Transition metals enclosed in supramolecular capsules: assembly, characterization and application in catalysis

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Chapter 3

Design of Metallo Diphosphine Capsules
3.1 Introduction

Supramolecular capsules are composed of two or more, not necessarily identical, building blocks programmed to self-assemble in solution into the desired structure.\(^1\) The capsule’s building blocks have a similar size, complementary functional groups and associate \textit{via} multiple reversible non-covalent interactions such as hydrogen bonds, metal-ligand and ionic interactions.\(^2-4\) Self-assembly of the capsules described in this Chapter is driven by multiple ionic interactions. Timmerman, Crego-Calama and co-workers have reported ionic-based capsules constituted of one tetrasulfonated calix[4]arene and one tetracationic Zn(II) porphyrinate or tetracationic calix[4]arene (Figure 1a).\(^4b-c,4g\) Schrader and co-workers have studied ionic-based capsules composed of one tetraanionic calix[4]arene and one tetracationic calix[4]arene (Figure 1b).\(^4a,4g\) Verboom and co-workers have reported ionic-based capsules constituted of two tetracationic cavitands and four monovalent anions (Figure 1c).\(^4e\) In contrast to hydrogen bonded capsules, ionic-based capsules are generally stable in polar solvents, do not require an external guest (but contain solvent) as a template for capsule formation, and undergo an exchange process fast on the NMR time scale between the capsule’s free and bound building blocks.

![Figure 1](image-url)  
**Figure 1** Supramolecular capsules based on ionic interactions and composed of a calix[4]arene and a Zn(II) porphyrinate (a), two calix[4]arenes (b), and two cavitands and four anions (c).

In Chapter 2 of this thesis we have reported an ionic-based capsule composed of a tetracationic xantphos-type diphosphine and a tetraanionic calix[4]arene.\(^5\) Encapsulation of a palladium atom within this capsule is achieved by using the metal complex of the tetracationic diphosphine ligand for the assembly process (Figure 2). In this templated approach to metal encapsulation, the transition metal complex is an integrated part of the capsule with the transition metal located inside the capsule and it is not involved in the assembly process.\(^3,6\) Hence, the encapsulated metal is still available for catalytic transformations.

Transition metal complexes containing diphosphine ligands represent an important class of catalysts.\(^7\) Our aim in this Chapter is to achieve a better understanding of the factors that determine capsule formation and stability, in order to enlarge the scope of metallo-diphosphine capsules. Here, we report diphosphine capsules based on a tetracationic diphosphine and a
tetraanionic calix[4]arene. To show the versatility of the diphosphine capsules we have used various tetracationic diphosphines with different backbones (ethylene, diphenylether and xanthene) and different binding motifs (\(p\)-C\(_6\)H\(_4\)-CH\(_2\)-ammonium, \(m\)-C\(_6\)H\(_4\)-ammonium and \(m\)-C\(_6\)H\(_4\)-guanidinium). In addition, we report the formation and characterization of the metallo-diphosphine capsules based on palladium complexes of the tetracationic diphosphines.\(^1\)

**Figure 2** Encapsulation of a palladium species within an ionic-based capsule composed of a Pd(diphosphine)-complex and a calix[4]arene: molecular and modeled structures.

### 3.2 Capsules based on cationic diphosphines: backbone variation

In this section we report the study on ionic-based capsules composed of a tetracationic diphosphine and a tetraanionic calix[4]arene.\(^5\) The tetracationic diphosphines used here have different shapes and flexibility properties as a result of their different backbones, \(i.e\). ethylene (dppe), diphenyl ether (DPEphos) and xanthene (Xantphos).

