Chapter 2

Diphosphine Based Capsules for the Encapsulation of Transition Metals

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2.1 Introduction

Supramolecular capsules present an important class of architectures that can reversibly accommodate smaller molecules in their cavities. These capsules consist of two or more building blocks that have a similar size, complementary functional groups and associate via multiple reversible non-covalent interactions such as hydrogen bonds, metal-ligand and ionic interactions. A wide variety of homo- and hetero-capsules based on functionalized calixarenes, resorcinarenes (cavitands) and other building blocks have been reported. The encapsulation properties of these hosts enable their utilization as nanosized reactor vessels (nanoreactors) and so far their use has been explored for the stabilization of reactive intermediates, for organic transformations and for catalysis.

The cyclic tetramer calix[4]arene in the cone conformation and the resorcinarene (cavitand) have a concave vase-like structure with an open cavity that can be used to accommodate smaller guest molecules. Functionalization of the ‘upper rim’ of calix[4]arene and resorcinarene with non-covalent binding motifs preorganizes them towards capsules assembly. Examples of supramolecular capsules based on the calix[4]arene and resorcinarene scaffolds are given in Figure 1. Timmerman, Crego-Calama and co-workers reported ionic based capsules constituted of one tetradsulfonated calix[4]arene and one tetracationic calix[4]arene or tetracationic porphyrin that can encapsulate reversibly cationic guests such as acetylcholine (Figure 1a). Dalcanale and co-workers have studied a molecular capsule based on metal-ligand interactions composed of two tetrapyridyl-substituted resorcin[4]arene cavitands coupled through four square-planar palladium complexes (Figure 1b). This coordination cage can encapsulate reversibly one methanol[60]fullerene derivative. Rebek and co-workers have reported homo- and hetero-dimeric capsules based on hydrogen bonds (Figure 1c). These capsules consist for example of tetraurea-substituted calix[4]arenes, and can reversible encapsulate small molecules such as (1R)-(−)-camphor.

Figure 1 Supramolecular capsules composed of functionalized resorcinarenes and calixarenes, based on non-covalent interactions such as ionic (a), metal-ligand (b) and hydrogen bonds (c).
Many reactions of interest require well-defined transition metal complexes as catalyst, and the activity and selectivity of these catalysts are determined to a large extent by the ligand associated with the metal. So far only a few supramolecular complexes have been reported in which the catalytic potential of an encapsulated transition metal has been explored. Raymond, Bergman and co-workers have encapsulated cationic iridium and rhodium complexes inside the chiral tetrahedral coordination cage \([M_4L_6]^{12-}\) via non-directional non-covalent bonds (Figure 2a). Encapsulation of the catalyst resulted in substrate selectivity on the basis of size and shape in the C–H bond activation of aldehydes and the isomerization of allylic alcohols.\(^{31,8}\) Reek and co-workers have introduced a templated approach for the encapsulation of ligands and their metal-complexes, in which the template-ligands have a bifunctional character in that they coordinate to the active metal center and function as a template for the capsule formation.\(^9\) Pyridylphosphines are successful template ligands as the nitrogen atoms of the pyridyl groups selectively coordinate to Zn\(^{II}\)-porphyrins or Zn\(^{II}\)-salphens, resulting in a hemispherical ligand-template capsule around the transition metal (Figure 2b). Such encapsulated rhodium complexes were shown to have unusual reactivity and selectivity in the hydroformylation of terminal and internal alkenes.

Diphosphine based metal complexes represent an important class of catalysts and we anticipated that hetero-capsules based on functionalized diphosphine ligands and well-known building blocks such as calix[4]arene would provide a new class of easily accessible supramolecular complexes.\(^{9a,10}\) In this strategy a well-defined transition metal complex is an integral part of the capsule with the transition metal located inside the capsule. More importantly, the metal is not involved in the assembly process and it is available for the catalytic process. Since the crucial building block, i.e. the diphosphine ligand, contains a donor-atom site for metal complexation as well as functional groups for capsule formation, the present strategy comprises a templated approach to metal encapsulation (Scheme 1).\(^9f\) Encapsulation of a
transition metal within a hetero-capsule results in an extra coordination sphere around the metal, which may also influence its catalytic performance. In this Chapter we report the formation and characterization of supramolecular hetero-capsules 1·2 that consist of a tetracationic diphosphine ligand 1a, or a palladium complex thereof (1b, 1c), and a tetraanionic calix[4]arene 2.

Scheme 1 Templated encapsulation of transition metals within supramolecular capsules.

2.2 Self-assembly of diphosphine capsules based on ionic interactions

Diphosphine ligands with a rigid backbone such as the xantphos-type ligands, generally have a concave structure defined by the xanthene backbone and the four phosphorus phenyl-groups. We realized that simple functionalization of these four phenyl groups would provide a building block of a size similar to that of a functionalized calix[4]arene and the two molecules should form a supramolecular capsule provided that the functional groups are complementary. The novel capsules developed in this Chapter are based on ionic interactions and consist of a tetracationic diphosphine ligand and a tetraanionic calix[4]arene.

2.2.1 Ionic building blocks

The tetracationic diphosphine ligand is synthesized from tetrakis(p-diethylbenzylamine) xantphos 1 as is depicted in Scheme 2. The amphiphilic ligand 1 was previously reported by van Leeuwen and co-workers and was used in the rhodium-catalyzed hydroformylation reaction in which the rhodium complex of 1 was recycled by extraction into an acidic aqueous phase.11 We have developed an improved synthesis route towards 1, which involves only two steps instead of five starting from xanthene and p-bromobenzyl-diethylamine, with an overall yield of 50% (Scheme 2a). The diphosphonite is prepared by lithiation of the xanthene backbone and a subsequent reaction with ClP(OEt)2.12 Reaction of the diphosphonite with the lithiated product of p-bromobenzyl-diethylamine yields the tetrakis(p-diethylbenzylamine) xantphos 1.13 Selective N-protonation of the tetraamine ligand 1 by HCl in diethyl ether yields the corresponding
tetrakis(p-diethylbenzylammonium) xantphos 1a (Scheme 2b). The electronic effect of the ammonium groups of 1a on the phosphorus atoms is negligible because of the presence of benzylic methylene spacer. Indeed, $^{31}$P{¹H} NMR data confirm that the phosphines are barely affected by the electron-withdrawing ammonium groups (Scheme 2b). All new compounds described in this Chapter have been characterized by NMR, IR and mass spectroscopy techniques (see Experimental section).

![Scheme 2 Synthesis of tetrakis(p-diethylbenzylamine) xantphos 1 (a) and tetrakis(p-diethylbenzylammonium) xantphos 1a (b).](image)

The tetraanionic calix[4]arene building block is the tetrasulfonatocalix[4]arene 2 which was synthesized in four steps following literature procedures (Scheme 3). In the first step p-tert-butylcalix[4]arene was obtained by the base-catalyzed condensation of p-tert-butylphenol and formaldehyde, with the tert-butyl groups functioning as positional protective groups. The tert-butyl groups on the ‘upper rim’ of p-tert-butylcalix[4]arene were removed by an AlCl₃-catalyzed retro-Friedel-Crafts alkylation. Subsequently, the ‘lower rim’ of tetrahydroxycalix[4]arene was alkylated with ethoxyethyl groups. This alkylation step was done prior to sulfonation to ensure the locking of the tetrasulfonatocalix[4]arene into the cone conformation. The obtained cone conformation and hence the $C_{4v}$ symmetry of the calix[4]arene was confirmed in the $^1$H NMR spectra by the presence of only one typical AB system for the ArCH₂Ar protons. Finally, sulfonation of the ‘upper rim’ of the alkylated calix[4]arene by concentrated sulfuric acid and neutralization by NaOH afforded the water soluble tetrasulfonatocalix[4]arene tetrasodium salt 2.

![Scheme 3 Synthesis of tetrasulfonatocalix[4]arene 2.](image)
2.2.2 Capsule self-assembly

Self-assembly of the ionic-based hetero-capsules 1a·2 is simply achieved by mixing solutions of their building blocks in polar (protic) solvents. The hetero-capsules 1a·2 are in equilibrium in solution with the monomeric building blocks. Mixing solutions of the tetracationic diphosphine 1a and the tetraanionic calix[4]arene 2 in water resulted in the precipitation of capsule 1a·2 as a white solid, which was isolated by filtration and appeared to be soluble in methanol and dmso (Scheme 4a). By precipitating the capsule in water, the four equivalents of sodium chloride formed could be separated from the capsule as was shown by a chloride test (see Experimental section). Unlike the building blocks, the capsule is not soluble in water because the charges are now less available for interaction with the polar solvent. The capsule can also be prepared in situ by just mixing methanol or dmso solutions of 1a and 2 in the proper ratio. Capsules that are prepared in situ contain four equivalents of the NaCl corresponding salt. Molecular modeling calculations performed at the PM3 level show that diphosphine 1a and calix[4]arene 2 are similar in size and complementary in function and should form capsule 1a·2 via multiple ionic interactions (Scheme 4b). According to the modeled structure of 1a·2, in which only one of the possible conformations is displayed, the opposite charges are not situated on top of one another but are arranged in an array around the capsule equator.4a

Scheme 4 Self-assembly of capsule 1a·2 (a) and modeled structure of 1a·2 (b).

