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Connection of Metallamacrocycles via Dynamic Covalent Chemistry: A Versatile Method for the Synthesis of Molecular Cages

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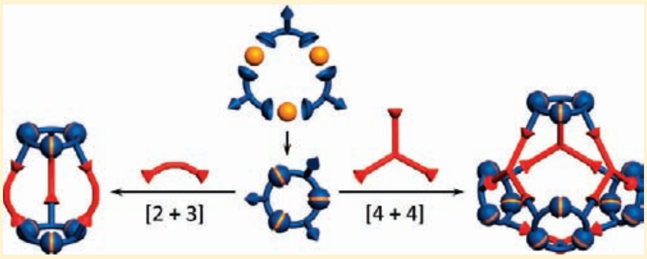
S Supporting Information



ABSTRACT: A modular approach for the synthesis of cage structures is described. Reactions of $[(\text{arene})RuCl_2]_2$ [arene = *p*-cymene, 1,3,5-$C_6H_3Me_3$, 1,3,5-$C_6H_3(i\text{-}Pr)_3$] with formyl-substituted 3-hydroxy-2-pyridone ligands provide trinuclear metallamacrocycles with pendant aldehyde groups. Subsequent condensation reactions with di- and triamines give molecular cages with 3, 6, or 12 Ru centers in a diastereoselective and chemoselective (self-sorting) fashion. Some of the cages can also be prepared in one-pot reactions by mixing $[(\text{arene})RuCl_2]_2$ with the pyridone ligand and the amine in the presence of base. The cages were comprehensively analyzed by X-ray crystallography. The diameter of the largest dodecanuclear complex is ~3 nm; the cavity sizes range from 290 to 740 Å^3. An amine exchange process with ethylenediamine allows the clean conversion of a dodecanuclear cage into a hexanuclear cage without disruption of the metallamacrocyclic structures.

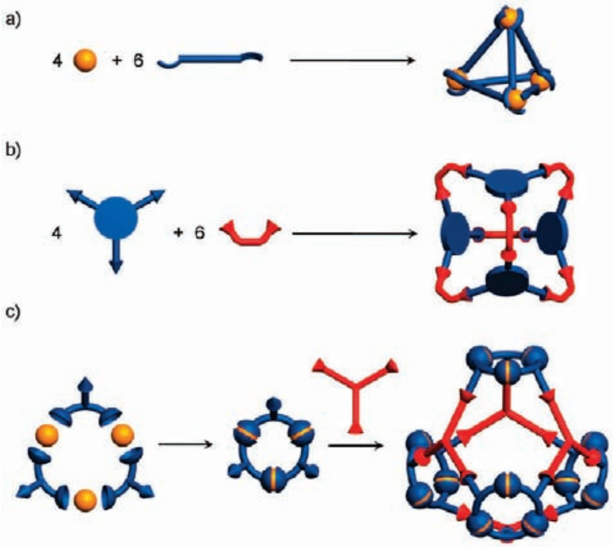
INTRODUCTION

Natural molecular cages such as viral capsids[1] or ferritin[2] are formed by self-assembly of protein building blocks. In a related fashion, synthetic molecular cages can be obtained by assembly of molecular building blocks via reversible covalent[3] or non-covalent bonds.[4,5] In terms of size, complexity, and functionality, most synthetic cages cannot rival protein-based nanocages. However, significant advances have been made in recent years, and interesting applications have begun to emerge. For example, synthetic cages have been used as nanoreactors for chemical reactions,[6] as transport vehicles for drugs,[7] as containers for reactive chemical species,[8] and as organizing structures for stacked π-systems.[5m,9]

The most widely used method for the preparation of synthetic cages involves the connection of metal complexes or metal ions via polytopic ligands.[5] The thermodynamically controlled synthesis of metal-free cages has been achieved by linking organic subunits via hydrogen bonds,[10] charge−charge interactions,[11] van der Waals forces,[12] or dynamic covalent bonds such as imines,[13] boronate esters,[14,15] and disulfides.[16] Reversible amine−aldehyde condensation reactions have also been used in conjunction with metallasupramolecular chemistry.[17] However, the imine bonds are usually formed in the first coordination sphere of the metal complex. Our group is interested in exploring the possibility of combining dynamic covalent chemistry and metal−ligand interactions in an orthogonal fashion, i.e., the reversible covalent bond is formed *independently* from the metal complex.

Scheme 1 describes different approaches for the synthesis of molecular cages with a tetrahedral geometry. Coordination cages can be obtained by reaction of metal ions with ditopic bridging

Scheme 1. Strategies for the Synthesis of Tetrahedral Cages[a]



[a] (a) Self-assembly of M_4L_6 coordination cages from metal ions and organic ligands. (b) [4 + 6] condensation reactions of trialdehydes with diamines. (c) Assembly of trinuclear metallamacrocycles with pendant aldehyde groups followed by [4 + 4] condensations with triamines. Cones, aldehyde groups; collars, amine groups; spheres, metal ions or complexes.

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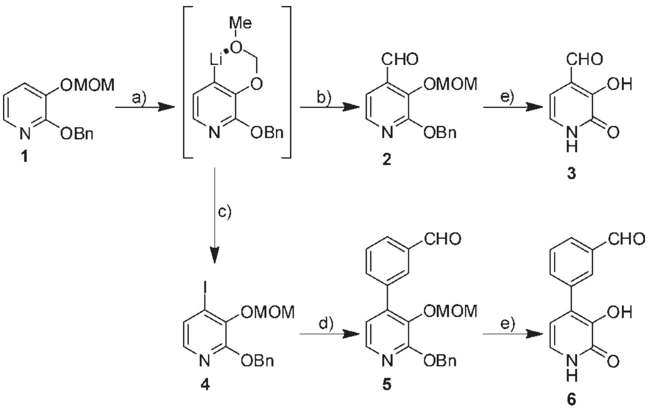
Scheme 2. Synthesis of the Formyl-Substituted 3-Hydroxy-2-pyridone Ligands 3 and 6[a]



[a] Reagents and conditions: (a) *t*-BuLi (2 equiv), THF, −80 °C; (b) $(CH_2)_5NCHO$, −80 °C to room temp, 65%; (c) I_2, −80 °C to room temp, 61−67%; (d) 3-formylphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe−EtOH−H_2O, reflux, 95%; (e) CF_3COOH−CH_2Cl_2, room temp, 82−89%.

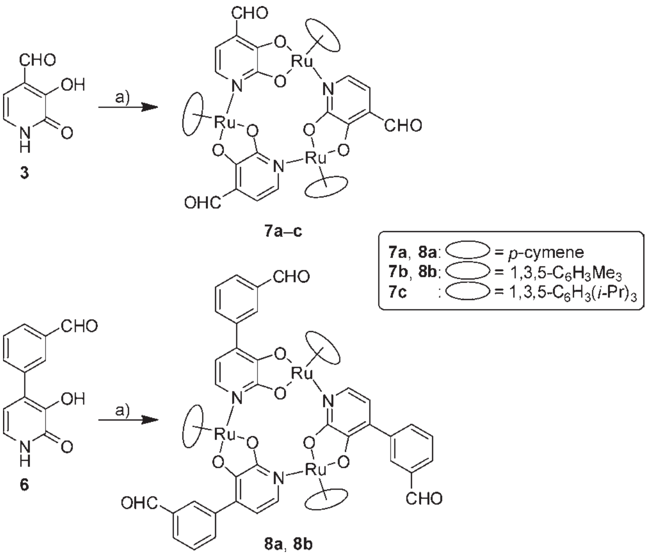
ligands in the ratio 4:6 (Scheme 1a). This methodology has been used by the groups of Raymond,[6c,d,18] Ward,[19] and others[5] to generate cages with different sizes and functionalities. Nitschke et al. recently demonstrated that the metal-binding part of the bridging ligand can also be formed in situ by an imine condensation reaction.[20] Purely organic cages with a tetrahedral geometry have been reported by Cooper,[13b,c] Gawronski,[13h] and Mastalerz.[13i] [4 + 6] polycondensation reactions of trialdehydes with diamines (Scheme 1b) or of dialdehydes with triamines were shown to result in the formation of cages in one step.

A reaction sequence which involves metallasupramolecular chemistry and dynamic covalent chemistry is shown in Scheme 1c. First, a trinuclear metallamacrocycle with three pendant aldehyde groups is formed by self-assembly. Subsequent condensation with a triamine gives the cage structure. Recently, we demonstrated that reaction sequences of this kind can be realized.[21] Dodecanuclear coordination cages were obtained by reaction of (arene)Ru^{II} complexes with 4-formyl-3-hydroxy-2-pyridone followed by [4 + 4] condensations with triamines. Below we show that the synthetic concept to combine Ru-based macrocycles containing formyl groups with amine linkers is highly versatile. By variation of the three different building blocks—the Ru complex, the formyl-substituted pyridone ligand, and the amine linker—it is possible to change not only the size and the solubility of the cages but also their topology. We will describe the syntheses and the molecular structures of tri-, hexa-, and dodecanuclear cages. It is shown that the cages, which contain chiral metal centers, are formed in a diastereoselective and chemoselective (self-sorting) fashion. Furthermore, we demonstrate that simple one-pot reactions are possible, and we will discuss the dynamic behavior of the complexes and how exchange processes can be used to interconvert cage structures.

