl)glycinol was chosen as the precursor for the tripodal oxazolines, because introducing the



**Scheme 1** Reagents and conditions: (a) (COCl)<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (b) MsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; (c) 1.0 M aq. NaOH, MeOH, rt, 6 h; (d) NaH, DMF; 4-bromomethylpyridine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h.

metal binding ligands *via* ether formation was readily conceivable. The tripodal oxazoline **5a** was thus synthesized from amino alcohol **3**<sup>5</sup> and tricarboxylic acid **4a** in a one-pot reaction according to the established procedure.<sup>4</sup> Then, deprotection of the silyl group of **5a**, followed by generation of its phenoxide ion and subsequent treatment with 4-bromomethylpyridine, afforded pyridyl-oxazoline **1a** as a white powder in overall 62% yield. Similarly, a more preorganized analogue **1b** was synthesized starting from **5b** in 53% yield (ESI†). Both **1a** and **1b** exhibited rather simple <sup>1</sup>H and <sup>13</sup>C NMR spectra at room temperature, consistent with their C<sub>3</sub> symmetric nature.

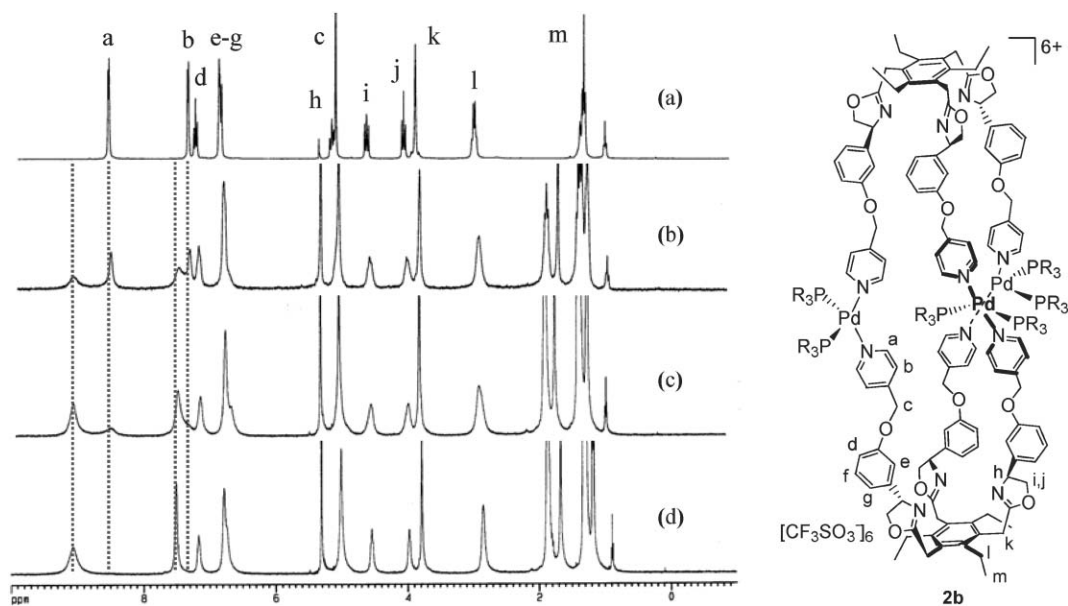
Next, the formation of metal-mediated supramolecular cages from homochiral tripodal oxazolines **1** was investigated using *trans*-palladium(II) bis(triflate) complexes, following literature conditions.<sup>2</sup> Judging from their NMR spectra, the more preorganized ligand **1b** produced a more discrete cage structure compared to **1a**. Thus, mixing **1b** and *trans*-Pd(OTf)<sub>2</sub>(PEt<sub>3</sub>)<sub>2</sub> in a 2 : 3 molar ratio at room temperature in a solvent such as CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, or CH<sub>3</sub>COCH<sub>3</sub> produced dimeric cage **2b** (Fig. 1), whose structure was characterized by the following experiments.