1H NMR Spectroscopy. 1H NMR spectroscopy is an important tool for characterization of supramolecular capsules. The 1H NMR spectra of capsule 1a·2 in CD3OD and in dmso-d6 show sharp resonances and significant upfield shifts for the diethylammoniummethyl substituents, CH2NH+(CH2CH3)2, with respect to those of 1a (in CD3OD: Δδ(CH2CH3) = 0.43, Δδ(CH2CH3) = 0.33, Δδ(CH2N) = 0.25 ppm) whereas the chemical shifts of the other protons remain relatively unaffected (Δδ less than 0.15 ppm) (Figure 3). The upfield shifts are similar to those reported by Crego-Calama, Corbellini and co-workers and point to partial inclusion of the diethylammoniummethyl substituents inside the hydrophobic cavity of the capsule.4c A higher
degree of encapsulation of these substituents was observed when the solvent polarity was increased by the addition of D$_2$O, as was evident from the larger upfield shifts.

A single set of proton resonances for the free and associated building blocks was observed in a temperature range of –40 to +50 °C (in CD$_3$OD). This indicates that a fast exchange process exists on the NMR time scale between the building blocks that are in the monomeric form (free) and those in the capsular form (bound). Due to the fast exchange process the lower symmetry of the capsule compared to calix[4]arene 2 ($C_{4v}$) is not apparent in the $^1$H NMR spectra. $^4b$ $^1$H NMR titrations were carried out in CD$_3$OD (298 K) providing a stability constant of $K_{1a\cdot2} = 6 \cdot 10^4$ M$^{-1}$ for capsule 1a·2 (Figure 4). The high association constant confirms that the diphosphine 1a and the tetrasulfonatocalix[4]arene 2 indeed fit well to form a stable capsule. The titration curve fitted to a 1:1 binding model is in line with the 1:1 stoichiometry of the capsule. A Job plot analysis of a titration experiment carried out in CD$_3$OD shows a maximum at a mol fraction of 0.5, proving indubitably the 1:1 stoichiometry of capsule 1a·2 in solution (Figure 4).

Figure 3 $^1$H NMR spectra in CD$_3$OD of capsule 1a·2. Top: diphosphine 1a; Middle: capsule 1a·2 (1a/2 = 2/3); Bottom: calix[4]arene 2. Asterisks indicate solvent signals.
**Figure 4** $^1$H NMR titration data fitted with a 1:1 binding model for diphosphine 1a with calix[4]arene 2 (left) and Job plot for 1a with 2 (right) ($Y = (\Delta \delta_{1a}) \times (\text{mol fraction } 1a)$) in CD$_3$OD at 298 K. Data points represent the absolute upfield shifts ($\Delta \delta_{1a}$) of CH$_2$NH$^+(CH_2CH_3)_2$ protons of 1a·2 relative to the chemical shifts of free 1a, ▲ CH$_2$CH$_3$, ● CH$_2$CH$_3$, ■ CH$_2$N.

**NOESY.** Nuclear Overhauser Effect (NOE) is a widely used NMR technique for the characterization of supramolecular structures. Magnetization transfer (spin coupling) through-space occurs between nuclear spins which are close in space (< 5Å). Small molecules (Mw < 1000) give positive NOE contacts and large molecules (Mw > 2000) give negative NOE contacts because of different intermolecular relaxation pathways.$^{15a-b}$ The 1D-NOESY spectrum of the hetero-dimeric capsule 1a·2 in CD$_3$OD displays significant negative intermolecular NOE contacts between the NH$^+(CH_2CH_3)_2$ protons of 1a and the aromatic protons of 2 upon selective saturation of the methyl protons NH$^+(CH_2CH_3)_2$ of 1a (Figure 5).$^{15c-d}$ This illustrates that the aryl-substituents of the diphosphine ligand 1a and the upper rim of the calix[4]arene 2 are facing one another to form the typical dimeric 1:1 capsular structure. The negative NOE enhancement confirms the large size of the capsule.

**Figure 5** 1D-NOESY spectrum of capsule 1a·2 in CD$_3$OD (inset: spectrum enlargement).
ESI mass spectrometry. Additional evidence for the formation of capsule 1a·2 and its stability in the gas-phase is obtained by electrospray ionization mass spectrometry (ESI-MS). ESI is a soft ionization technique that can be used to study weakly non-covalently bound supramolecular structures in their gaseous ionic state. The positive-mode ESI-MS spectrum of 1a·2 in CH$_3$OH shows a prominent monoisotopic ion peak of the capsule at $m/z$ 998.33 corresponding to [1a·2 + 2Na]$^{2+}$ (Figure 6). All the capsule’s ion peaks correspond to 1:1 complexes and no ion peaks for higher aggregates were detected. Moreover, comparison of the measured isotope pattern of 1a·2 with the calculated one confirms the elemental composition and charge state. The assignment of the capsule’s ion peaks is in agreement with ESI-MS/MS collision induced dissociation experiments, upon which the isolated capsule’s ion peak (partly) disappeared and product ion peaks appeared that correspond to the capsule’s building blocks. These MS/MS experiments reveal the gas-phase stability of the capsule. Guest encapsulation is an important property of supramolecular capsules. The absence of inclusion complexes for capsule 1a·2 in the gas-phase can be rationalized by entropic considerations.

![Figure 6 ESI-MS spectrum of capsule 1a·2 (inset: measured isotope pattern).](image)

2.3 Encapsulation of a transition metal

Encapsulation of a transition metal within capsule 1a·2 is achieved by using the metal complex of the tetracationic diphosphine ligand 1a for the assembly process. In the metallo hetero-capsole the transition metal complex is an integral part of the capsule with the transition metal located inside the capsule and it is not involved in the assembly process. Encapsulation of a neutral palladium metal inside the supramolecular capsule is achieved by using the neutral palladium complex [(trans-1a)Pd(p-C$_6$H$_4$CN)(Br)] 1b, containing the tetracationic diphosphine ligand 1a, as the complementary building block for the tetraanionic calix[4]arene 2 (Scheme 5). The neutral palladium complex 1b was synthesized in 80% yield from the reaction of the palladium dimer {[(o-tolyl)$_3$P]Pd(p-C$_6$H$_4$CN)Br}$_2$ with two equivalents of 1a. Since many catalytic cycles involve a cationic palladium species as intermediate we were also interested in
capsules containing the corresponding cationic palladium complex 1c [(trans-1a)Pd(p-
C₆H₄CN)]⁺[CF₃SO₃]⁻. The cationic palladium complex 1c was prepared in 77% yield by salt
metathesis of 1b with five equivalents of silver triflate (Scheme 5). All counterions in palladium
complex 1c are triflates, which means that the chlorides of 1a have been exchanged.

Scheme 5 Synthesis of the neutral and cationic palladium complexes 1b and 1c.