RESULTS AND DISCUSSION

Synthesis of 3-Hydroxy-2-pyridone Ligands. Our approach for the synthesis of 4-substituted derivatives of 3-hydroxy-2-pyridone relies on the regioselective lithiation of the pyridine derivative **1** (Scheme 2). The latter is readily prepared from the commercially available 2-chloro-3-hydroxypyridine. The *ortho*-directing effect of the methoxymethoxy (MOM) group on the lithiation of the pyridine ring is well-documented, and it is supposedly due to the chelation of lithium by one or both of the oxygen atoms of the protecting group.[22] However, we observed that 2 equiv of *t*-BuLi was necessary for a complete conversion of **1**, presumably because 1 equiv of the reagent is chelated by the nitrogen atom and the benzyloxy group.

Scheme 3. Synthesis of the Metallamacrocycles 7a−c and 8a,b[a]



[a] Reagents and conditions: (a) $[(arene)RuCl_2]_2$, Cs_2CO_3, CH_2Cl_2−MeOH, room temp, 70−90%.

Reaction of lithiated **1** with *N*-formylpiperidine gave the 1,2-diprotected isonicotinaldehyde **2**, whereas quenching with iodine gave the 4-iodopyridine derivative **4** in comparable yields (60−67%). Reaction of **4** with 3-formylphenylboronic acid under the standard conditions of Suzuki coupling ($Pd(PPh_3)_4$, K_2CO_3, toluene−water) gave the diprotected aldehyde **5**, which may be considered as a phenyl homologue of isonicotinaldehyde **2**. Both protecting groups of **2** and **5** were removed under acidic conditions (50% trifluoroacetic acid in dichloromethane) to give the formyl-substituted 3-hydroxy-2-pyridone derivatives **3** and **6** in good yields (80−90%) without the need for purification.

Synthesis and Structures of Metallamacrocyclic Trialdehydes. The base-induced self-assembly of (arene)Ru^{II} complexes with 3-hydroxy-2-pyridone ligands was first described in 2001.[23] It was shown that trinuclear metallamacrocycles are formed in which the (arene)Ru centers are bridged by two-fold-deprotonated pyridone ligands. Subsequently, we and others have used this structural motif for the construction of specific receptors for cations[24] and anions.[25] In the course of these investigations, it was found that substituents at position 4 of the 3-hydroxy-2-pyridone ligand do not interfere with the self-assembly process.[24b,g,i] It was thus expected that the ligands **3** and **6** are suited for the construction of trimeric (arene)Ru complexes. Indeed, reactions of the chloro-bridged dimers $[(p\text{-cymene})RuCl_2]_2$, $[(1,3,5\text{-}C_6H_3Me_3)RuCl_2]_2$, or $[\{1,3,5\text{-}C_6H_3(i\text{-}Pr)_3\}RuCl_2]_2$ with ligand **3** or **6** in the presence of base (Cs_2CO_3) gave the trinuclear macrocyles **7a**−**c** and **8a**,**b** in 70−90% yield (Scheme 3). Overall, the spectroscopic properties of the metallamacrocycles were similar to what has been

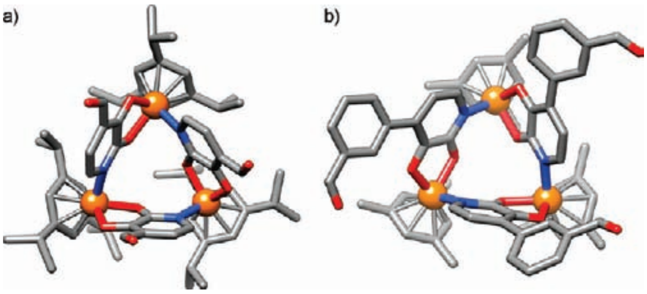


Figure 1. Structures of the trinuclear complexes **7c** (a) and **8b** (b) in the solid state. Solvent molecules and hydrogen atoms are omitted for clarity. In the case of **7c**, one of the isopropyl chains occupies two alternate positions; the one with the higher occupancy factor (0.6) is shown. Colors: C gray, N blue, O red, Ru orange.

described for other trimers of this kind.[23−25] In addition, characteristic signals for aldehyde groups were observed by ^{1}H and ^{13}C NMR spectroscopy (δ_H = 10.0−10.3 ppm; $\delta_C \approx$ 190 ppm; $CDCl_3$).

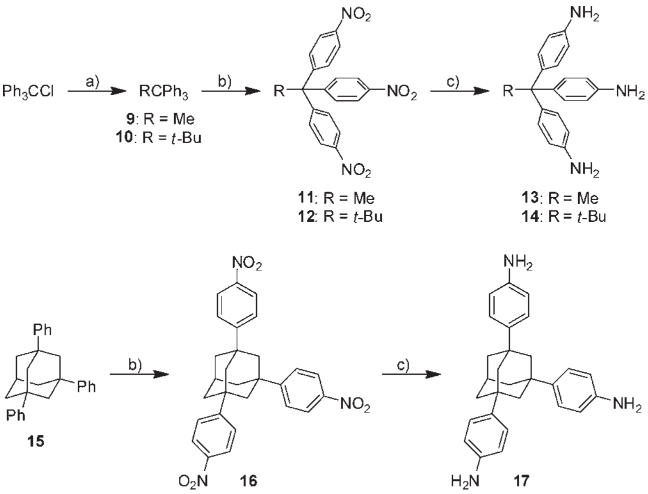
The molecular structures of **7b**,[21] **7c** (Figure 1a), **8a** (Supporting Information (SI), Figure S1b), and **8b** (Figure 1b) in the solid state were determined by single-crystal X-ray analyses (SI, Table S1). The Ru−O (2.04−2.10 Å) and Ru−N (2.12−2.15 Å) bond distances fall within the expected range.[23−25] The average distance between the oxygen atoms of the aldehyde groups of the (1,3,5-$C_6H_3Me_3$)Ru complex **7b** is 7.8 Å, whereas a value of 6.9 Å is found for the [1,3,5-C_6H_3(*i*-Pr)$_3$]Ru complex **7c**. This difference can be attributed to the steric bulk of the π-ligand [1,3,5-C_6H_3(*i*-Pr)$_3$], which results in a distortion of the cone-shaped macrocycle.

In the case of **8a,b**, the aldehyde groups may adopt different orientations due to rotation of the phenyl groups with respect to the metallamacrocyclic framework. Thus, the distances between the oxygen atoms of the aldehyde groups in **8a,b** vary between 8.1 and 15.0 Å.

Metallamacrocycles with bridging 3-hydroxy-2-pyridone ligands are known to undergo ligand exchange reactions in polar solvents such as methanol or water, a behavior which has been used for the generation of dynamic combinatorial libraries.[26] The formyl-substituted complexes **7a**−**c** displayed reduced lability, at least under the conditions employed. Due to low solubility in pure methanol, ligand exchange reactions were studied in CD_2Cl_2−CD_3OH (1.75:1 v/v). The ^{1}H NMR spectrum of an equimolar mixture of **7a** and **7b** (3 mM each) showed no evidence for the formation of heterotrimeric species after 7 days at room temperature. Under the same conditions, a mixture of the trimers **8a** and **8b** contained about 25% of mixed complexes, which indicates that complexes containing ligand **6** display a slightly higher lability. Since the additional phenyl groups of **8a** and **8b** are well separated, we attribute the difference in lability of complexes **7** and **8** to electronic rather than steric effects. A mixture of **7a** and **8b** did not undergo ligand exchange, in line with inertness of the former macrocycle (SI, Figure S2).

It can be concluded that the macrocyclic trialdehydes **7a**−**c** are highly preorganized building blocks, which are essentially inert under the conditions used for the synthesis of cages (*vide infra*). The phenyl homologues **8a,b** are largely inert as well, but their functional aldehyde groups are less preorganized due to increased conformational freedom.

Scheme 4. Synthesis of the C_3-Symmetric Triamines 13, 14, and 17[a]



[a] Reagents and conditions: (a) RMgCl, Et_2O, room temp, **9**, 64%, **10**, 11%; (b) HNO_3, H_2SO_4, 0 °C, **11**, 36%, **12**, 24%, **16**, 70%; (c) H_2 (1 atm), Pd/C, EtOH, **13** and **14**, ~quant., **17**, 74%.