#### 3.2.1 Tetracationic diphosphines with various backbones

The cationic charges on the diphosphine ligands are created by functionalizing the four phenyl groups on the phosphorus atoms. The tetrakis-ammonium diphosphine ligands A and B are prepared from the corresponding tetrakis-amine precursors a and b. Tetrakis(\(p\)-diethylbenzylamine)-dppe a and tetrakis(\(p\)-diethylbenzylamine)-DPEphos b are prepared by the reaction of the lithiated product of \(p\)-bromobenzylidineamine with a phosphorus electrophile, \(i.e\). the corresponding bisdichlorophosphines, similar to tetrakis(\(p\)-diethylbenzylamine)-xantphos c.\(^8\) Reaction of the commercially available 1,2-bis(dichlorophosphino)ethane with the lithiated product of \(p\)-bromobenzylidineamine gave the tetrakis(\(p\)-diethylbenzylamine)-dppe a in 60% yield (Scheme 1a).\(^9\) The synthesis of the precursor 2,2’-bis(dichlorophosphino)-4,4’-dimethyl-diphenyl ether was done as reported by van Leeuwen, Müller and co-workers.\(^10\) First, the bisdiethylamino phosphane was prepared by lithiation of the 4,4’-dimethylidiphenyl ether

\(^{1}\) In the appendix of this Chapter an overview is given of the notations and structures of the compounds used in this Chapter, \(i.e\). diphosphines, palladium-diphosphine complexes, calix[4]arene and the corresponding capsules.
backbone and a subsequent reaction with CIP(NEt$_2$)$_2$. Next, the bisdichlorophosphine compound was prepared by reaction with HCl. Reaction of the bisdichlorophosphine with the lithiated product of $p$-bromobenzylidihyamine gave the tetrakis($p$-diethylbenzylamine)-DPEphos $b$ in 60% yield (Scheme 1b).

Selective $N$-protonation of tetrakis($p$-diethylbenzylamine)-diphosphines $a$ and $b$ by HCl in diethyl ether resulted in the corresponding tetrakis($p$-diethylbenzylammonium)-diphosphine ligands A-HCl and B-HCl, similar to the xantphos-type diphosphine C-HCl (Scheme 2). The electronic effect of the ammonium groups of A-HCl and B-HCl on the phosphorus atoms is negligible because of the presence of the benzyl methylene-spacer. Indeed, $^{31}$P NMR data confirm that the phosphines are barely affected by the electron-withdrawing ammonium groups, see Scheme 2.$^{8b,11}$

The tetraanionic building block tetraruhsonatocalix[4]arene tetrasodiumsal $2$-$SO_3$Na is prepared according to a literature procedure and is subsequently acidified to give the tetrasulfonicacid-calix[4]arene 2-$SO_3$H (Scheme 3).$^{8a,4b,12}$ During the synthesis of the tetrasodium salt, we did not succeed in isolating the corresponding tetraacid prior to neutralization. Fortunately, exchange of the sodium cations of 2-$SO_3$Na with protons was easily achieved with the strongly acidic Amberlyst$^{®}$ 15 ion-exchange resin to give 2-$SO_3$H. All new compounds described in this Chapter have been characterized by NMR and mass spectrometry techniques (see Experimental section).

Scheme 1 Synthesis of tetrakis($p$-diethylbenzylamine)-diphosphines of the dppe-type $a$ ($a$) and the DPEphos-type $b$ ($b$).
Design of Metallo Diphosphine Capsules

Scheme 2 Selective \(N\)-protonation of \(a\) and \(b\) to give the tetrakis(\(p\)-diethylbenzylammonium)-diphosphines \(A\)-HCl and \(B\)-HCl.

Scheme 3 Acidification of tetrasulfonatocalix[4]arene tetrasodiumsalt \(2\text{-SO}_3\text{Na}\) to give the tetrasulfonicacid-calix[4]arene \(2\text{-SO}_3\text{H}\).