Self-assembly of the metallo hetero-capsules 1b·2 and 1c·2 is achieved by mixing
solutions of the palladium complexes 1b or 1c, and the calix[4]arene 2 (Scheme 6). The neutral
Pd-complex 1b has a distorted square planar geometry with the oxygen atom of the ligand
backbone in the apical position. In spite of the higher rigidity of the palladium complex 1b
compared to the free ligand 1a, molecular modeling calculations of capsule 1b·2 performed at
the PM3 level illustrate that 1b and 2 fit well and can form a capsule with the palladium metal
located inside the capsule and the p-cyanophenyl group of 1b sticking out of the capsule and is
situated above the capsule equator (Figure 7a). Mixing solutions of 1b and 2 in water led to the
precipitation of capsule 1b·2 as a yellow solid. In contrast to capsule 1a·2, capsule 1b·2 is only
sparingly soluble in methanol and dissolves well in methanol/dichloromethane mixtures (9/1,
v/v) and in dmso. The Pd-aryl moiety might disturb the formation of capsule 1b·2. However, the
ESI-MS spectrum of a diluted mixture of 1b and 2 in CH₃OH shows the formation of capsule
1b·2 and no peaks for higher aggregates were detected (vide infra). The cationic palladium
complex 1c adopts a square planar geometry with the ligand acting as an η³ terdentate P,O,P
ligand. The modeled structure of capsule 1c·2 illustrates that 1c and 2 fit nicely and that the
palladium metal as well as the p-cyanophenyl group of 1c are located inside the capsule (Figure
7b). Mixing solutions of 1c and 2 in methanol or dmso resulted in clear solutions of capsule 1c·2.
The diethylammoniummethyl protons of capsules 1b·2 and 1c·2 exhibit high upfield shifts with respect to those of 1b and 1c in their $^1$H NMR spectra (1b·2 in dmső-6: $\Delta \delta$(CH$_2$CH$_3$) = 0.41, $\Delta \delta$(CH$_2$CH$_3$) = 0.27, $\Delta \delta$(NH) = 1.14 ppm and 1c·2 in CD$_3$OD: $\Delta \delta$(CH$_2$CH$_3$) = 0.58, $\Delta \delta$(CH$_2$CH$_3$) = 0.39, $\Delta \delta$(CH$_2$N) = 0.17 ppm), see Figure 8. These upfield shifts upon capsule formation point to partial inclusion of the alkyl tails. $^1$H NMR titration experiments for capsule 1c·2 in CD$_3$OD (298 K) gave an association constant of $K_{1c·2} = 6 \cdot 10^3$ M$^{-1}$ for capsule 1c·2 (1:1 binding model). The association constant for capsule 1c·2 is ten times lower than the association constant of capsule 1a·2 ($K_{1a·2} = 6 \cdot 10^4$ M$^{-1}$). A plausible explanation is the poorer complementarity between 1c and 2. The more flexible free ligand 1a can adapt to the favoured geometry to optimize interactions with 2, whereas the Pd–aryl complex 1c is too rigid to do so. Interestingly, the phosphorus chemical shifts of 1a, 1b and 1c in the capsular form 1·2 did not exhibit a noteworthy shift compared to the monomeric form ($\Delta \delta < 0.6$ ppm), indicating that the geometry around the phosphorus atoms did not change. According to the modeling pictures, the bite angles of 1b and 1c hardly change upon capsule formation (e.g. 1c 167° vs 1c·2 161°). The 1D-NOESY spectra of capsules 1b·2 and 1c·2 show significant negative intermolecular NOE contacts between the NH$^+$(CH$_2$CH$_3$)$_2$ protons of the Pd-complexes 1b and 1c and the aromatic protons of the calix[4]arene 2. These results indicate that, similar to 1a·2, the upper rim of the calix[4]arene is associated with 1b and 1c, which confirms the proposed geometry of the dimeric capsules.
The ESI-MS spectrum of capsule 1b·2 in CH₃OH shows a prominent ion peak of the capsule at \( m/z \) 719.55 corresponding to \([1b \cdot 2 - \text{Br} + 2\text{H}]^{3+}\) (Figure 9). The ESI-MS spectrum of capsule 1c·2 in CH₃OH shows a prominent ion peak of the capsule at \( m/z \) 719.70 corresponding to \([1c \cdot 2 - \text{CF}_3\text{SO}_3 + 2\text{H}]^{3+}\). Interestingly, capsule 1b·2 remains stable after Br⁻ dissociation from the palladium, and the corresponding ionic capsule detected by ESI-MS gives the same ion peaks as the capsule based on the cationic palladium complex 1c. The assignment of the capsule’s ion peaks is in agreement with the ESI-MS/MS collision induced dissociation experiments, upon which the isolated capsule’s ion peak (partly) disappeared and product ion peaks appeared that correspond to the capsule building blocks (Figure 10). These MS/MS experiments reveal the gas-phase stability of the capsules.

![Figure 8](image_url)  
**Figure 8** \(^1\)H NMR spectra in CD₃OD of capsule 1c·2. Top: Pd-complex 1c; Middle: capsule 1c·2 (1c/2 = 2/3); Bottom: calix[4]arene 2. Asterisks indicate solvent signals.

![Figure 9](image_url)  
**Figure 9** ESI-MS spectrum of capsule 1b·2 (inset: measured isotope pattern).
Reactivity of the encapsulated metal. Preliminary studies show that the metal center inside the capsule retains its reactivity. Bubbling carbon monoxide through a methanol solution of \( \text{1c-2} \) resulted in a quantitative insertion of CO in the palladium–aryl bond and yielded capsule \( \text{1d-2} \) (\( \text{1d} = [(\text{trans-1a})\text{Pd(C(O)p-C_6H_4CN)}]^+\text{[CF}_3\text{SO}_3^-] \)) (Scheme 7).\(^{20a-b}\) All counterions in Pd-complex \( \text{1d} \) are \( \text{CF}_3\text{SO}_3^- \) ions, which means that the \( \text{Cl}^- \) ions of \( \text{1a} \) have been exchanged. The insertion of CO was fast and comparable to the insertion reaction in Pd-complex \( \text{1c} \) (\( t_{1/2} < 1 \text{ min} \)) as expected for cationic palladium complexes.\(^{20c-d}\) The proton NMR spectrum of capsule \( \text{1d-2} \) confirms that the capsule remains intact upon insertion of CO. As found for other \( \text{trans} \)-coordinating palladium diphosphine complexes, capsule \( \text{1d-2} \) as well as complex \( \text{1d} \) did not further react with methanol to provide the methanolysis product.\(^{20c}\)

**Scheme 7** CO-insertion in the Pd-aryl bond of capsule \( \text{1c-2} \) to give capsule \( \text{1d-2} \).
2.4 Diffusion-ordered NMR spectroscopy (DOSY)

Diffusion-Ordered Spectroscopy (DOSY) is an NMR technique that measures the mobility rates i.e. the diffusion coefficients of molecules or assemblies and correlate these to the proton resonances. Spectra of mixtures of compounds in solution can be separated on grounds of the difference in diffusion coefficients. Information about the molecular size, shape and aggregation state of molecules or assemblies in solution can be obtained because the diffusion coefficients are related to the hydrodynamic radius \( r \) through the Stokes-Einstein equation. The diffusion coefficients of the free building blocks \( \text{1a}, \text{1b}, \text{1c} \) and \( 2 \) and their corresponding capsules \( \text{1a}·2, \text{1b}·2, \text{1c}·2 \) were calculated through the Stejskal-Tanner equation (Figure 11 and Table 1). The diffusion coefficients \( D \) of the three capsules are lower than those of the corresponding free building blocks (e.g. \( D_{\text{1c}·2} = 2.04 \) and \( D_{\text{1c}} = 3.21 \times 10^{-6} \) \( \text{cm}^2 \text{s}^{-1} \)) and the hydrodynamic radii \( r \) of the capsules are larger than those of the corresponding free building blocks (e.g. \( r_{\text{1c}·2} = 20.45 \) and \( r_{\text{1c}} = 13.00 \) \( \text{Å} \)). The hydrodynamic radii of the capsules obtained by DOSY approximately match those obtained by molecular modeling. The larger size of the hydrodynamic radii \( r \) of the capsules support the capsules formation.

The relatively poor complementarity of \( \text{1c} \) and \( 2 \) compared to \( \text{1a} \) and \( 2 \) (vide supra) is also supported by DOSY. The diffusion coefficient of capsule \( \text{1c}·2 \) is lower than that of capsule \( \text{1a}·2 \) (\( D_{\text{1c}·2} = 2.04 \) and \( D_{\text{1a}·2} = 2.46 \times 10^{-6} \) \( \text{cm}^2 \text{s}^{-1} \)), indicating that \( \text{1c}·2 \) is larger than \( \text{1a}·2 \). These results imply that the more rigid Pd-complex \( \text{1c} \) fits less well on the calix[4]arene \( 2 \) than the free ligand \( \text{1a} \), which results in a longer distance between \( \text{1c} \) and \( 2 \) and hence a larger capsule.

![Stejskal-Tanner plot](image.png)

**Figure 11** Stejskal-Tanner plot: natural logarithm of the normalized signal decay \( \ln(I/I_0) \) as a function of the \( b \) value \( (b = \gamma^2 \delta^2 G^2(\Delta–\delta/3)) \). The dotted lines represent linear least square fits to the data (\( R > 0.998 \) in \( \text{CD}_{3}\text{OD} \) and \( R > 0.985 \) in \( \text{dmsod}_{6} \)) and the slope of the line corresponds to the diffusion coefficient \( –D \). In \( \text{CD}_{3}\text{OD} \): \( \text{1a}, \text{1c}, 2, \text{1a}·2, \text{1c}·2 \) (a) and in \( \text{dmsod}_{6} \): \( 1b, 2, \text{1b}·2 \) (b).
Table 1 Diffusion coefficients $D$ and hydrodynamic radii $r$ of the free building blocks $1a$, $1b$, $1c$ and $2$, and of capsules $1a\cdot2$, $1b\cdot2$ and $1c\cdot2$.$^{a,d}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds $^a$</th>
<th>Solvent</th>
<th>$D$ $^c$ $(10^{-6} \text{ cm}^2\text{s}^{-1})$</th>
<th>$r$ $^d$ (Å)</th>
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<tr>
<td>1</td>
<td>free $1a$</td>
<td>CD$_3$OD</td>
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<td>12.45</td>
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<td>CD$_3$OD</td>
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<tr>
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<td>dmoso-$d_6$</td>
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<tr>
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<td>dmoso-$d_6$</td>
<td>0.74</td>
<td>12.21</td>
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</table>

$^a$ The protons of the building blocks in Bold were used for the calculation of $D$.