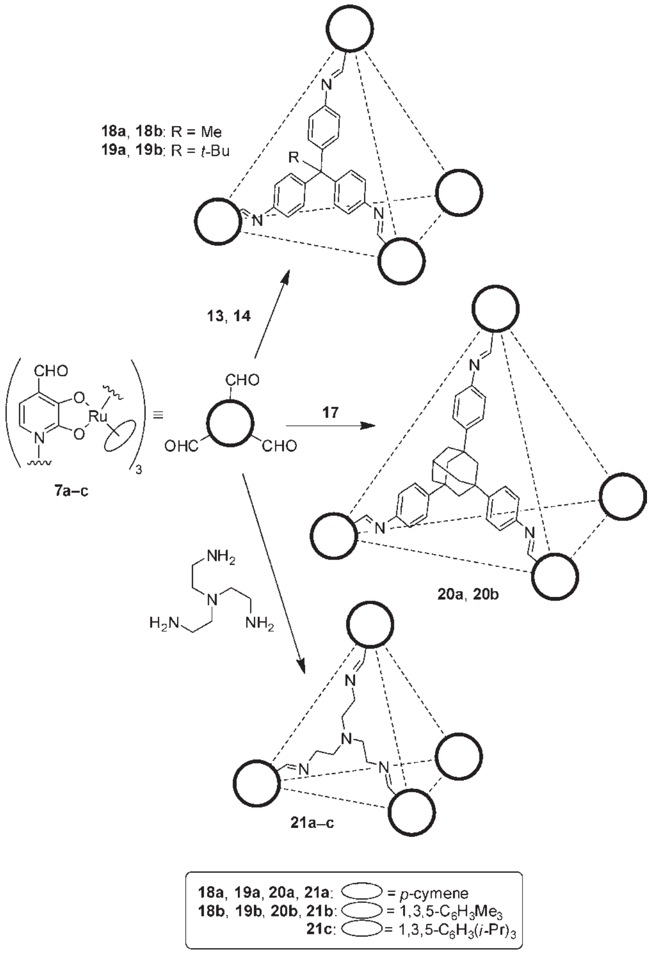
Synthesis of C_3-Symmetric Triamines. The C_3-symmetric triamines **13** and **14** are derivatives of tris(4-aminophenyl)methane with different alkyl substituents at the core carbon atom (methyl vs *tert*-butyl). They were prepared in three steps by reaction of trityl chloride with the corresponding Grignard reagents, followed by nitration of the 1,1,1-triphenylalkanes **9** and **10** and catalytic hydrogenation of the 1,1,1-tris(4-nitrophenyl)alkanes **11** and **12** (Scheme 4). In a similar fashion, 1,3,5-tris(4-aminophenyl)adamantane (**17**) was prepared from the readily available[27] 1,3,5-triphenyladamantane (**15**).

Tetrahedral Cages by [4 + 4] Condensation Reactions. In a recent communication we reported that 1,1,1-tris(4-aminophenyl)pentane reacts with trimers **7a,b** to give dodecanuclear cages.[21] The tris(4-aminophenyl)methane derivatives **13** and **14** and the adamantane-derived triamine **17** undergo similar [4 + 4] condensation reactions: when CH_2Cl_2−MeOH solutions (1.75:1 v/v) of equal amounts of either **7a** or **7b** and the respective triamine were allowed to react for 5−7 days at room temperature, the formation of cages was observed (Scheme 5). The (1,3,5-$C_6H_3Me_3$)Ru complexes **18b** (yield, 45%) and **20b** (33%) precipitated from the reaction mixture, the former as an orange powder and the latter in the form of orange, needle-like crystals. The complexes **18a**, **19a**, **19b**, and **20a** were isolated in 35−50% yields as amorphous solids, which formed upon removal of dichloromethane from the solutions adiabatically under vacuum.

Clear evidence for the formation of dodecanuclear [4 + 4] condensation products was obtained by high-resolution mass spectrometry (ESI). The ^{1}H and ^{13}C NMR spectra of the complexes **18**−**20** show only one set of signals for the 12 arene π-ligands and one for the four bridging imine ligands (the latter with apparent C_3 symmetry). These data suggest that cage formation proceeds in a diastereoselective fashion, an assumption which is confirmed by the crystallographic analyses described below.

Reactions of the triamines **13** and **14** with the [1,3,5-C_6H_3(*i*-Pr)$_3$]Ru complex **7c** were also attempted. However, slow decomposition of the metal complex during the course of the

Scheme 5. Synthesis of Tetrahedral Cages[a]



[a] Conditions: CH_2Cl_2−MeOH (1.75: 1 v/v), room temp, 7 days (**18**−**20**) or 24 h (**21**).

reaction was observed, as manifested by the formation of unbound triisopropylbenzene (detected by ^{1}H NMR spectroscopy). The low stability of the [1,3,5-C_6H_3(i-Pr)$_3$]Ru is likely related to the steric bulk of the π-ligand. In fact, the facile substitution of the 1,3,5-C_6H_3(i-Pr)$_3$ ligand from Ru^{II} complexes has already been observed in studies in the context of catalysis.[28]

Initially we assumed that the triamine had to be rather rigid to prevent the formation of smaller (e.g., [1 + 1] condensation)[29,30] or ill-defined condensation products (formation of a dynamic mixture or of oligomers). We were thus surprised to discover that reactions of **7a,b** with the flexible triamine tris(2-aminoethyl)amine (TREN) also resulted in the formation of [4 + 4] condensation products (**21a,b**). Moreover, the reactions with TREN were much faster, and complete condensation was observed after just 24 h. The increased reaction rate is presumably due to the higher nucleophilicity of the aliphatic amino groups of TREN. The products **21a** and **21b** were isolated as spectroscopically pure solids in 58% and 65% yield, respectively. However, the crude yield of the reactions was more than 90% according to ^{1}H NMR. The very clean formation of **21a,b** is in contrast to what has been observed for reactions with the triamines **13**, **14**, and **17**, where significant amounts of imine side products were detected in the crude reaction mixtures.

The shorter reaction time also enabled us to obtain the [1,3,5-C_6H_3(i-Pr)$_3$]Ru-containing cage **21c** from metallamacrocycle **7c**, albeit with low isolated yield (29%). The low yield is due to the high solubility of **21c**, which hampered its isolation.

The larger cages with phenyl groups in their walls (**18**−**20**) are moderately or poorly soluble in halogenated solvents ($CHCl_3$, CH_2Cl_2, C_6H_5F), but their solubility dramatically increases in the presence of small amounts of methanol as cosolvent (5−10% v/v). At the same time, they are essentially insoluble in pure methanol as well as in most other common solvents. The cages **21a**−**c** display higher solubility in halogenated solvents and in methanol, presumably due to the presence of polar tertiary amine groups. Overall, the following trends were observed: with respect to the nature of the triamine building block, the solubility of the cage products decreases in the order N(CH_2CH_2)$_3$ ≫ nBu-CPh_3[21] > t-BuCPh_3 > MeCPh_3 > 1,3,5-triphenyladamantane; with respect to the nature of the π-ligand, the solubility decreases in the order 1,3,5-C_6H_3(i-Pr)$_3$ > p-cymene > mesitylene. Thus, complex **20b** displays poor solubility in all solvents tested, whereas **21c** is well-soluble (≥10 mg mL^{-1}) in $CHCl_3$, THF, and MeOH.

Large (1−2 mm) single crystals of the cages **18a,b** and **19a,b** could be obtained by vapor diffusion of Et_2O into $CHCl_3$−MeOH or CH_2Cl_2−MeOH solutions (90:10 to 95:5 v/v). However, most of these crystals diffracted X-rays very poorly, and acceptable diffraction data sets could only be collected for **18b**. Crystals of **20b**, which were obtained directly from the reaction mixture, and crystals of the smaller cages **21a,b** (obtained from C_6H_5F−MeOH or $CHCl_3$) were also analyzed successfully by X-ray diffraction (XRD). Selected refinement details and structural features of the cages are given in Table 1 (for more details see SI, Table S2); the molecular structures of the cages are shown in Figure 2.

Table 1. Selected Structural Data for the Cages 18b, 20b, 21a, and 21b

	18b	**20b**	**21a**	**21b**
space group	$C2/c$	$C2/c$	$P2/n$	$Pcca$
R_1 ($I > 2\sigma$)	0.1260	0.0800	0.1109	0.1557
internal cavity volume (Å^3)[a]	500	740	290	290
maximal Ru···Ru distance (Å)	23.434(5)	26.117(9)	20.391(3)	20.388(5)

[a] Calculated as described in ref 21. The error is ±10%.

Overall, the geometries of the cages **18b**, **20b**, **21a**, and **21b** are similar: four trimeric Ru complexes are linked via imine bonds with four organic ligands to give dodecanuclear cages of approximate T symmetry (Figure 2). However, the sizes of the cages differ substantially. For the TREN-based cages **21a** and **21b**, the maximum Ru···Ru distance is 20.391(3) and 20.388(5) Å, respectively, whereas the corresponding value for the adamantane-containing cage **20b** is 26.117(9) Å (Table 1). Accordingly, the cavity volume increases from ~290 to ~740 Å^3.[31] In each case, highly disordered solvent molecules occupy the space in and around the cages. The crystals thus diffracted poorly at high angles and gave intensity data of limited quality. A more detailed discussion of bond lengths and angles is therefore not given.