3.2.2 Self-assembly of the diphosphine capsules

The hetero-dimeric diphosphine capsules \(A\cdot2\), \(B\cdot2\) and \(C\cdot2\) consist of the tetracationic diphosphines \(A\), \(B\) and \(C\) and the complementary tetraanionic calix[4]arene \(2\). Self-assembly of these ionic-based capsules is simply achieved by mixing methanol solutions of the corresponding building blocks. Capsule formation is evidenced by NMR spectroscopy and mass spectrometry. We have developed two approaches for capsule assembly. The first approach involves mixing of the pre-charged building blocks e.g. tetraammonium-diphosphine \(A\)-HCl and tetrasulfonatocalix[4]arene tetrasodiumsalt \(2\text{-SO}_3\text{Na}\) to give capsule \((A\text{-HCl})\cdot2\) (Scheme 4a). Capsules \((B\text{-HCl})\cdot2\) and \((C\text{-HCl})\cdot2\) are prepared in a similar fashion. All the capsules are instantaneously formed upon mixing methanol solutions of the building blocks and contain four equivalents of the corresponding NaCl salt. The second approach involves mixing of the neutral building blocks e.g. tetraamine-diphosphine \(a\) and tetrasulfonicacid-calix[4]arene \(2\text{-SO}_3\text{H}\) to give capsule \((A)\cdot2\) (Scheme 4b). Capsules \((B)\cdot2\) and \((C)\cdot2\) are prepared in a similar fashion. Upon mixing methanol solutions of the neutral building blocks, the tetrasulfonicacid-calix[4]arene quantitatively protonates the tetraamine-diphosphines. The charged building blocks assemble into capsules \((A)\cdot2\), \((B)\cdot2\) and \((C)\cdot2\) without salt formation as co-product. Capsules are more stable, i.e. have a higher association constant, when no salt is present in solution. Still, in both approaches the capsules are in equilibrium with their charged and/or neutral building blocks. All diphosphine based capsules appear to be soluble and stable in the polar, protic methanol, as will be clear from the evidence presented in the next section.
Scheme 4 Self-assembly of capsules A·2, B·2 and C·2 by the use of pre-charged (a) and neutral (b) building blocks (schematic picture).

### 3.2.3 Characterization of the diphosphine capsules

The evidence for the formation of the diphosphine based capsules A·2 and B·2, composed of dppe- and DPEphos-type ligands A and B, is similar to that obtained for capsule C·2 based on the xantphos-type ligand C, which was reported in Chapter 2. As can be seen in Figure 3 and Table 1, the $^1$H NMR spectra of capsules A·2, B·2 and C·2 in CD$_3$OD show sharp resonances and large upfield shifts for the diethylammoniummethyl substituents, CH$_2$NH(CH$_2$CH$_3$)$_2$, with respect to those of the corresponding free diphosphines A, B and C. The chemical shifts of the other protons are less affected ($\Delta \delta < 0.20$ ppm). The upfield shifts point to partial inclusion of the diethylammoniummethyl substituents inside the hydrophobic cavity of the capsules.

$^1$H NMR titrations were carried out in CD$_3$OD (298 K) providing stability constants of $K_{A·2} = 3 \cdot 10^4$, $K_{B·2} = 8 \cdot 10^4$ and $K_{C·2} = 6 \cdot 10^4$ M$^{-1}$ for capsules (A-HCl)·2, (B-HCl)·2 and (C-HCl)·2, respectively (Table 1 and Figure 4). Crego-Calama, Corbellini and co-workers have found association constants in the range of $10^6$ M$^{-1}$ for ionic-based capsules composed of two calix[4]arenes in CD$_3$OD. The high association constants found for the diphosphine-capsules confirm that the diphosphine ligands and the tetrasulphonatocalix[4]arene fit well to form stable capsules at low concentrations. The titration curve fitted to a 1:1 binding model is in line with the 1:1 stoichiometry of the capsules. As can be seen in Figure 3, a single set of proton resonances for the free and associated building blocks was observed for capsules self-assembled from charged or neutral building blocks. This indicates a fast exchange process on the NMR time.
scale between the building blocks that are in the monomeric form (free) and those in the capsular form (bound). Consequently, the lower symmetry of the capsules compared to the calix[4]arene \( \text{2} \) \( (C_{4v}) \) and possible changes in ligand conformation upon capsule formation are not apparent in the \(^1\text{H}\) NMR spectra.\(^{4b}\)

Figure 3 \(^1\text{H}\) NMR spectra in \( \text{CD}_3\text{OD} \) at 20 °C. \textit{Top}: \( \text{A-HCl (dppe)} \); \textit{Middle}: capsule \(( \text{A-HCl)}\cdot\text{2} \) \( (\text{A}/2 = 2/3, [\text{A}] = 2 \text{ mM}) \); \textit{Bottom}: \( 2\text{-SO}_3\text{Na} \). Asterisks indicate solvent signals.