$^b$ The free and bound building blocks exchange fast on the NMR timescale and therefore the observed diffusion coefficients of the capsules are the weighted average of the diffusion coefficients of the free and bound building blocks.$^{21a,c}$

$^c$ The difference in solvent viscosity is responsible for the differences in $D$ between methanol and dmoso.

$^d$ The calculated hydrodynamic radius $r$ is prone to error because the viscosities of the solutions were not measured.

2.5 $N$-quaternization attempts of tetraaminodiphosphine

Acidic functionalities such as the four ammonium groups of ligand $1$ can interfere with the performance of the corresponding organometallic catalysts. To extend the applicability of ligand $1$ we have attempted to quaternize its four amino groups with methylating agents (this was previously attempted by van Leeuwen and Buhling).$^{22a}$ Direct methylation of $1$ with methyl triflate and trimethyloxonium tetrafluoroborate (Me$_3$O$^+BF_4$) resulted in a mixture of ammonium and phosphonium salts.$^{22b-e}$ The nucleophilic character of both the phosphorus and nitrogen atoms is responsible for the non-selective $N$-methylation and therefore the phosphorus atoms had to be protected.$^{22e-f}$ Phosphorus protection was done by oxidation with bleach (sodium hypochlorite, NaClO). Protection by borane was considered, but this reagent can complex to the phosphorus atoms as well as to the nitrogen atoms.$^{22g}$ After $N$-methylation with methyl iodide, Buhling tried to deprotect the phosphine oxides by reduction with HSiCl$_3$, Si$_2$Cl$_6$ or PhSiH$_3$ without success.$^{22a,22h}$ The phosphorus atoms of the xantphos-type ligand $1$ are sterically protected, which hinder the reduction of the corresponding phosphine oxides. However, Shioiri and co-workers have reported the reduction of a dioxidized xantphos-type ligand by applying titanium tetraisopropoxide and polymethyl hydrosiloxane as the reduction agents.$^{22i}$ Unfortunately, reduction of the corresponding dioxidized tetraakis($N$-methylated) xantphos ligand
of 1 (OTf as counterion) by Ti(OiPr)$_4$ was unsuccessful, probably because of the sensitivity of Ti(OiPr)$_4$ to the ammonium groups.

2.6 Conclusions

In conclusion, we have introduced a simple strategy for the formation of a new type of metallocapsules, which is based on functionalized diphosphine ligands (and the metal complexes thereof) and calix[4]arene equipped with complementary binding motifs. In the current example the assembly process is based on ionic interactions. The tetraammonium functionalized diphosphine ligand 1a or the metal complexes thereof 1b and 1c readily associate with the tetraanionic calix[4]arene 2, forming supramolecular capsules as indicated by $^1$H-NMR, 1D-NOESY and DOSY experiments, and ESI-MS. The metal center inside the capsule retains its reactivity. Encapsulation of these transition metals opens up new opportunities to control the activity, stability and selectivity of the potential homogeneous catalysts.

2.7 Experimental section

General remarks. All reactions were carried out under a dry, inert atmosphere of purified nitrogen or argon using standard Schlenk techniques, unless stated otherwise. Solvents were dried and distilled under nitrogen prior to use. Diethyl ether, tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone. Dichloromethane, methanol, acetonitrile and dimethylformaldehyde were distilled from CaH$_2$. Deuterated solvents were distilled from the appropriate drying agents. $^{13}$CO was purchased from Praxair and all other chemicals were obtained from commercial suppliers and used as received. The palladium dimer [{(o-tolyl)$_3$P}Pd(p-C$_6$H$_4$CN)Br]$_2$ was synthesized according to a reported procedure.$^{17}$

NMR spectra were recorded on Varian Inova 500 ($^1$H NMR titrations, 1D-NOESY and DOSY measurements), Bruker Avance DRX 300 and Varian Mercury 300 NMR spectrometers. Chemical shifts are given relative to TMS ($^1$H and $^{13}$C NMR), 85% H$_3$PO$_4$ ($^{31}$P NMR) and Cl$_3$CF ($^{19}$F NMR). Chemical shifts are given in ppm. Elemental analyses were performed at the H. Kolbe Mikroanalytisches laboratorium in Mülheim (Germany). High-resolution fast atom bombardment mass spectrometry (HRMS FAB) measurements were carried out on a JEOL JMS SX/SX 102A at the Department of Mass Spectrometry at the University of Amsterdam. Low-resolution electrospray-ionization mass spectra (ESI-MS) in CH$_3$OH were recorded on a Shimadzu LCMS-2010A via direct injection. Electrospray ionization mass spectrometry (ESI-MS) measurements were carried out on a Q-TOF (Micromass, Waters, Whyttenshawe, UK) mass spectrometer equipped with a Z-spray orthogonal nanoelectrospray source, using Econo Tips (New Objective, Woburn, MA) to create an off-line nanospray, at the Department of Mass Spectrometry of Biomacromolecules at the University of Amsterdam. The MS spectra were processed with software tools embedded in Masslynx software (Micromass, Waters, Whyttenshawe, UK) and additional isotopic pattern analysis was performed with the use of the Bruker Daltonics Isotope Pattern software program (Bruker Daltonik, Bremen, Germany, version 1.0.125.0). Infrared spectra were
recorded on a Bruker Vertex 70 FT-IR spectrophotometer. Molecular modeling calculations were performed using Spartan’04 V1.0.3 software, on the semi-empirical PM3-level.

Carbon atoms numbering of the xantphos-type diphosphines:

![Carbon atoms numbering of the xantphos-type diphosphines](image1)

**Synthesis**

*(p-Bromobenzyl)diethylamine*

This compound is synthesized according to a reported procedure. This reaction was not carried out with distilled solvents, nor under inert atmosphere. A solution of *(p-bromobenzyl) bromide (25.00 g, 0.10 mol)* in 60 ml diethyl ether was added to an excess of diethylamine (110 ml, 1.07 mol) in 1 h. The reaction is slightly exothermic. After stirring for 2 h the white precipitate was filtered off and washed with diethyl ether. After removing the volatiles *in vacuo* *(p-bromobenzyl)diethylamine was obtained as a yellow oil without the need for further purification (21.58 g, 0.089 mol, 89%). *1H NMR (300 MHz, CDCl3, 293 K)*: δ = 7.39 (d, J = 8.3 Hz, 2H, H3), 7.20 (d, J = 8.7 Hz, 2H, H10), 3.48 (s, 2H, ArCH2), 2.48 (q, J = 7.2 Hz, 4H, CH2CH3), 1.00 (t, J = 7.1 Hz, 6H, CH3); *13C{1H} NMR (76 MHz, CDCl3, 293 K)*: δ = 139.6 (s, Cq, C4a), 131.6 (s, CH, C3a), 130.9 (s, CH, C4a), 120.8 (s, Cq, C3a), 57.3 (s, CH2N), 47.1 (s, CH2CH3), 12.2 (s, CH3); GC-MS (m/z): 241/243 [M]+, 226/228 [M – CH3]+, 169/171 [M – NEt2]+, 90 [M – NEt2 – Br].

*4,5-Bis(diethoxyphosphonito)-9,9-dimethylxanthene*

This compound is synthesized according to a reported procedure. A yellow solution of 9,9-dimethylxanthene (10.17 g, 48.36 mmol) and tetramethylethylenediamine TMEDA (21.89 ml, 145.08 mmol) in 120 ml diethyl ether was cooled to 0 °C. Next, *n*-butyllithium (2.5 M in hexanes, 46.43 ml, 116.06 mmol) was added dropwise and the reaction mixture was stirred overnight. The resulting dark red solution was cooled to –78 °C, and a solution of diethyl chlorophosphite (18.07 ml, 125.74 mmol) in 120 ml diethyl ether was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated *in vacuo* giving a yellow oil. The salts were extracted by adding 100 ml dichloromethane and 100 ml degassed water to the crude product. After vigorous stirring, the organic layer was washed twice with degassed water and dried over MgSO4. Evaporation of the solvent resulted in 4,5-bis(diethoxyphosphino)-9,9-dimethylxanthene as a yellow sticky oil (21.13 g, 46.91 mmol, 97%). *1H NMR (300 MHz, CDCl3, 293 K)*: δ = 7.60 (d, J = 7.4 Hz, 2H, H2), 7.43 (d, J = 7.6 Hz, 2H, H1), 7.11 (t, J = 7.4 Hz, 2H, H3), 3.94 (dm, 8H, OC(CH3)2), 1.59 (s, 6H, C(CH3)2), 1.25 (t, J = 7.1 Hz, 12H, OCH2CH3); *31P{1H} NMR (122 MHz, CDCl3, 293 K): δ = 149.5 (s); *13C{1H} NMR (76 MHz, CDCl3, 293 K): δ = 152.4 (br t, C4a), 130.1 (s, Cq, C4a), 129.1 (s, CH, C4a), 128.7 (s, Cq, C3a), 128.2 (s, CH, C3a), 123.4 (s, CH, C3a), 63.3 (s, CH2CH3), 34.4 (s, C(CH3)2), 32.6 (s, C(CH3)2), 17.7 (s, CH2CH3).
4,5-Bis[4-(diethylamino)methyl]phenylphosphino]-9,9-dimethylxanthene: 1

*n-Butyllithium* (2.5 M in hexanes, 12.88 ml, 32.20 mmol) was added to 100 ml THF at 0 °C, and the solution was further cooled to −65 °C. A yellow solution of (*p*-bromobenzyl)diethylamine (7.80 g, 32.20 mmol) in 35 ml THF was added to the *n*-butyllithium solution in 1 h. The resulted pink reaction mixture was stirred for another 30 min at −45 °C. After cooling the resulting orange reaction mixture to −65 °C, a solution of 4,5-bis(diethoxyphosphino)-9,9-dimethylxanthene (2.90 g, 6.44 mmol) in 25 ml THF was added in 30 min. The resulted green reaction mixture was allowed to warm to room temperature overnight. The pale orange reaction mixture was hydrolyzed with 3 ml degassed water, and the solvent was removed *in vacuo*. Subsequently, the yellow viscous oil was dissolved in diethyl ether and washed with degassed water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried with MgSO₄, and the solvent was removed *in vacuo*. The resulting dark-orange viscous oil was purified by column chromatography (silica gel: hexanes, 0-30% EtOAc, 3% NEt₃). The product 1 was obtained as a white solid (3.02 g, 3.25 mmol, 51%).