The 12 ruthenium atoms of the cages are stereogenic centers. The metal atoms within the trimetric building blocks **7** have necessarily the same relative configuration.[23] Interestingly, the cages are obtained in the form of a single diastereoisomer (as evidenced by NMR), and the crystallographic analyses show that the four Ru trimers have the same configuration. The diastereoselectivity is particularly remarkable for the cages

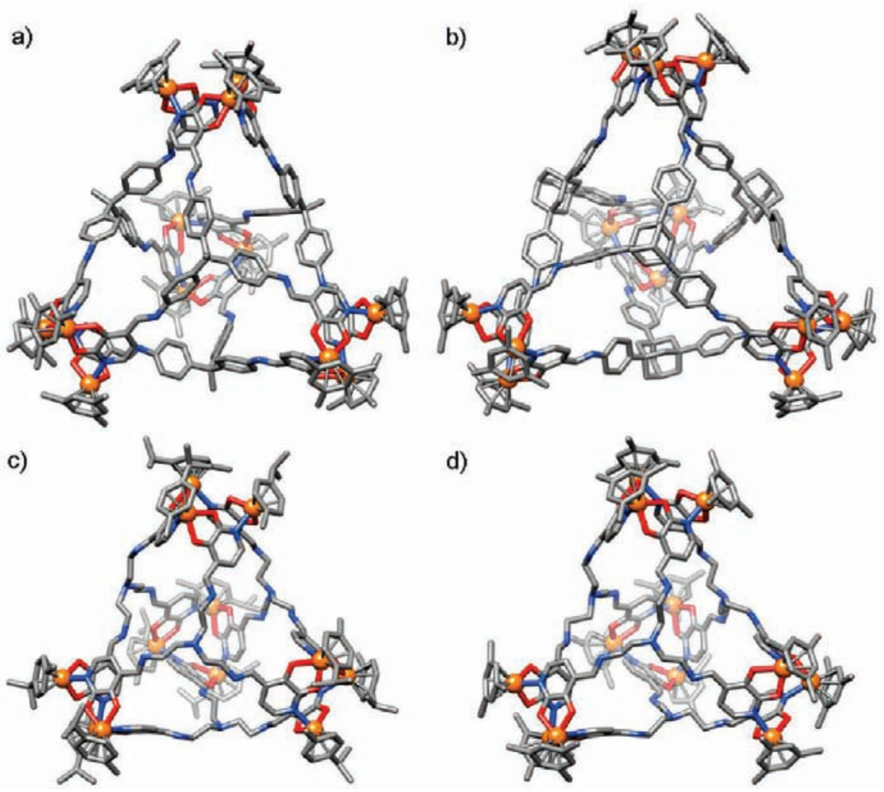
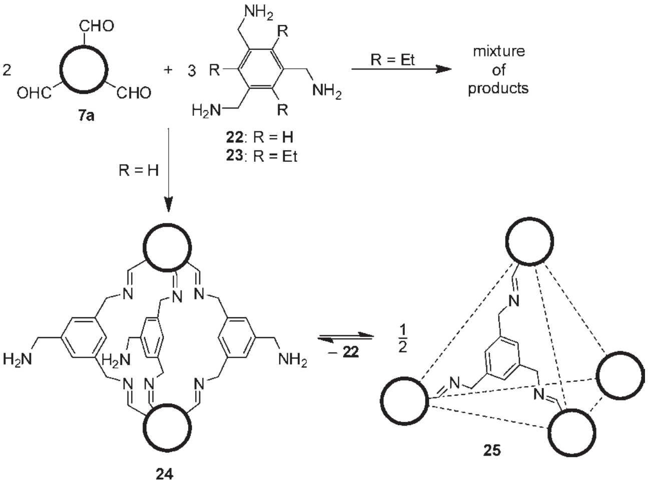


Figure 2. Structures of the dodecanuclear cages **18b** (a), **20b** (b), **21a** (c), and **21b** (d) in the solid state. Solvent molecules and hydrogen atoms are omitted for clarity. Colors: C gray, N blue, O red, Ru orange.

21a−**c**, which are obtained in nearly quantitative yield from a highly flexible TREN.

Reactions with 1,3,5-Tris(aminomethyl)benzene: Cage−Cylinder Equilibria. After having found that an aliphatic amine such as TREN is very reactive in condensation reactions with the metallamacrocycles **7**, we turned our attention to other alkylamines, namely the 1,3,5-tris(aminomethyl)benzenes **22** (improved synthetic procedure, see Supporting Information) and **23**.[32] Upon reaction of equimolar amounts of **7a** and **22** under the conditions employed before (CD_2Cl_2−CD_3OH 1.75:1, v/v), ^1H NMR monitoring of the reaction mixture indicated the presence of several condensation products, with equilibrium being established after ∼24 h. At this point, mass spectrometric analysis revealed the presence of the expected product of the [4 + 4] condensation, along with unexpected minor peaks for the products of the [2 + 3] and the [3 + 3] condensations (SI, Figure S3). The attempted isolation of the [4 + 4] product failed to give the cage in pure form. However, when the trialdehyde **7a** and the triamine **22** were mixed in a 2:3 ratio instead of 1:1, ^1H NMR analysis of the reaction mixture indicated the formation of a single product (**24**; crude yield, >95%). Complex **24** precipitated in the form of an orange powder upon removal of dichloromethane under vacuum (isolated yield, 32%). The ^1H and ^{13}C NMR spectra of **24** showed that the C_3 symmetry of the metal trimers was maintained in the product. However, the 1,3,5-trisubstituted benzene fragment displayed a lower symmetry. Two singlets at $\delta = 6.67$ and 7.02 ppm with an integral ratio of 2:1 were observed in the aromatic region of the ^1H NMR spectrum, along with a singlet at $\delta = 3.17$ ppm (66.2 ppm in ^{13}C NMR), which was assigned to a "free" aminomethyl group. On the basis of NMR and high-resolution MS data, complex **24** was proposed to be a hexanuclear (*p*-cymene)Ru complex resulting from the condensation of two metallamacrocyclic units **7a** with three molecules of triamine **22** (Scheme 6). This proposition was confirmed by an XRD analysis of single crystals, which were obtained by vapor diffusion of Et_2O into a solution of **24** in fluorobenzene (Figure 3; refinement data, SI, Table S3).

Scheme 6. Reactions of Metallamacrocycle 7a with 1,3,5-Tris(aminoethyl)benzene Derivatives 22 and 23



Complex **24** displays a cylindrical shape with a length of ∼2.5 nm (maximum C···C distance). A unique feature of

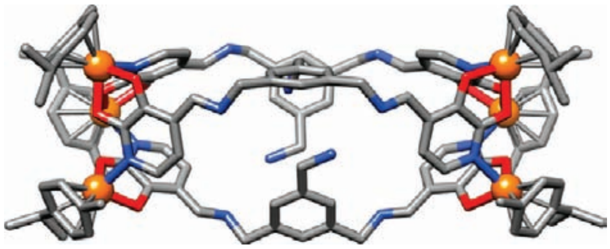


Figure 3. Structure of the hexanuclear complex **24** in the solid state. Solvent molecules and hydrogen atoms are omitted for clarity. Colors: C gray, N blue, O red, Ru orange.

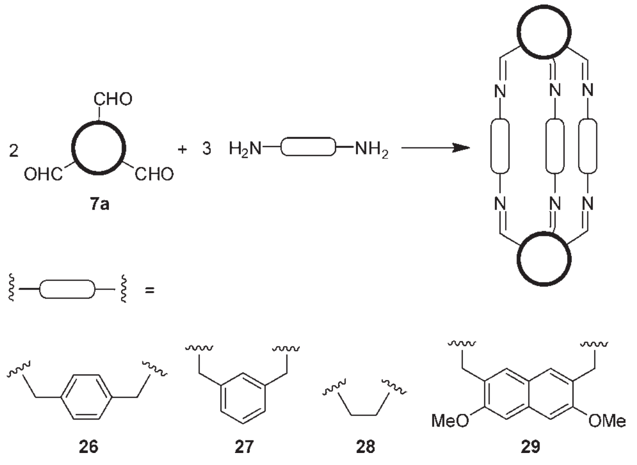
complex **24** is the presence of three "free" amine groups. Unlike what was observed for the dodecanuclear cages, the two Ru trimers have opposite chirality (achiral *meso*-form). Since the crude reaction mixture did not contain other products in significant amounts (as indicated by ^{1}H NMR), it may be concluded that the formation of **24** proceeds in a highly diastereoselective fashion.

When a solution of **24** in $CDCl_3$ was allowed to stand for 1−3 days, the NMR analysis showed the formation of a new complex along with signals of the free triamine ligand **22**. The new complex was shown to be a [4 + 4] condensation product (**25**, Scheme 6) on the basis of NMR and high-resolution MS data (SI, Figure S4). Cage **25** precipitated from solution, which allowed its isolation (yield 41%). Remarkably, this rearrangement was not observed if methanol was added as a cosolvent (5% v/v). A plausible reason is that the "free" amine groups are stabilized by hydrogen bonds to the protic cosolvent. It is interesting to note that a related conversion of a cage into a cylindrical compound with pendant amine groups was observed in the case of organic rhombicuboctahedral nanocapsules synthesized from formyl-substituted cavitands.[13l]

The reaction of **7a** with the triethyl-substituted triamine **23** was also attempted. However, complex mixtures of products were observed, regardless of the stoichiometry (1:1 or 2:3). Apparently, the high rigidity of **23**, which exists preferentially in the alternate (*ababab*) conformation with all three amine groups facing one side of the aromatic plane,[33] is not favorable for the formation of either cylindrical ([2 + 3]) or tetrahedral ([4 + 4]) cage structures.