Table 1 Upfield shifts (\( \Delta\delta \)) for the \( \text{CH}_2\text{NH}^+(\text{CH}_2\text{CH}_3)_2 \) protons of the diphosphine capsules with respect to the corresponding free diphosphines \( \text{A-HCl}, \text{B-HCl} \) and \( \text{C-HCl} \), the association constants and the Gibbs free energy of the corresponding diphosphine capsules \( (K) \).

<table>
<thead>
<tr>
<th>Capsule</th>
<th>( \Delta\delta(\text{CH}_2\text{CH}_3)^{a,b} ) (ppm)</th>
<th>( \Delta\delta(\text{CH}_2\text{CH}_3)^{a,b} ) (ppm)</th>
<th>( \Delta\delta(\text{CH}_2\text{N})^{a,b} ) (ppm)</th>
<th>( K^a ) (M(^{-1}))</th>
<th>( \Delta G^c ) (KJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dppe: ((\text{A-HCl)}\cdot\text{2})</td>
<td>0.46</td>
<td>0.31</td>
<td>0.15</td>
<td>( 3\cdot10^4 )</td>
<td>25.5</td>
</tr>
<tr>
<td>DPEphos: ((\text{B-HCl)}\cdot\text{2})</td>
<td>0.42</td>
<td>0.32</td>
<td>0.20</td>
<td>( 8\cdot10^4 )</td>
<td>28.0</td>
</tr>
<tr>
<td>xantphos: ((\text{C-HCl)}\cdot\text{2})</td>
<td>0.43</td>
<td>0.33</td>
<td>0.25</td>
<td>( 6\cdot10^4 )</td>
<td>27.3</td>
</tr>
</tbody>
</table>

\(^a\) Measured in \( \text{CD}_3\text{OD} \) at 298 K. \(^b\) \((\text{A-C})/2 = 1/3\), capsules assembled from the pre-charged building blocks. \(^c\) Gibbs free energy was calculated according to \( \Delta G = -RT\ln K \).
Figure 4 The $^1$H NMR titration data fitted with a 1:1 binding model for B-HCl (DPEphos) with 2-SO$_3$Na in CD$_3$OD at 298 K. Data points represent the absolute upfield shifts ($\Delta\delta_{B}$) of CH$_2$NH(CH$_2$CH$_3$)$_2$ protons of B-2 relative to the chemical shifts of free B-HCl, ▲ CH$_2$CH$_3$, ● CH$_2$CH$_3$, ■ CH$_2$N.

**NOESY.** The 1D-NOESY spectra of the hetero-dimeric capsules A·2 and B·2 in CD$_3$OD display significant negative intermolecular NOE contacts between the NH(CH$_2$CH$_3$)$_2$ protons of the diphosphines A and B and the aromatic protons of 2 upon selective saturation of the methyl protons of A and B (Figure 5). This illustrates that the aryl-substituents of the diphosphines and the upper rim of the calix[4]arene are facing one another to form the typical dimeric 1:1 capsular structure. Small molecules (Mw < 1000) give positive NOE contacts and large molecules (Mw > 2000) give negative NOE contacts because of different intermolecular relaxation pathways. The negative NOE enhancements observed for the capsules confirm their large size.$^{14}$

Figure 5 1D-NOESY spectrum of capsule A·2 in CD$_3$OD (inset: spectrum enlargement).
ESI mass spectrometry. Additional evidence for capsule formation and their stabilities in the gas-phase was obtained by electrospray ionization mass spectrometry (ESI-MS). The ESI-MS spectra of capsules A·2 and B·2 in CH₃OH show prominent ion peaks of the capsules at m/z 908.95 for [A·2 + 2Na]²⁺ and at m/z 981.99 for [B·2 + H + Na]²⁺ (Figure 6). All the capsule’s ion peaks correspond to 1:1 complexes and no ion peaks for higher aggregates were detected. 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. These MS/MS experiments reveal the gas-phase stability of the capsule.