1H NMR (300 MHz, CDCl₃, 293 K): δ = 7.34 (d, *J* = 7.8 Hz, 2H, H₃), 7.17 (d, *J* = 7.8 Hz, 8H, PC₆H₄), 7.12 (m, 8H, PC₆H₄), 6.90 (t, *J* = 7.6 Hz, 2H, H₂), 6.52 (d, *J* = 7.6 Hz, 2H, H₁), 3.51 (s, 8H, CH₂N), 2.49 (q, *J* = 7.1 Hz, 16H, CH₂CH₃), 1.61 (s, 6H, C(CH₃)₂), 1.01 (t, *J* = 7.1 Hz, 24H, CH₂C₆H₃); 31P{1H} NMR (122 MHz, CDCl₃, 293 K): δ = –18.3 (s); 13C{1H} NMR (76 MHz, CDCl₃, 293 K): δ = 152.6 (br t, C₄a), 140.3 (s, Cq, CAr), 136.1 (s, Cq, CAr), 134.3 (s, CH, PC₆H₄), 132.4 (s, C₁), 130.1 (s, Cq, CAr), 129.1 (s, CH, PC₆H₄), 126.6 (s, C₃), 123.5 (s, C₂), 57.7 (s, CH₂N), 47.1 (s, C(CH₃)₂), 34.8 (s, C(CH₃)₂), 32.5 (s, C(C₆H₃)), 12.1 (s, CH₂C₆H₃); Anal. calcd. for C₅₉H₇₆N₄OP₂: C 77.09, H 8.33, N 6.10; found: C 76.88, H 8.39, N 5.96; HRMS (FAB+): found 919.5574; calcd. for [C₅₉H₇₆ON₄P₂Cl₄ + H]⁺ 919.5573.

4,5-Bis[4-(diethylammoniumchloride)methyl]phenylphosphino]-9,9-dimethylxanthene: 1a

A 1 M solution of HCl in diethyl ether (3.10 ml, 3.10 mmol) was added dropwise to a solution of 4,5-bis[4-(diethylamino)methyl]phenylphosphino]-9,9-dimethylxanthene 1 (0.57 g, 0.62 mmol) in 20 ml diethyl ether and a light yellow precipitation appeared immediate. After stirring for 45 min, the volatiles were removed *in vacuo* and 1a was obtained as a light yellow powder in quantitative yield. 1H NMR (500 MHz, CD₃OD, 293 K): δ = 7.59 (d, *J* = 8.1 Hz, 10H, H₃ + PC₆H₄), 7.33-7.30 (m, 8H, PC₆H₄), 7.03 (t, *J* = 7.7 Hz, 2H, H₂), 6.48 (d, *J* = 7.6 Hz, 2H, H₁), 4.40 (s, 8H, CH₂N), 3.29-3.19 (m, 16H, CH₂CH₃), 1.68 (s, 6H, CCH₃), 1.38 (dt, *J* = 3.0 and 7.5 Hz, 24H, CH₂CH₃); 13C{1H} NMR (126 MHz, CDCl₃, 293 K): δ = 12.12 (s, 4H, NH⁺); 31P{1H} NMR (202 MHz, CDCl₃, 293 K): δ = –16.8 (s); 13C{1H} NMR (126 MHz, CD₂OD, 293 K): δ = 153.2 (t, *J* = 9.6 Hz, CO), 140.6 (t, *J* = 7.2 Hz), 136.0 (t, *J* = 10.9 Hz), 132.8 (s, C₁), 132.4 (t, *J* = 3.2 Hz), 131.9 (s), 131.6 (s), 129.0 (s), 125.4 (t, *J* = 8.9 Hz), 125.2 (s, C₂), 57.0 (s, CH₂N), 48.3 (s, CH₂CH₃), 48.2 (s, CH₂CH₃), 35.7 (s, CCH₃), 32.7 (s, CCH₃), 9.3 (s, CH₂CH₃), 9.2 (s, CH₂CH₃); HRMS (FAB+): found 919.5573; calcd. for [C₅₉H₇₆ON₄P₂Cl₄ – 4Cl – 3H]⁺ 919.5573; ESI-MS (CH₃OH): m/z = 307.05 [1a – 4Cl – 1H]³⁺, 460.15 [1a – 4Cl – 2H]²⁺, 919.25 [1a – 4Cl – 3H]⁺. 

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A yellow solution of \(\left\{\left(\text{O-tolyl}\right)\text{Pd}(p-\text{C}_6\text{H}_4\text{CN})\text{Br}\right\}_2\) (148 mg, 0.125 mmol) and 1a (266 mg, 0.250 mmol) in 10 ml of methanol-dichloromethane (1:10, v/v) was stirred overnight at room temperature. The orange solution was concentrated in vacuo to ca. 3 ml. Next, 10 ml of diethyl ether was added which resulted in the precipitation of a yellow powder. The suspension was filtered and the remaining powder was dried in vacuo to give 1b as a yellow powder (271 mg, 80%). \(^1\)H NMR (500 MHz, CD\(_3\)OD, 293 K): \(\delta = 7.90\) (d, \(J = 7.0\) Hz, 2H, H\(_{1,2}\)), 7.52-7.43 (m, 16H, PC\(_6\)H\(_4\)), 7.33 (t, \(J = 7.7\) Hz, 2H, H\(_2\)), 7.22-7.19 (m, 2H, H\(_{1,3}\)), 6.99 (d, \(J = 7.5\) Hz, 2H, C\(_6\)H\(_4\)CN), 6.55 (d, \(J = 7.2\) Hz, 2H, C\(_6\)H\(_4\)CN), 4.36 (d, \(J = 11.7\) Hz, 4H, CH\(_2\)N), 4.32 (d, \(J = 12.1\) Hz, 4H, CH\(_2\)N), 3.28-3.10 (m, 16H, CH\(_2\)N), 1.84 (s, 6H, CCH\(_3\)), 1.38 (t, \(J = 7.0\) Hz, 12H, CH\(_2\)C\(_6\)H\(_5\)), 1.37 (t, \(J = 7.0\) Hz, 12H, CH\(_2\)C\(_6\)H\(_5\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)/CD\(_2\)CN 2/3, 293 K): \(\delta = 8.9\) (s); \(^{13}\)C\({}^{\text{1H}}\) NMR (126 MHz, CD\(_2\)OD, 293 K): \(\delta = 168.1\) (br s), 155.5 (s, \(J = 5.9\) Hz, 136.2 (br s), 135.7 (br s), 135.3 (t, \(J = 6.6\) Hz, 132.6 (t, \(J = 22.6\) Hz), 132.3 (s), 130.8 (t, \(J = 5.0\) Hz), 129.3 (s), 128.9 (s), 125.0 (s), 119.8 (s), 119.5 (t, \(J = 22.9\) Hz), 104.3 (s), 55.1 (s, CH\(_2\)N), 47.4 (s, CH\(_2\)CH\(_3\)), 46.7 (s, CH\(_3\)C\(_6\)H\(_5\)), 46.4 (s, CH\(_2\)C\(_6\)H\(_5\)), 36.4 (s, CCH\(_3\)), 27.9 (s, CCH\(_3\)), 8.0 (s, CH\(_3\)C\(_6\)H\(_5\)), 7.8 (s, CH\(_2\)CH\(_3\)); HRMS (FAB+): found 1126.4987; calculated for \([\text{C}_{66}\text{H}_{84}\text{ON}_{5}\text{P}_{2}\text{Cl}_{4}\text{Br}\text{Pd} - 4\text{Cl} - \text{Br} - 4\text{H}]^+\) 1126.4895; ESI-MS (CH\(_3\)OH): \(m/z = 376.25\) [1b – 4Cl – Br – 2H]\(^+\), 563.20 [1b – 4Cl – Br – 3H]\(^2+\), 1126.20 [1b – 4Cl – Br – 4H]\(^3+\).