Cylindrical Cages by [2 + 3] Condensation Reactions. The reaction with 1,3,5-tris(aminomethyl)benzene (**22**) demonstrated that cylindrical cages can be obtained. The use of diamines instead of triamines was expected to provide a more straightforward access to such structures because [2 + 3] condensations would give cylindrical cages without "free" amine groups. However, it should be pointed out that polycondensation reactions of C_3-symmetric trialdehydes with diamines are potentially very complex. For purely organic building blocks, it has been observed that such reaction can give tetrahedral cages via [4 + 6] condensations,[13c,h,i] large cubic cages via [8 + 12] condensations,[13k] and interpenetrated structures[13b] as well as polymers.[34]

Scheme 7. Synthesis of Cylindrical Cages by [2 + 3] Condensations[a]



[a] Conditions: CH_2Cl_2−MeOH (1.75:1 v/v), room temp, 18 h; alternative conditions for **26** and **27**, CH_2Cl_2−MeCN (1:1 v/v), AcOH (2 mol %), room temp, 48 h.

First, we performed reactions with *p*- and *m*-xylylenediamine, as these amines are related to the benzylic triamine **22**. Investigations of the [4 + 4] condensations had shown that the trialdehyde **7c** is potentially problematic because the π-ligand is easily replaced from the Ru center, and complex **7b** was found to give compounds of rather low solubility. We therefore focused on reactions with the (*p*-cymene)Ru trimer **7a**. After a solution of *p*-xylylenediamine and **7a** (ratio 3:2) in a mixture of CH_2Cl_2 and MeOH (1.75:1, v/v) was stirred for 18 h, NMR analysis of the reaction mixture indicated the formation of two products (ratio ∼1:5) whose spectra were similar. At the same time, the mass spectrum showed several peaks, all of which corresponded to the expected [2 + 3] condensation product **26** (Scheme 7). Similar results were obtained for reactions with *m*-xylylenediamine (SI, Figures S5 and S6). These results suggested that the complexes **26** and **27** were obtained as a mixture of diastereoisomers, in which the two Ru trimers have either the same (D_3-symmetric cylinder) or the opposite chirality (C_{3h}-symmetric cylinder; *meso* form). For complex **26** it was possible to separate the D_3-symmetric isomer from the *meso* form by selective precipitation. However, this required a change of the reaction conditions: instead of CH_2Cl_2−MeOH we used CH_2Cl_2−MeCN (1:1 v/v) and 2 mol % of acetic acid as a Brønsted acid catalyst. Under these conditions, complex **26** precipitated after 40 h in 56% yield in the form of a single isomer. The assignment of the isomer was achieved with the help of a single-crystal XRD analysis (Figure 4a). In the case of the reaction with *m*-xylylenediamine, the use of CH_2Cl_2−MeCN also led to a precipitation of cage **27**. However, the precipitate contained a mixture of the two stereoisomers (ratio ∼1:1).

Reactions of **7a** with either ethylenediamine or 2,7-bis(aminomethyl)-3,6-dimethoxynaphthalene (**30**; for synthesis see SI, Scheme S1) in CH_2Cl_2−MeOH (1.75:1 v/v) proceeded rapidly and gave one main product in each case (**28** and **29**, Scheme 7). The high-resolution MS data were in agreement with structures resulting from a [2 + 3] condensation, and the ^{1}H and ^{13}C NMR spectra pointed to the formation of a single diastereoisomer. A crystallographic analysis of cage **28** showed that it has a cylindrical structure with D_3 symmetry (Figure 4b), similar to what was observed for cage **26**. In the solid state, both **26** and **28** form columnar stacks, which are packed in a honeycomb-like fashion (Figure 4c). As a result, one can observe thin channels propagating along the crystallographic *c*-axis.

Self-Sorting and Amine Exchange Reactions. When multiple building blocks with cross-reactive functionalities are employed in self-assembly processes, the system can display a self-sorting

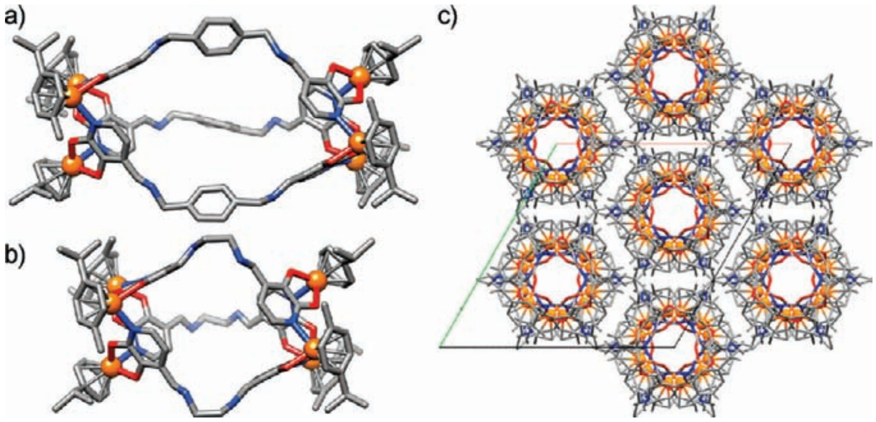
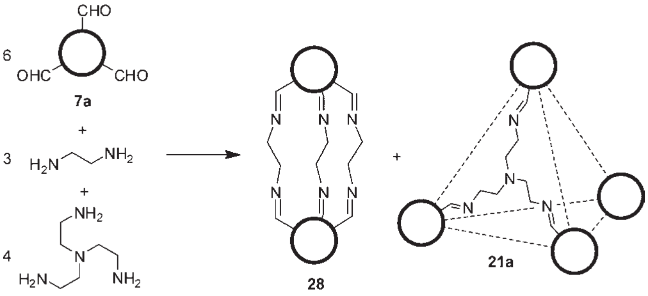


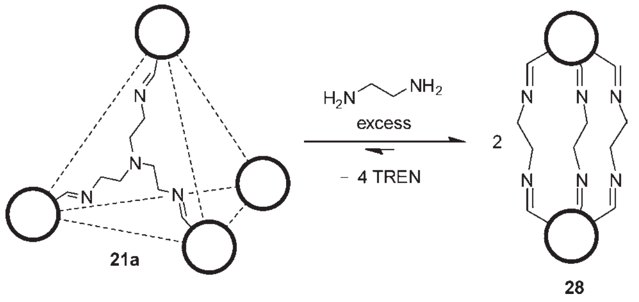
Figure 4. Structures of the hexanuclear cages **26** (a) and **28** (b) in the solid state, and packing of **26** viewed along the crystallographic *c*-axis (c). Solvent molecules and hydrogen atoms are omitted for clarity. Colors: C gray, N blue, O red, Ru orange.

Scheme 8. Condensation Reactions with a Mixture of Ethylenediamine and TREN Occur under Self-Sorting[a]

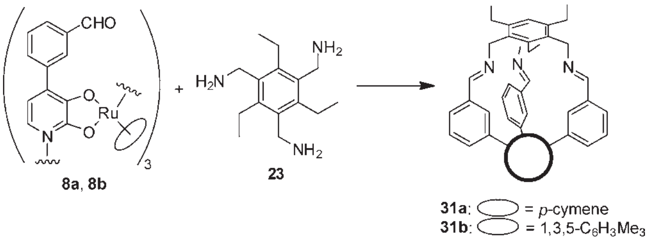


[a] Conditions: CD_2Cl_2−CD_3OD (1.75:1 v/v), room temp.

Scheme 9. Reaction of Cage 21a with an Excess of Ethylenediamine Results in Clean Conversion to Cylinder 28



Scheme 10. Synthesis of Small Cages 31a,b by [1 + 1] Condensations of Extended Trialdehydes 8a,b with Triamine 23[a]



[a] Conditions: CH_2Cl_2−MeOH (1.75:1 v/v), room temp, 18 h.

behavior, i.e., homoaggregates are favored over heteroaggregates. Self-sorting is frequently encountered in the area of metallasupramolecular chemistry,[35] but it is a rarely explored phenomenon in the field of dynamic covalent chemistry.[36] We were interested in whether self-sorting of amine building blocks would take place upon cage formation. Therefore, we examined the reaction of the metallamacrocyclic trialdehyde **7a** with a mixture of ethylenediamine and TREN (ratio 6:3:4). ^{1}H NMR analysis of the reaction mixture after 18 h revealed the exclusive formation of two imine products: the cylindrical cage **28** and the tetrahedral cage **21a** (Scheme 8; SI, Figure S7). NMR analysis of the mixture at a later stage revealed no changes in product distribution, indicating that the system was in its thermodynamically most stable state.

The imine bonds in the cage structures remain dynamic and can participate in exchange reactions. When a solution of the tetrahedral cage **21a** was mixed with an excess of ethylenediamine (10 equiv), a structural rearrangement took place, resulting in the clean formation of cylindrical complex **28** along with free TREN (Scheme 9; SI, Figure S8). It is interesting to note that we did not observe any decomplexation of the pyridonate ligands from the Ru centers despite the fact that we have used an excess of ethylenediamine, which is known to be a good chelate ligand. The ligand-induced reorganization of **21a** into **28** is reminiscent of the work of Nitschke, who has investigated extensively imine exchange reactions in metallasupramolecular structures.[17a,c] However, the imine bonds were situated in the first coordination sphere of transition metal ions (mostly Cu^I), whereas **21a** and **28** feature unsupported imines.