Formation of cage **2b**† could be monitored by following the <sup>1</sup>H NMR spectrum upon changing the molar ratio of the ligand and Pd source (**1b**/[Pd(II)]).§ When the molar ratio was less than 2 : 3,

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**Fig. 1** Self-assembly of **1b** and *trans*-[Pd(OTf)<sub>2</sub>(PEt<sub>3</sub>)<sub>2</sub>], monitored by <sup>1</sup>H NMR in CD<sub>2</sub>Cl<sub>2</sub> at 25 °C: (a) Free **1b** (the peaks assigned are for the ligand itself), (b) a mixture of **1b** and *trans*-Pd(OTf)<sub>2</sub>(PEt<sub>3</sub>)<sub>2</sub> in a ratio of 2 : 1, (c) 1 : 1 and (d) 2 : 3.

two sets of signals were observed, including the ligand's peaks. The peak's relative intensities were dependent upon their molar ratio, which was clearly indicated by following the  $\alpha$ -pyridyl protons (indicated with dotted lines in Fig. 1). These two sets of signals merged into one set at the molar ratio 2 : 3; a point equivalent of dimeric cage formation. The <sup>31</sup>P NMR spectrum of **2b** exhibited a sharp singlet at 26.2 ppm, which indicates that the six Et<sub>3</sub>P groups are equivalent and the cage is highly symmetrical. Its <sup>19</sup>F NMR spectrum also exhibited a sharp singlet at -77.7 ppm, which indicates no localization of the triflate ions. The molecular entity of the dimeric cage was also supported by vapor pressure osmometry in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C, which gave a molecular weight (3930) close to the calculated value for the dimeric cage (3841). Further evidence for cage formation was obtained by cold-spray ionization mass (CSI MS) analysis of the 2 : 3 mixture, which showed rather weak but discernable peaks at *m/z* = 3691 and 3841.9, corresponding to [M - CF<sub>3</sub>SO<sub>3</sub>]<sup>+</sup> and [M + H]<sup>+</sup> fragments. It is worthwhile to note that cage formation was either incomplete or inhibited by polar solvents such as CH<sub>3</sub>CN, Me<sub>2</sub>SO and DMF. The less preorganized ligand **1a** also produced the corresponding dimeric cage under similar conditions; however, in this case, a broad and less well-resolved <sup>1</sup>H NMR spectrum was observed compared to the case of **1b**.

Cage **2b** seems to provide a cylindrical cavity, the volume of which was calculated to be about 2100 Å<sup>3</sup> by fitting an ellipsoid of rotation whose principal axes were *a* = 28 Å, *b* = 10 Å and *c* = 10 Å.¶ This cage may have "twist chirality"<sup>6</sup> owing to the screw-sense chirality of the oxazoline phenyl substituents. However, we could not confirm such helicity either for the cage itself or for its (*R*)- $\alpha$ -phenylethylammonium complex by circular dichroism spectroscopy, possibly due to their flexible nature. VT-NMR experiments from -35 to 40 °C for cage **2b** resulted in further splitting of the peaks; for example, two major peaks for the  $\alpha$ -pyridyl protons, which might have been due to the twist chirality. A slight peak at 8.6 ppm due to free  $\alpha$ -pyridyl protons

was observed below 10 °C, suggesting that open structures exist in only slight amounts, if at all.†

We studied the disassembly of **2b** using Et<sub>3</sub>N as a competing ligand. Upon adding Et<sub>3</sub>N, the cage in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C began to disassemble into ligand **1b**, and a complete disassembly was observed in the presence of 10 equivalents of Et<sub>3</sub>N.

Based on our successful cage formation, we investigated the molecular encapsulation ability of cage **2b** towards ammonium ions. As we have demonstrated previously, ligands **1** can efficiently bind ammonium and organoammonium ions through tripodal hydrogen bonding and cation  $\pi$ -interactions.<sup>4</sup> When cage **2b** was titrated with NH<sub>4</sub><sup>+</sup>PF<sub>6</sub><sup>-</sup> in CD<sub>2</sub>Cl<sub>2</sub> at room temperature, significant complexation-induced chemical shifts (CICS) were observed when two equivalents of the ammonium ion were added, readily observable for one of the oxazoline ring protons ( $\delta$  3.97 → 4.23;  $\Delta\delta$  = 0.26) and the benzylic ( $\delta$  2.84 → 2.56;  $\Delta\delta$  = 0.28) protons.‡ This result indicates, as expected, that **2b** binds two equivalents of the ammonium ion at both of the internal oxazoline binding sites. This binding experiment also confirms that the cage has a dimeric structure. At this point, we confirmed that a 1 : 1 inclusion complex between **1b** and NH<sub>4</sub><sup>+</sup>PF<sub>6</sub><sup>-</sup> could also form the corresponding guest-included cage complex, upon addition of the palladium precursor through a self-assembly process. Thus, we can generate the ammonium ion-included cage either by cage formation followed by guest inclusion or *vice versa*.