A solution of 1b (160 mg, 0.118 mmol) and silver trflate (152 mg, 0.590 mmol) in 10 ml of dichloromethane-acetonitrile (5:1, v/v) was stirred in the dark for 1 h. Next, Norit was added and the reaction mixture was stirred for another hour. The suspension was filtered through Celite filter aid and the filtrate was evaporated to dryness in vacuo yielding 1c as a brown microcrystalline (170 mg, 77%). Compound 1c is not soluble in water. \(^1\)H NMR (500 MHz, CD\(_2\)OD, 293 K): \(\delta = 8.06\) (d, \(J = 8.0\) Hz, 2H, H\(_{1,2}\)), 7.70 (d, \(J = 8.5, 8.5\) Hz, PC\(_6\)H\(_4\)), 7.67-7.63 (m, 10H, H\(_{1,3}\) and PC\(_6\)H\(_4\)), 7.52 (t, \(J = 7.7\) Hz, 2H, H\(_2\)), 7.24 (d, \(J = 8.5\) Hz, 2H, C\(_6\)H\(_4\)CN), 7.16 (d, \(J = 8.5\) Hz, 2H, C\(_6\)H\(_4\)CN), 4.43 (s, 8H, CH\(_2\)N), 3.31-3.21 (m, 16H, CH\(_2\)N), 1.86 (s, 6H, CCH\(_3\)), 1.37 (t, \(J = 7.2\) Hz, 24H, CH\(_2\)CH\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)/CD\(_3\)CN 2/3, 293 K): \(\delta = 8.18\) (br s, 4H, NH\(_+\)); \(^{31}\)P\({}^{\text{1H}}\) NMR (202 MHz, CD\(_2\)OD, 293 K): \(\delta = 18.9\) (s); \(^{31}\)P\({}^{\text{1H}}\) NMR (202 MHz, dmso-\(d_6\), 293 K): \(\delta = 18.7\) (s); \(^{13}\)C\({}^{\text{1H}}\) NMR (126 MHz, CD\(_2\)OD, 293 K): \(\delta = 154.9\) (t, \(J = 8.1\) Hz), 152.6 (m), 136.3 (s), 136.1 (br s), 135.8 (t, \(J = 7.2\) Hz), 135.3 (s), 134.8 (s), 133.8 (br s), 133.4 (t, \(J = 5.8\) Hz), 132.0 (s), 129.9 (t, \(J = 26.0\) Hz), 128.8 (br s), 121.9 (q, \(J = 318.6\) Hz, CF\(_3\)), 119.9 (s), 119.3 (t, \(J = 20.5\) Hz), 109.1 (s), 56.6 (s, CH\(_2\)N), 48.5 (s, CH\(_2\)CH\(_3\)), 36.2 (s, CCH\(_3\)), 33.8 (s, CCH\(_3\)), 9.1 (s, CH\(_2\)CH\(_3\)); \(^{19}\)F NMR (282 MHz, CD\(_3\)OD, 293 K) –80.2 (s); HRMS (FAB+): found 1725.3197; calculated for \([\text{C}_{73}\text{H}_{88}\text{OF}_{19}\text{F}_{15}\text{P}_{2}\text{S}_{12}\text{Pd} - \text{CF}_3\text{SO}_3 - \text{H}]^+\) 1725.3210; ESI-MS (CH\(_3\)OH): \(m/z = 376.85\) [1c – 5CF\(_3\)SO\(_3\) – 2H]\(^+\), 563.50 [1c – 5CF\(_3\)SO\(_3\) – 3H]\(^2+\), 1126.50 [1c – 5CF\(_3\)SO\(_3\) – 4H]\(^3+\), 426.85 [1c – 4CF\(_3\)SO\(_3\) – 1H]\(^3+\), 638.30 [1c – 4CF\(_3\)SO\(_3\) – 2H]\(^2+\), 476.80 [1c – 3CF\(_3\)SO\(_3\)]\(^3+\), 713.80 [1c – 3CF\(_3\)SO\(_3\) – 1H]\(^2+\), –148.70 [CF\(_3\)SO\(_3\)]\(^+\).
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[(1a)\text{Pd(C(O)-p-C}_6\text{H}_4\text{CN)}]^{+}[\text{OTf}]^–: \text{1d (1a contains four triflate counterions instead of chlorides)}
\]

Carbon monoxide was bubbled for 10 min. through a solution of 1c in distilled CD\text{3}OD at room temperature (in a NMR tube) which resulted in 1d. IR (CH\text{3}OH, 293 K): 1732 cm\text{ }^{-1} [\nu(\text{CO})]; ^1\text{H NMR} (300 MHz, CD\text{3}OD, 293 K): \delta = 8.02 (d, J = 7.8 Hz, 2H, \text{H}_{1,3}), 7.85-7.60 (m, 20H, PC\text{6}H\text{4}, \text{H}_{1,3} \text{and } \text{H}_2), 7.49 (d, J = 7.8 Hz, 2H, C\text{6}H\text{4}CN), 7.39 (d, J = 8.1 Hz, 2H, C\text{6}H\text{4}CN), 4.40 (s, 8H, CH\text{2}N), 3.29-3.10 (m, 16H, \text{C}\text{H}_2\text{CH}_3), 1.34 (t, J = 7.2 Hz, 24H, \text{CH}_2\text{C}_\text{3}H\text{3}); ^{13}\text{C NMR} (75 MHz, CD\text{3}OD, 293 K): \delta = \text{212.6 (s, PdCO)}; ^{31}\text{P}^{[1\text{H}]} \text{NMR} (121 MHz, CD\text{3}OD, 293 K): \delta = \text{11.5 (s).}


This compound is synthesized according to a reported procedure.\text{14a-b} This reaction was not carried out with distilled solvents, nor under inert atmosphere. A mixture of 37% formaldehyde (31 ml, 1.2 mol) was added to p-tert-butyl phenol (50 g, 0.3 mol) in a 1 L three-necked round-bottom flask equipped with a mechanical stirrer. Sodium hydroxide (0.6 g, 1.5 mmol) was added and the reaction mixture was stirred uncovered for 15 min at room temperature. Subsequently, the reaction mixture was stirred for ca. 2 h at 120 \textdegree C under a steady flow of nitrogen. Upon the evaporation of water, the clear solution becomes very viscous and yellow. The reaction mixture was cooled to room temperature giving a more viscous brown solid. When stirring became impossible, the residue was dissolved in 500 ml hot diphenyl ether and was heated to 120 \textdegree C for 3 h with a heating mantle while nitrogen was bubbled into the reaction mixture to facilitate the removal of water. Next, while continuing bubbling N\textsubscript{2} into the solution, the flask is fitted with a condenser, and after reaching the reflux temperature of 350 \textdegree C the brown reaction mixture was left to reflux for 3h. After cooling the reaction mixture to room temperature 750 ml ethyl acetate was added which resulted in white precipitation. The crude product was subsequently washed with ethyl acetate, acetic-aced and water. The off white crude product was recrystallized from boiling toluene giving 5,11,17,23-tetrakis(tert-butyl)-25,26,27,28-tetrakis(hydroxy)calix[4]arene as a white microcrystalline (27.16 g, 41.85 mol, 56%). ^1\text{H NMR} (300 MHz, CDCl\text{3}, 293 K): \delta = 7.02 (s, 8H, \text{H Ar}), 4.23 (d, J = 14.3 Hz, 4H, \text{H ax}), 3.47 (d, J = 13.8 Hz, 4H, \text{Heq}), 1.18 (s, C(CH\text{3})\text{3}); ^{13}\text{C}^{[1\text{H}]} \text{NMR} (76 MHz, CDCl\text{3}, 293 K): \delta = \text{147.1 (s), 144.8 (s), 128.1 (s), 126.3 (s), 34.4 (s), 33.0 (s), 31.8 (s); HRMS (FAB+): found 649.4250; calcd. for [C}_{44}\text{H}_{56}\text{O}_{4} + \text{H}]^+ 649.4257.}

25,26,27,28-Tetrakis(hydroxy)calix[4]arene

This compound is synthesized according to a reported procedure.\text{14a,14c} A white slurry of p-tert-butylcalix[4]arene (16.18 g, 24.93 mmol) and phenol (2.35 g, 24.93 mmol) were stirred in 300 ml anhydrous toluene at room temperature. After a few minutes AlCl\text{3} (14.13 g, 124.65 mmol) was added slowly and in small portions to the reaction mixture. The red slurry was vigorously stirred for 18 h at room temperature. After cooling the reaction mixture with an ice bath, excess of AlCl\text{3} was carefully neutralized by the slow addition of 300 ml of a 1M HCl solution. After vigorously stirring for 45 minutes the slurry turned into orange. Subsequently, the water layer was extracted twice with dichloromethane and the combined organic layers were washed with brine. The
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organic layer was dried over MgSO₄, the solvents were evaporated and the crude product was triturated twice with methanol. The product 25,26,27,28-tetrakis(hydroxy)calix[4]arene was obtained as a pink powder (8.96 g, 21.11 mmol, 85%). ¹H NMR (300 MHz, CDCl₃, 293 K): δ = 10.19 (s, 4H, OH), 7.04 (d, J = 7.5 Hz, 8H, HAr), 6.72 (t, J = 7.6 Hz, 4H, HAr), 4.24 (br d, 4H, Hax), 3.53 (br d, 4H, Heq); ¹³C{¹H} NMR (76 MHz, CDCl₃, 293 K): δ = 149.2 (s, Cq), 129.4 (s, CH), 128.7 (s, Cq), 122.7 (s, CH), 32.1 (s, ArCH₂Ar); HRMS (FAB+): found 425.1758; calcd. for [C₂₈H₂₄O₄ + H]+ 425.1753.