Small Cages via [1 + 1] Condensation Reactions. The reactivity of the extended trialdehydes **8a**,**b** toward various amines was also investigated. In the case of aromatic triamines such as **13**, **14**, and **17**, no condensation was observed, even in the presence of acetic acid as a catalyst. Apparently, **8a**,**b** display a lower intrinsic reactivity when compared to the smaller aldehydes **7a**,**b**. We attribute the diminished reactivity to steric rather than electronic effects because the chemical shifts of the ^{1}H and ^{13}C NMR signals of the aldehyde groups in **7** and **8** are quite similar.

Reactions with more nucleophilic alkylamines such as 2,7-bis(aminomethyl)-3,6-dimethoxynaphthalene (**30**), *p*-xylylenediamine, TREN, or 1,3,5-tris(aminomethyl)benzene (**22**) were also

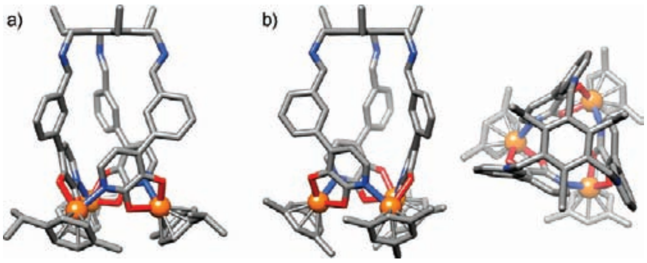


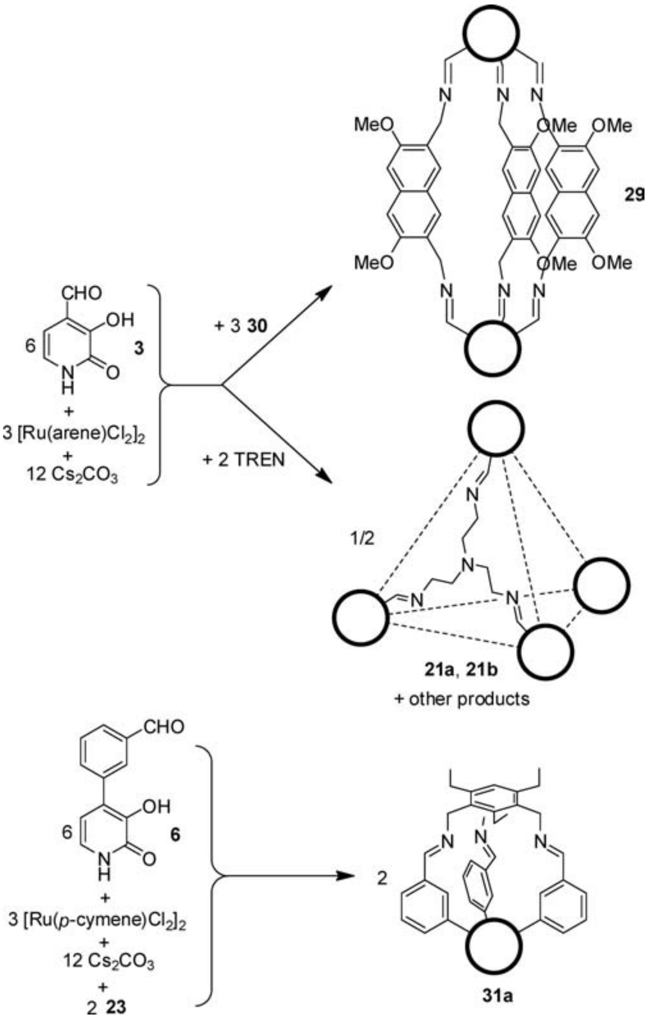
Figure 5. Structures of the trinuclear complexes **31a** (a) and **31b** (b) in the solid state. Solvent molecules and hydrogen atoms are omitted for clarity. Colors: C gray, N blue, O red, Ru orange.

inefficient, and incomplete condensation was observed after extended periods of time. Only reactions with the conformationally restricted triamine **23** gave in high yields single products (**31a,b**). On the basis of NMR and high-resolution MS data, it was deduced that **31a,b** are [1 + 1] condensation products resulting from the "capping" of the concave metallamacrocycles with the triamine (Scheme 10).

Single crystals of **31a,b** were analyzed by XRD. In both complexes, the hexasubstituted benzene ring is situated perpendicular to the C_3 axis of the metallamacrocycle (Figure 5). The complexes feature small cavities, but neither appears to be of sufficient volume to accommodate solvent molecules. Notably, racemic **31a** spontaneously resolves during crystallization, giving an equal quantity of the two stereoisomers in enantiopure form. However, the cubic morphology of the crystals (space group $R\bar{3}$) prevented naked eye distinction between the two enantiopure forms, and the crystals could therefore not be manually separated.

One-Pot Self-Assembly Reactions. All cage structures described so far were obtained in a stepwise fashion, i.e., the amine building blocks were mixed with preformed metallamacrocycles **7** and **8**. Such a two-step procedure appeared advantageous because—as discussed above—the metallamacrocycles are largely inert during the condensation reactions. Furthermore, it is possible to perform the condensations in the presence of Brønsted acid catalysts, whereas the formation of the metallamacrocycles requires the addition of base. Still, we were interested in exploring the possibility of obtaining cages in one-pot reactions. As targets, we chose cylinder **29**, the tetrahedral cages **21a,b**, and the trinuclear complex **31a**, because the condensation reactions starting with the preformed metallamacrocycles had given very good yields and stereoselectivities.

Scheme 11. One-Pot Self-Assembly Reactions[a]



[a] Conditions: $CD_2Cl_2-CD_3OD$ (1.75:1 v/v), room temp, 18 h.

First, we investigated the one-pot reaction of the pyridone ligand **3** with [(*p*-cymene)RuCl$_2$]$_2$ and the diamine **30** (ratio 6:3:3) in $CD_2Cl_2-CD_3OH$ (1.75:1 v/v) in the presence of Cs_2CO_3 as base (Scheme 11). An NMR analysis of the reaction mixture after 18 h revealed the quantitative formation of cylinder **29** (SI, Figure S8). The attempted one-pot synthesis of the tetrahedral cages **21a,b** was less successful. In reactions with [(*p*-cymene)RuCl$_2$]$_2$, it was possible to detect the NMR signals of cage **21a**, but there were large amounts of unidentified side products. Reactions with [(1,3,5-$C_6H_3Me_3$)RuCl$_2$]$_2$ were more selective and provided cage **21b** with a crude yield of 37% as determined by ^{1}H NMR spectroscopy (SI, Figure S10). This yield is lower than the overall yield for the two-step procedure (65%), but it is still respectable, given that the assembly of **21b** requires the formation of 48 bonds (36 Ru−L and 12 imine bonds). Isolation of complex **21b** from the reaction mixture was possible by selective precipitation (yield 13%). Finally, the one-pot reaction of the extended pyridone ligand **6** with [(*p*-cymene)RuCl$_2$]$_2$ and triamine **23** was investigated. As in the case of cylinder **29**, a nearly quantitative formation of complex **31a** was observed (SI, Figure S10). From these selected examples it can be concluded that one-pot reactions are feasible for simpler structures, but larger cages such as **21** are better obtained in a two-step fashion.

■ CONCLUSIONS

We have demonstrated that the combination of metallasupramolecular chemistry with dynamic covalent chemistry can be used for the rapid and efficient synthesis of molecular cages. Our approach is based on three types of building blocks: (arene)Ru^{II} complexes, formyl-substituted hydroxypyridone ligands, and amine linkers. By variation of the building blocks, we were able to change the size and the topology of the cages substantially. It was thus possible to obtain small trinuclear cages, hexanuclear cages with a cylindrical shape, and dodecanuclear cages with huge cavities. Notably, all dodecanuclear and most hexanuclear cages were formed in a highly diastereoselective fashion. A unique feature of our approach is the fact that the dynamic covalent bonds are formed independently, i.e., the imine bonds are not formed in the first coordination sphere of the metals. Reactivity studies have shown that it is possible to address the imine bonds selectively, as demonstrated by the conversion of a tetrahedral cage into a cylindrical cage via an imine exchange reaction. The goal of the present study was to establish the scope and the limitations of the synthetic approach, with special focus on the building blocks mentioned above. It appears likely, however, that the basic concept of linking metallasupramolecular building blocks via dynamic covalent bonds[37] can be extended to other metal complexes (e.g., Pd^{II}-based assemblies) and to different types of organic linkers. Further investigations in this direction are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details; ^{1}H and ^{13}C NMR spectra of the cages; crystallographic data; additional figures; and complete ref 13c. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Sitharam, M.; Agbandje-McKenna, M. *J. Comput. Biol.* **2006**, *13*, 1232–1265. (b) Zlotnick, A. *J. Mol. Recognit.* **2005**, *18*, 479–490. (c) Zlotnick, A.; Stray, S. J. *Trends Biotechnol.* **2003**, *21*, 536–542.

(2) (a) Harrison, P. M.; Arosio, P. *Biochim. Biophys. Acta, Bioenerg.* **1996**, *1275*, 161–203. (b) Gerl, M.; Jaenicke, R. *Eur. Biophys. J.* **1987**, *15*, 103–109. (c) Gerl, M.; Jaenicke, R. *Biochemistry* **1988**, *27*, 4089–4096.