As the tripodal oxazoline ligands derived from phenylglycinol itself bind ammonium and organoammonium ions efficiently,<sup>4</sup> cages **2**, which contain similar binding pockets, are also expected to selectively recognize other chiral and/or achiral organoammonium ions that fit the cavity. A preliminary binding study towards the  $\alpha$ -phenylethylammonium ion (as its perchlorate salt) indicated that **2b** forms distinct (*R,R*)- and (*S,S*)-diastereomeric inclusion complexes. Upon addition of the (*R*)- or (*S*)-guest to **2b** in a 2 : 1 molar ratio, the  $\alpha$ -methyl group of each of the enantiomeric guests showed a significant upfield shift (0.17 and -0.04 ppm for

the (*R,R*)- and (*S,S*)-inclusion complexes, respectively; 1.63 ppm in the absence of **2b**). A similar upfield shift was observed previously in the case of “open” tripodal oxazoline receptors similar to **5**, explained by the diamagnetic shielding of the guest surrounded by the oxazoline phenyl rings.<sup>4</sup> When four molar equivalents of a racemic mixture of the  $\alpha$ -phenylethylammonium ion were added to **2b**, interestingly, the  $\alpha$ -methyl group of the guest was split into three peaks of ratio 10 : 7 : 2, in which the two major peaks could be assigned to the (*R,R*)- and (*S,S*)-inclusion complexes, respectively; the new minor peak appearing at  $-0.21$  ppm was tentatively assigned to the (*R,S*)-inclusion complex.<sup>†</sup> A further study of the enantiodiscriminatory behavior of **2b** towards other chiral organoammonium ions is necessary to address the scope and limitation of our cage system as a chiral selector.

In summary, we have constructed homochiral coordination cages for the first time that provide two well-defined internal binding sites for ammonium and organoammonium ions. The cages are constructed by Pd(II)-mediated dimerization of  $C_3$  symmetric tripodal oxazoline units bearing pyridine pendant groups. A preliminary binding study indicates that the cages can recognize organoammonium ions, including chiral examples.<sup>‡</sup>

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## Notes and references

<sup>‡</sup> Cage **2b** was assembled by mixing **1b** with Pd(OTf)<sub>2</sub>(PEt<sub>3</sub>)<sub>2</sub> in a molar ratio 2 : 3 in CH<sub>2</sub>Cl<sub>2</sub> at rt for 5 min. Removal of the solvent *in vacuo* afforded the desired cage in quantitative yield:  $\delta_{\text{H}}$  (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>, Me<sub>4</sub>Si, 323 K) 9.1 (12 H, s), 7.5 (12 H, br s), 7.2 (6 H, br s), 6.8 (18 H, br s), 5.0 (18 H, br s), 4.5 (6 H, br s), 4.0 (6 H, br s), 3.8 (12 H, br s), 2.8 (12 H, br s), 1.9–1.8 (36 H, m), 1.7 (18, br s) and 1.3–1.25 (54 H, m);  $\delta_{\text{P}}$  (81 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 26.2;  $\delta_{\text{F}}$  (188.3 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $-77.7$ ; CSI-MS: *m/z* 3200.9 [M – CF<sub>3</sub>SO<sub>3</sub>]<sup>+</sup> and 3841.9 [M + H]<sup>+</sup>.

<sup>§</sup> With the corresponding *cis* Pd(II) source, no cage formation was observed. This result corresponds to the modelling study that indicates the

dimeric cage is preferred over other complexes due to the geometry of **1b**. The result also excludes the possibility of *cis*–*trans* equilibration of the *trans*-Pd source under the given conditions.

<sup>¶</sup> Molecular mechanics computations were performed using Spartan Windows '04, purchased from Wavefunction, Inc.

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