25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene

This compound is synthesized according to a reported procedure. Sodium hydride 60% (6.52 g, 163.07 mmol) was added to 500 ml distilled DMF and the solution was stirred for a few minutes. Subsequently, 25,26,27,28-tetrahydroxycalix[4]arene (10.65 g, 25.09 mmol) and 2-bromoethyl-ethyl-ether 90% (16.03 ml, 127.95 mmol) were added slowly to the solution. The reaction mixture was heated to 100 °C giving a brown solution, and allowed to stir for 1 h. A second portion of 2-bromoethyl-ethyl-ether 90% (8.02 ml, 65.23 mmol) was added dropwise and the reaction mixture was stirred for 3 h. Next, a second portion of NaH 60% 6.52 g, 163.07 mmol) and a third portion of 2-bromoethyl-ethyl-ether 90% (16.03 ml, 127.95 mmol) were added and the reaction mixture was stirred for another hour. Finally, a fourth portion of 2-bromoethyl-ethyl-ether 90% (8.02 ml, 65.23 mmol) was added, after which the resulting brown reaction mixture was stirred for overnight at 100 °C. Next morning the reaction mixture was quenched with a few drops of water and the DMF was removed under reduced pressure giving a yellow-orange residue. The crude product was dissolved in dichloromethane and was purified by washing with water (3x). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was triturated with methanol and collected by filtration. After drying under vacuum 25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene was obtained as an off-white microcrystalline solid (12.00 g, 16.83 mmol, 67 %). ¹H NMR (300 MHz, CDCl₃, 293 K): δ = 6.62-6.52 (m, 12H, HAr), 4.47 (d, J = 13.4 Hz, 4H, Hax), 4.09 (t, J = 5.8 Hz, 8H, CH₂CH₂), 3.82 (t, J = 5.8 Hz, 8H, CH₂CH₂), 3.52 (q, J = 7.0 Hz, 8H, CH₂CH₂), 3.27 (d, J = 13.4 Hz, 4H, Heq), 1.18 (t, J = 7.0 Hz, 12H, CH₃); ¹³C{¹H} NMR (76 MHz, CDCl₃, 293 K): δ = 156.7 (s, Cq), 135.5 (s, Cq), 128.6 (s, CH), 122.6 (s, CH), 73.5 (s, CH₂), 70.1 (s, CH₂), 66.8 (s, CH₂), 30.1 (s, ArCH₂Ar), 15.7 (s, CH₃); HRMS (FAB+): found 713.4053; calcd. for [C₄₄H₅₆O₈ + H]+ 713.4053.


This compound is synthesized according to a reported procedure. This reaction was not carried out with distilled solvents, nor under inert atmosphere. 25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene (10.00 g, 14.03 mmol) was dissolved in concentrated H₂SO₄ (96%, 25 ml) and stirred at room temperature for 3 h. The brown reaction mixture was then quenched by pouring it carefully into water at 0 °C. Next, the mixture was neutralized by addition small aliquots of a concentrated solution of NaOH (~ 5 M) at 0 °C, giving a white solution. The water was then evaporated giving a white solid residue. The majority of the inorganic sulfates were removed from the crude product using a Soxhlet extractor with methanol overnight at 100 °C. Finally the crude product was purified by reversed phase chromatography (LiChroprep RP8, 40-63 μm) eluting initially with pure water until no more inorganic sulfates were detected: no precipitation observed upon addition of BaCl₂-solution to the eluate (the presence of organic compounds was excluded.
by UV prior to the addition of BaCl₂). Subsequently, the pure product was obtained by elution in a step-gradient to 70% EtOH/H₂O (v/v). After concentration under vacuum to remove most of the ethanol, the remaining water was removed by freeze-drying overnight to afford 2 as a white solid (8.58 g, 7.65 mmol, 55%). 

\[ \text{1H NMR (300 MHz, CD₃OD, 293 K): } \delta = 7.32 (s, 8H, Hₐ), 4.65 (d, J = 13.3 Hz, 4H, Hₐ), 4.21 (t, J = 5.4 Hz, 8H, CH₂CH₂), 3.86 (t, J = 5.0 Hz, 8H, CH₂CH₂), 3.52 (q, J = 6.8 Hz, 8H, CH₂CH₂), 3.40 (d, J = 13.4 Hz, 4H, Hₐ), 1.17 (t, J = 7.0 Hz, 12H, CH₃); \]

\[ \text{13C{1H} NMR (76 MHz, CD₃OD, 293 K): } \delta = 158.3 (s, Cq), 139.1 (s, Cq), 134.8 (s, Cq), 126.5 (s, CH), 73.9 (s, CH₂), 69.9 (s, CH₂), 66.4 (s, CH₂), 31.2 (s, ArCH₂Ar), 13.7 (s, CH₃). \]

HRMS (FAB+): found 1121.1624; calcd. for [C₄₄H₅₂Na₄O₂₀S₄ + H]⁺ 1121.1604.

**General procedure for capsules self-assembly**

Capsule self-assembly was done in situ. Equimolar methanol, dmso or water solutions of the tetracationic diphosphine ligand 1a or the palladium complexes thereof 1b and 1c and the tetraanionic calix[4]arene 2 were mixed at room temperature, resulting in the immediate formation of the corresponding capsules (1a·2, 1b·2, and 1c·2, respectively).

**NMR characterization of capsules 1a·2, 1b·2, and 1c·2**

The assignment of the ¹H NMR spectra of the capsules is fully supported by COSY NMR. Not all the proton resonances were visible in the ¹H NMR spectra because of overlap with other signals or because of H-D exchange with CD₃OD.

The ³¹P{¹H} NMR spectra of 1a, 1b, 1c, 1a·2, 1b·2, and 1c·2 in CD₃OD, D₂O and dmso-d₆ confirms their stability in the different solvents. ³¹P{¹H} NMR (202 MHz, 293 K) and upfield shifts (Δδ) (500 MHz, 293 K) of the CH₂NH⁺(CH₂CH₃)₂ protons of 1a, 1b, and 1c upon capsule formation in different solvents:

**Capsule 1a·2 (CD₃OD):** ³¹P{¹H} NMR = –17.4; Δδ(CH₂CH₃) = 0.43, Δδ(CH₂N) = 0.25 ppm.

**Capsule 1a·2 (dmso-d₆):** ³¹P{¹H} NMR = –17.7; Δδ(CH₂CH₃) = 0.49, Δδ(CH₂CH₃) = 0.32, Δδ(NH⁺) = 1.40 ppm.

**Capsule 1b·2 (dmso-d₆):** ³¹P{¹H} NMR = 9.3; Δδ(CH₂CH₃) = 0.41, Δδ(CH₂CH₃) = 0.27, Δδ(NH⁺) = 1.14 ppm.

**Capsule 1c·2 (CD₃OD):** ³¹P{¹H} NMR = 19.4; Δδ(CH₂CH₃) = 0.58, Δδ(CH₂CH₃) = 0.39, Δδ(CH₂N) = 0.17 ppm.

**Carbon monoxide was bubbled for 10 min. through a solution of 1c·2 (1c:2 = 1:2) in distilled CD₃OD at room temperature (in a NMR tube) which resulted in capsule 1d·2. IR (CH₃OH, 293 K): 1732 cm⁻¹ [ν(CO)]; ¹H NMR (300 MHz, CD₂OD, 293 K): δ = 7.93-7.45 (m, 26H, H₁, H₂, H₃, PC₆H₄), 7.43 (s, 16H, Hmeta of 2), 4.72 (d, J = 12.6 Hz, 8H, Hₐ), 4.28 (br s, 24H, CH₂N and ArOCH₂), 3.90 (t, J = 5.0 Hz, 16H, ArOCH₂CH₂), 3.56 (q, J = 6.9 Hz, 16H, OCH₂CH₂), 3.35 (d, J = 13.8 Hz, 8H, Hₐ), 3.05-2.90 (m, 16H, NH⁺(CH₂CH₃)₂), 1.62 (s, 6H, CCH₃), 1.22 (t, J = 7.2 Hz, 24H, OCH₂CH₃), 0.95-0.85 (m, 24H, NH⁺(CH₂CH₃)₂); ¹³C NMR (75 MHz, CD₂OD, 293 K): δ = 213.0 (s, PdC(O)); ³¹P{¹H} NMR (121 MHz, CD₂OD, 293 K): δ = 12.1 (s).