(3) Mastlerz, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5042–5053.

(4) (a) Scarso, A.; Rebek, J., Jr. *Top. Curr. Chem.* **2006**, *265*, 1–46. (b) Müller, A.; Roy, S. *J. Mater. Chem.* **2005**, *15*, 4673–4677. (c) Johnston, M. R.; Latter, M. J. *Supramol. Chem.* **2005**, *17*, 595–607. (d) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508.

(5) (a) Jin, P.; Dalgarno, S. J.; Atwood, J. L. *Coord. Chem. Rev.* **2010**, *254*, 1760–1768. (b) Ward, M. D. *Chem. Commun.* **2009**, 4487–4499. (c) Therrien, B. *Eur. J. Inorg. Chem.* **2009**, 2445–2453. (d) Han, Y.-F.; Jia, W.-G.; Yu, W.-B.; Jin, G.-X. *Chem. Soc. Rev.* **2009**, *38*, 3419–3434. (e) Saalfrank, R. W.; Maid, H.; Scheurer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8794–8824. (f) Tranchemontagne, D. J.; Ni, Z.; O'Keeffe, M.; Yaghi, O. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 5136–5147. (g) Dalgarno, S. J.; Power, N. P.; Atwood, J. L. *Coord. Chem. Rev.* **2008**, *252*, 825–841. (h) Schmittel, M.; Kalsani, V. *Top. Curr. Chem.* **2005**, *245*, 1–53. (i) Maurizot, V.; Yoshizawa, M.; Kawano, M.; Fujita, M. *Dalton Trans.* **2006**, 2750–2756. (j) Hamilton, T. D.; MayGillivray, L. R. *Cryst. Growth Des.* **2004**, *4*, 419–430. (k) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972–983. (l) Wang, M.; Zheng, Y.-R.; Ghosh, K.; Stang, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 6282–6283. (m) Bar, A. K.; Mostafa, G.; Mukherjee, P. S. *Inorg. Chem.* **2010**, *49*, 7647–7649. (n) Bar, A. K.; Chakrabarty, R.; Mostafa, G.; Mukherjee, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 8455–8459.

(6) (a) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 114–137. (b) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438. (c) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2009**, *42*, 1650–1659. (d) Koblenz, T. S.; Wassenaar, J.; Reek, J. N. H. *Chem. Soc. Rev.* **2008**, *37*, 247–262. (e) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349–358.

(7) (a) Zava, O.; Mattsson, J.; Therrien, B.; Dyson, P. J. *Chem. Eur. J.* **2010**, *16*, 1428–1431. (b) Therrien, B.; Süss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3773–3776.

(8) (a) Breiner, B.; Clegg, J. K.; Nitschke, J. R. *Chem. Sci.* **2011**, *2*, 51–56. (b) Rebek, J., Jr. *Nature* **2006**, *444*, 557.

(9) Review: (a) Klosterman, J. K.; Yamauchi, Y.; Fujita, M. *Chem. Soc. Rev.* **2009**, *38*, 1714–1725. For recent examples see: (b) Yamauchi, Y.; Hanaoka, Y.; Yoshizawa, M.; Akita, M.; Ichikawa, T.; Yoshio, M.; Kato, T.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132*, 9555–9557. (c) Murase, T.; Otsuka, K.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132*, 7864–7865. (d) Osuga, T.; Murase, T.; Ono, K.; Yamauchi, Y.; Fujita, M. *J. Am. Chem. Soc.* **2010**, *132*, 15553–15555.

(10) For selected examples see: (a) Atwood, J. L.; Szumna, A. *J. Am. Chem. Soc.* **2002**, *124*, 10646–10647. (b) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376–2377. (c) Prins, L. J.; De Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **2000**, *408*, 181–184. (d) Klok, H.-A.; Jolliffe, K. A.; Schauer, C. L.; Prins, L. J.; Spatz, J. P.; Möller, M.; Timmerman, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1999**, *121*, 7154–7155. (e) Rivera, J. M.; Martín, T.; Rebek, J., Jr. *Science* **1998**, *279*, 1021–1023. (f) Martín, T.; Obst, U.; Rebek, J., Jr. *Science* **1998**, *281*, 1842–1845. (g) Timmerman, P.; Vreekamp, R. H.; Hulst, R.; Verboom, W.; Reinhoudt, D. N.; Rissanen, K.; Udachin, K. A.; Ripmeester, J. *Chem. Eur. J.* **1997**, *3*, 1823–1832. (h) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469–472. (i) Kang, J.; Rebek, J., Jr. *Nature* **1996**, *382*, 239–241. (j) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem. Int. Ed.* **1996**, *35*, 1215–1218. (k) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed.* **1993**, *32*, 1699–1671.

(11) (a) Cresswell, A. L.; Piepenbrock, M.-O. M.; Steed, J. W. *Chem. Commun.* **2010**, *46*, 2787–2789. (b) Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Eur. J. Org. Chem.* **2006**, 2810–2816. (c) Corbellini, F.; Knegtel, R. M. A.; Grootenhuis, P. D. J.; Crego-Calama, M.; Reinhoudt, D. N. *Chem. Eur. J.* **2005**, *11*, 298–307. (d) Corbellini, F.; Costanzo, L. D.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946–9947. (e) Zadmard, R.; Junkers, M.; Schrader, T.; Grawe, T.; Kraft, A. *J. Org. Chem.* **2003**, *68*, 6511–6521. (f) Zadmard, R.; Schrader, T.; Grawe, T.; Kraft, A. *Org. Lett.* **2002**, *4*, 1687–1690. (g) Corbellini, F.; Flammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569–6575.

(12) (a) Ananchenko, G. S.; Moudrakovski, I. L.; Coleman, A. W.; Ripmeester, J. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 5616–5618. (b) Coleman, A. W.; Jebors, S.; Shahgaldian, P.; Ananchenko, G. S.; Ripmeester, J. A. *Chem. Commun.* **2008**, 2291–2303. (c) Ananchenko, G. S.; Udachin, K. A.; Pojarova, M.; Jebors, S.; Coleman, A. W.; Ripmeester, J. A. *Chem. Commun.* **2007**, 707–709. (d) Ananchenko, G. S.; Udachin, K. A.; Dubes, A.; Ripmeester, J. A.; Perrier, T.; Coleman, A. W. *Angew. Chem. Int. Ed.* **2006**, *45*, 1585–1588. (e) Ananchenko, G. S.; Udachin, K. A.; Pojarova, M.; Dubes, A.; Ripmeester, J. A.; Jebors, S.; Coleman, A. W. *Cryst. Growth Des.* **2006**, *6*, 2141–2148. (f) Ananchenko, G. S.; Udachin, K. A.; Ripmeester, J. A.; Perrier, T.; Coleman, A. W. *Chem. Eur. J.* **2006**, *12*, 2441–2447.

(13) (a) Jin, Y.; Voss, B. A.; Noble, R. D.; Zhang, W. *Angew. Chem. Int. Ed.* **2010**, *49*, 6348–6351. (b) Hasell, T.; Wu, X.; Jones, J. T. A.; Bacsa, J.; Steiner, A.; Mitra, T.; Trewin, A.; Adams, D. J.; Cooper, A. I. *Nature Chem.* **2010**, *2*, 750–755. (c) Tozawa, T.; et al. *Nature Mater.* **2009**, *8*, 973–978. (d) Tartaggia, S.; Scarso, A.; Padovan, P.; De Lucchi, O.; Fabris, F. *Org. Lett.* **2009**, *11*, 3926–3929. (e) Liu, X.; Sun, J.;

Warmuth, R. *Tetrahedron* **2009**, *65*, 7303–7310. (f) Xu, X.-N.; Wang, L.; Wang, G.-T.; Lin, J.-B.; Li, G.-Y.; Jiang, X.-K.; Li, Z.-T. *Chem. Eur. J.* **2009**, *15*, 5763–5774. (g) Steinmetz, V.; Couty, F.; David, O. R. P. *Chem. Commun.* **2009**, 343–345. (h) Skowronek, P.; Gawronski, J. *Org. Lett.* **2008**, *10*, 4755–4758. (i) Mastalerz, M. *Chem. Commun.* **2008**, 4756–4758. (j) Kunert, N.; Le-Gresley, A. *Tetrahedron Lett.* **2008**, *49*, 1274–1276. (k) Xu, D.; Warmuth, R. *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521. (l) Liu, Y.; Liu, X.; Warmuth, R. *Chem. Eur. J.* **2007**, *13*, 8953–8959. (m) Liu, X.; Warmuth, R. *J. Am. Chem. Soc.* **2006**, *128*, 14120–14127. (n) Liu, X.; Liu, Y.; Li, G.; Warmuth, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 901–904.