**Chloride test of capsule 1a·2**

Mixing water solutions of 1a and 2 resulted in the precipitation of capsule 1a·2. The chloride test with silver nitrate was used to determine the concentration of sodium chloride in the precipitated capsule, as is described below. The molar solubility of AgCl in CH₃OH was visually determined by the addition of one
drop of a saturated aqueous AgNO₃ solution to NaCl solutions in methanol (0.01-10 mM) and was found to be 0.50 mM. Next, one drop of the AgNO₃ solution was added to capsule 1a·2 formed in situ in methanol (1a/2 = 1:1, 2 mM). As expected, AgCl precipitated immediately confirming the presence of chloride ions in solution. Subsequently equimolar water solutions of 1a and 2 were mixed, the precipitate was filtered, washed with water (the water layers were combined), dried and re-dissolved in methanol. Upon addition of one drop of the AgNO₃ solution to the combined water layers AgCl precipitated immediately. However, addition of one drop of the AgNO₃ solution to the re-dissolved capsule in methanol (2 mM) did not result in any precipitation. The maximum concentration of NaCl that can be present in the solution of capsule 1a·2 is ≤ 0.50 mM, indicating that at most 6 % of the chloride that was initially present in 1a (8 mM) is present in capsule 1a·2. These chloride tests show that mixing equimolar water solutions of 1a and 2 results in the precipitation of capsule 1a·2 in the absence of NaCl and the presence of NaCl in the water filtrate. This experiment was performed in duplo.

Job Plot

Equimolar solutions (2 mM) of 1a and 2 in CD₃OD were prepared and mixed in various ratios. In this way the total concentration of 1a and 2 was kept constant at 2 mM and only the 1a/2 ratio was varied. ¹H NMR spectra of the mixtures were recorded, and the chemical shifts of 1a were analyzed by Job’s method of continuous variation, i.e. a plot of the capsule concentration as a function of the mol fraction of 2.²³

¹H NMR titrations

The ¹H NMR titrations of 2 with 1a and of 2 with 1c were measured in CD₃OD at 298 K under inert conditions. Because of solubility reasons the concentration of 2 was kept constant and low in all the samples (1 mM) whereas the concentrations of 1a and 1c were varied from 0 to 3 mM. The chemical shifts of the diphosphine protons CH₂NH(CH₂CH₃)₂ of 1a·2 and 1c·2, relative to the chemical shifts of 1a respectively 1c were followed and fitted to a 1:1 binding model using a least-squares fitting procedure.²⁴a The association constants K for a single run were calculated as the mean of the values obtained for each of the followed diphosphine signals, weighted by the observed changes in chemicals shift.²⁴b The association constants from different runs were then averaged. The titrations were carried out in duplo. The association constant found for capsule 1a·2 is K₁a·2 = 6·10⁴ M⁻¹ and for capsule 1c·2 is K₁c·2 = 6·10³ M⁻¹. Lines in the titration curves are best-fit curves calculated by nonlinear regression.

1D-NOESY measurements

1D transient NOE experiments (DPFGSE excitation = double pulsed field gradient spin-echo) of capsule 1a·2 (1a/2 = 1:2, [1a] = 3 mM, CD₃OD), capsule 1b·2 (1b/2 = 1:2, [1b] = 3 mM, CD₃OD), capsule 1c·2 (1c/2 = 1:2, [1c] = 3 mM, dmso-d₆) were carried out at 298 K. Negative NOE enhancements were observed between the NH(CH₂CH₃)₂ protons of the diphosphine building block (1a, 1b or 1c), and the aromatic protons of 2 upon selective saturation of the methyl protons NH(CH₂CH₃)₂ of the diphosphine.¹⁵b

DOSY measurements

In all the DOSY experiments of the free building blocks as well of the capsules, the concentrations of 1a, 1b, 1c and 2 were kept constant at 2 mM, this resulted in a 1:1 ratio of the capsules building blocks 1 and
2. The NH(CH₂CH₃)₂ protons of 1a, 1b and 1c and the OCH₂CH₃ protons of 2 were used for the calculation of the diffusion coefficients. The diffusion measurements were carried out on a Varian Inova 500 equipped with a Performa II pulsed gradient unit able to produce magnetic field pulse gradients of about 30 Gcm⁻¹ in the z-direction. The ¹H DOSY experiments were carried out in a 5 mm inverse probe at 296 K. The magnetic field pulse gradients were of 1.5 ms duration followed by a stabilization time of 2 ms. The diffusion delay was set to 0.2 s. The magnetic field pulse gradients were incremented from 0 to 25 Gcm⁻¹ in ten steps and the stimulated spin echo experiment was performed with compensation for convection. The pulse sequence was developed by Evans and Morris (University of Manchester). The diffusion coefficients \(D\) are calculated according to the Stejskal-Tanner equation: \(\ln(I/I₀) = -[\gamma^2 \delta^2 G^2 (\Delta - \delta/3)]D\), where \(I\) is the peak area, \(I₀\) is the peak area in the absence of gradients, \(\gamma\) the magnetogry ratio of the observed nucleus, \(\delta\) is the gradient duration, \(G\) the strength of the gradient pulse in T/m, \(\Delta\) the diffusion time and \(D\) the diffusion coefficient. The hydrodynamic radius \(r\) was calculated according to the Stokes-Einstein equation: \(D = (k_BT)/(6\pi\eta r)\), where \(D\) is the diffusion coefficient, \(k_B\) is the Boltzmann constant, \(T\) is the temperature in Kelvin, \(\eta\) is the viscosity of the solution, and \(r\) is the radius of the molecular sphere (hydrodynamic radius). The viscosity of neat methanol-\(d_4\) at 295 K and neat dmoso-\(d_6\) at 293 K was used.

ESI-MS measurements
Samples of the capsules 1a·2, 1b·2, and 1c·2 (PP/calix = 1/1) with initial concentrations of 100-250 μM were diluted in 70% MeOH sometimes with the addition of formic acid to a final concentration of 1%. Comparison of the measured isotope patterns of capsules 1a·2, 1b·2, and 1c·2 with the calculated ones confirm their elemental composition and charge state. The capsules ion peaks correspond to 1:1 complexes and no ion peaks for higher aggregates were detected. From the survey MS spectra individual candidate ions were selected for collision induced dissociation (CID) MSMS with Argon as collision gas. The assignment of the capsule’s ion peaks is confirmed by CID experiments. Upon collision induced dissociation of the capsule’s ion peaks, product peaks appeared that correspond to the diphosphine building blocks 1a, 1b, and 1c respectively at \(m/z\) 460.4 for [1a – 4Cl – 2H]²⁺, at \(m/z\) 562.8 for [1b – 4Cl – Br – 3H]²⁺, and at \(m/z\) 562.9 for [1c – 5CF₃SO₃ – 3H]²⁺. Comparison of the ESI-MS spectra of 1b (see synthesis) and of capsule 1b·2 shows in both cases a heterolytic splitting of the Pd-Br bond. The reported \(m/z\) correspond to the monoisotopic ion peak (first isotope). 

**Capsule 1a·2** (C103H132N₄O₂₁P₂S₄) ESI-MS (\(m/z\), CH₃OH): [1a·2 + 2H]³⁺ found 651.263, calcd. 651.265; [1a·2 + 2H + 1Na]³⁺ found 658.602, calcd. 658.593; [1a·2 + 1H + 2Na]⁵⁺ found 665.921, calcd. 665.920; [1a·2 + 3Na]⁵⁺ found 673.251, calcd. 673.247; [1a·2 + 2H]²⁺ found 976.354, calcd. 976.394; [1a·2 + 1H + 1Na]²⁺ found 987.327, calcd. 987.385; [1a·2 + 2Na]²⁺ found 998.325, calcd. 998.375. 

**Capsule 1b·2** (C110H136N₅O₂₁P₂PdS₄Br) ESI-MS (\(m/z\), CH₃OH): [1b·2 + 2H – Br]³⁺ found 719.549, calcd. 719.576; [1b·2 + 1H + 1Na – Br]³⁺ found 726.881, calcd. 726.909; [1b·2 + 2Na – Br]⁵⁺ found 734.219, calcd. 734.230; [1b·2 + 1H – Br]²⁺ found 1078.823, calcd. 1078.860. 

**Capsule 1c·2** (C111H136N₅O₂₄P₂PdS₅F₃) ESI-MS (\(m/z\), CH₃OH): [1c·2 – CF₃SO₃ + 2H]³⁺ found 719.696, calcd. 719.576; [1c·2 – CF₃SO₃ + 1H]²⁺ found 1079.045, calcd. 1078.860. 

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2.9 References


Diphosphine Based Capsules for the Encapsulation of Transition Metals