(14) (a) Nishimura, N.; Kobayashi, K. *J. Org. Chem.* **2010**, *75*, 6079–6085. (b) Nishimura, N.; Yoza, K.; Kobayashi, K. *J. Am. Chem. Soc.* **2010**, *132*, 777–790. (c) Takahagi, H.; Fujibe, S.; Iwasawa, N. *Chem. Eur. J.* **2009**, *15*, 13327–13330. (d) Içli, B.; Christinat, N.; Tönnemann, J.; Schüttler, C.; Scopelliti, R.; Severin, K. *J. Am. Chem. Soc.* **2009**, *131*, 3154–3155. (e) Kataoka, K.; Okuyama, S.; Minami, T.; James, T. D.; Kubo, Y. *Chem. Commun.* **2009**, 1682–1684. (f) Nishimura, N.; Kobayashi, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6255–6258. (g) Christinat, N.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 1848–1852. (h) Salazar-Mendoza, D.; Guerrero-Alvarez, J.; Höpfl, H. *Chem. Commun.* **2008**, 6543–6545. (i) Hutin, M.; Bernardinelli, G.; Nitschke, J. R. *Chem. Eur. J.* **2008**, *14*, 4585–4593. (j) Kataoka, K.; James, T. D.; Kubo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 15126–15127. (k) Barba, V.; Betanzos, I. *J. Organomet. Chem.* **2007**, *692*, 4903–4908.

(15) Reviews: (a) Severin, K. *Dalton Trans.* **2009**, 5254–5264. (b) Fujita, N.; Shinkai, S.; James, T. D. *Chem. Asian J.* **2008**, *3*, 1076–1091.

(16) Horng, Y.-C.; Lin, T.-L.; Tu, C.-Y.; Sung, T.-J.; Hsieh, C.-C.; Hu, C.-H.; Lee, H. M.; Kuo, T.-S. *Eur. J. Org. Chem.* **2009**, 1511–1514.

(17) (a) Cambell, V. E.; Nitschke, J. R. *Synlett* **2008**, 3077–3090. (b) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 1705–1723. (c) Nitschke, J. R. *Acc. Chem. Res.* **2007**, *40*, 103–112. (d) Fan, J.; Bats, J. W.; Schmittel, M. *Inorg. Chem.* **2009**, *48*, 6338–6340.

(18) (a) Brumaghim, J. L.; Michels, M.; Raymond, K. N. *Eur. J. Org. Chem.* **2004**, 4552–4559. (b) Brumaghim, J. L.; Michels, M.; Pagliero, D.; Raymond, K. N. *Eur. J. Org. Chem.* **2004**, 5115–5118. (c) Ziegler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 4119–4121. (d) Caulder, D. L.; Powers, R. E.; Parac, T. N.; Raymond, K. N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1840–1843. (e) Parac, T. N.; Caulder, D. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 8003–8004. (f) Beissel, T.; Powers, R. E.; Raymond, K. N. *Angew. Chem. Int. Ed.* **1996**, *35*, 1084–1086.

(19) (a) Argent, S. P.; Riis-Johannessen, T.; Jeffery, J. C.; Harding, L. P.; Ward, M. D. *Chem. Commun.* **2005**, 4647–4649. (b) Paul, R. L.; Argent, S. P.; Jeffery, J. C.; Harding, L. P.; Lynam, J. M.; Ward, M. D. *Dalton Trans.* **2004**, 3453–3458.

(20) (a) Riddell, I. A.; Smulders, M. M. J.; Clegg, J. K.; Nitschke, J. R. *Chem. Commun.* **2011**, *47*, 457–459. (b) Mal, P.; Nitschke, J. R. *Chem. Commun.* **2010**, *46*, 2417–2419. (c) Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J. R. *Science* **2009**, *324*, 1697–1699.

(21) Granzhan, A.; Riis-Johannessen, T.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5515–5518.

(22) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101–2108. (b) Le Strat, F.; Harroween, D. C.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 489–498. (c) Azzouz, R.; Bischoff, L.; Fruit, C.; Marsais, F. *Synlett* **2006**, 1908–1912.

(23) (a) Piotrowski, H.; Polborn, K.; Hilt, G.; Severin, K. *J. Am. Chem. Soc.* **2001**, *123*, 2699–2700. (b) Piotrowski, H.; Hilt, G.; Schulz, A.; Mayer, P.; Polborn, K.; Severin, K. *Chem. Eur. J.* **2001**, *7*, 3196–3208.

(24) (a) Gao, J.; Rochat, S.; Qian, X.; Severin, K. *Chem. Eur. J.* **2010**, *16*, 513–5017. (b) Rochat, S.; Severin, K. *Org. Biomol. Chem.* **2009**, *7*, 1147–1153. (c) Katsuta, S.; Imoto, T.; Kudo, Y.; Takeda, Y. *Anal. Sci.* **2008**, *24*, 1215–1217. (d) Katsuta, S.; Iwabe, Y.; Kato, Y.; Kudo, Y.; Takeda, Y. *Inorg. Chim. Acta* **2008**, *361*, 103–108. (e) Mimassi, L.; Cordier, C.; Guyard-Duhayon, C.; Mann, B. E.; Amouri, H. *Organometallics* **2007**, *26*, 860–864. (f) Grote, Z.; Wizemann, H.-D.; Scopelliti, R.; Severin, K. *Z. Anorg. Allg. Chem.* **2007**, *633*, 858–864. (g) Grote, Z.; Scopelliti, R.; Severin, K. *J. Am. Chem. Soc.* **2004**, *126*, 16959–16972. (h) Mimassi, L.; Guyard-Duhayon, C.; Rager, M. N.; Amouri, H. *Inorg. Chem.* **2004**, *43*, 6644–6649. (i) Grote, Z.; Lehaire, M.-L.; Scopelliti, R.; Severin, K. *J. Am. Chem. Soc.* **2003**, *125*, 13638–13639. (j) Lehaire, M.-L.; Schulz, A.; Scopelliti, R.; Severin, K. *Inorg. Chem.* **2003**, *42*, 3576–3581. (k) Piotrowski, H.; Severin, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4997–5000.

(25) (a) Olivier, C.; Grote, Z.; Solari, E.; Scopelliti, R.; Severin, K. *Chem. Commun.* **2007**, 4000–4002. (b) Lehaire, M.-L.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 1419–1421.

(26) (a) Grote, Z.; Scopelliti, R.; Severin, K. *Eur. J. Inorg. Chem.* **2007**, 694–700. (b) Saur, I.; Scopelliti, R.; Severin, K. *Chem. Eur. J.* **2006**, *12*, 1058–1066. (c) Grote, Z.; Scopelliti, R.; Severin, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3821–3825.

(27) (a) Newman, H. *Synthesis* **1972**, 692–693. (b) Men, Y.-B.; Sun, J.; Huang, Z.-T.; Zheng, Q.-Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 2873–2876.

(28) (a) Solari, E.; Gauthier, S.; Scopelliti, R.; Severin, K. *Organometallics* **2009**, *28*, 4519–4526. (b) Albrecht, C.; Gauthier, S.; Wolf, J.; Scopelliti, R.; Severin, K. *Eur. J. Inorg. Chem.* **2009**, 1003–1010. (c) Wolf, J.; Thommes, K.; Briel, O.; Scopelliti, R.; Severin, K. *Organometallics* **2008**, *27*, 4464–4474. (d) Quebatte, L.; Haas, M.; Solari, E.; Scopelliti, R.; Nguyen, Q. T.; Severin, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1084–1088.

(29) Chand, D. K.; Bharadwaj, P. K. *Tetrahedron* **1997**, *53*, 10517–10522.

(30) Ghosh, P.; Bharadwaj, P. K. *Dalton Trans* **1997**, 2673–2676.

(31) The volume of the cavity was estimated by calculating the volume of a polyhedron, which fits inside the cage. For details see ref 21.

(32) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. *Synthesis* **2005**, 2080–2083.

(33) Stack, T. D. P.; Hou, Z.; Raymond, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 6466–6467.

(34) (a) Weigelt, S.; Busse, C.; Bombis, C.; Knudsen, M.; Gothelf, K.; Lægsgaard, E.; Besenbacher, F.; Linderoth, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4406–4410. (b) Nielsen, M.; Thomsen, A. H.; Jensen, T. R.; Jakobsen, H. J.; Skibsted, J.; Gothelf, K. V. *Eur. J. Org. Chem.* **2005**, 342–347.

(35) (a) Northrop, B. H.; Zheng, Y.-R.; Chi, K.-W.; Stang, P. J. *Acc. Chem. Res.* **2009**, *42*, 1554–1563. (b) Mahata, K.; Saha, M. L.; Schmittel, M. *J. Am. Chem. Soc.* **2010**, *132*, 15933–15935.

(36) Han, J.-M.; Pan, J.-L.; Lei, T.; Liu, C.; Pei, J. *Chem. Eur. J.* **2010**, *16*, 13850–13861.

(37) The connection of metallamacrocyclic building blocks via additional *coordination bonds* has been reported: (a) Clegg, J. K.; Iremonger, S. S.; Hayter, M. J.; Southon, P. D.; Macquart, R. B.; Duriska, M. B.; Jensen, P.; Turner, P.; Jolliffe, K. A.; Kepert, C. J.; Meehan, G. V.; Lindoy, L. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1075–1078. (b) Mirtschin, S.; Slabon-Turski, A.; Scopelliti, R.; Velders, A. H.; Severin, K. *J. Am. Chem. Soc.* **2010**, *132*, 14004–14005. (c) Clegg, J. K.; Lindoy, L. F.; McMurtrie, J. C.; Schilter, D. *Dalton Trans.* **2005**, 857–864.

(38) Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. *J. Comput. Chem.* **2004**, *25*, 1605–1612.