![Figure 6](image)

**Figure 6** ESI-MS spectrum of capsule (B-HCl)·2 in CH₃OH (inset: measured isotope pattern).

3.2.4 Structure and stability of the diphosphine capsules

Successful formation of stable supramolecular capsules with proper capsular structures requires their building blocks to be preorganized, *i.e.* well-programmed for the self-assembly process. In general, the building blocks should have comparable sizes, complimentary shapes and functional groups, and contain the proper balance between flexibility/rigidity. Self-assembly of the hetero-dimeric capsules A·2, B·2 and C·2 is primarily driven by the formation of multiple intermolecular ionic interactions between the cationic diphosphine and the anionic calix[4]arene. The three diphosphines contain the same p-diethylbenzylammonium groups but have different backbones: ethylene A, diphenyl ether B and xanthene C. The molecular size of the diphosphines is quite similar to that of concave rigid calix[4]arene 2. On the other hand, their shape and conformational rigidity varies, which allows us to have a closer look at the influence of the preorganization properties of the building blocks on the capsule’s structure and stability.
The xantphos-type diphosphine C has a rigid xanthene backbone, two parallel P–C\textsubscript{xanthene} bonds and four cationic benzylic groups which are pointing in the same direction i.e. below the ligand plane, as can be seen in the modeled structure (PM3-level) of C (Scheme 5c). Consequently, C has a defined concave structure and is preorganized for capsule formation. The modeled structure of capsule C·2 shows that the two building blocks are complementary and that the capsule has a defined and proper capsular structure (Scheme 5c). The high association constant of capsule (C-HCl)·2, \(K_{C\cdot2} = 6\cdot10^4\text{ M}^{-1}\) (\(\Delta G_{C\cdot2} = 27.3\text{ KJ/mol}\)), reflects that C and 2 form a stable capsule. The conformations of free C and bound C are similar, as a consequence of the rigid C and that only rotation around the two P–C\textsubscript{xanthene} bonds is possible.

The diphenyl ether backbone of the DPEphos-type diphosphine B has a size similar to that of the xanthene backbone of C, but it is flexible as it can rotate around its ether functionality and P–C\textsubscript{backbone} bonds (Scheme 5b). The ethylene backbone of the dppe-type diphosphine A results in a slightly smaller diphosphine compared to B and C and is flexible as it can rotate around three bonds (Scheme 5a). The diphosphines A and B are less preorganized for capsule formation compared to C as they have no concave structure and their four cationic benzylic groups are pointing at different directions. Nevertheless, the modeled structure of capsules A·2 and B·2 show that the diphosphines and the calix[4]arene are complementary and that the capsules have a defined and proper capsular structure (Scheme 5). The high association constants of capsules (A-HCl)·2 and (B-HCl)·2 (\(K_{A\cdot2} = 3\cdot10^4\text{ M}^{-1}\), \(\Delta G_{A\cdot2} = 25.5\text{ KJ/mol}\) and \(K_{B\cdot2} = 8\cdot10^4\text{ M}^{-1}\), \(\Delta G_{B\cdot2} = 28.0\text{ KJ/mol}\)) reflect their stability. The flexibility of A and B allows them to adopt the optimal conformation needed to form a stable capsule. The expected larger entropy loss for A and B as compared to C does not lead to a major difference in \(\Delta G\).

The rigid and concave calix[4]arene 2 fixes the flexible diphosphines A and B into the proper conformation needed to form a stable capsule. During this fixation the diphosphine is frozen in its rotation around a few bonds. Hence, only one of the two building blocks needs to be rigid in order to form a stable capsule with a defined and proper capsular structure.\textsuperscript{16b-c} The fine-tuning needed to reach a proper capsular structure is achieved for all the diphosphine capsules by introducing flexibilities at the periphery of the ligand, i.e. rotation of the P-Ar and Ar-CH\textsubscript{2} bonds.

The modeled structures of A and A·2 show that in both the free and bound state the phosphines are in trans-conformation, with a C\textsubscript{2} symmetry of A (Scheme 5a). We have also noticed that the free electron pairs on the phosphorus atoms of A·2 are pointing away from the capsule while the free electron pairs on the phosphorus atoms of B·2 and C·2 are pointing to the capsule interior. Clearly, in order to form a metallo-diphosphine capsule, diphosphine capsule A·2 will have to undergo another conformational change.
3.3 Capsules based on cationic diphosphines: binding motif variation

The tetracationic diphosphines studied so far contain a \( \text{CH}_2\)-ammonium group at the \textit{para} position of the phosphorus aryl groups. In this section we describe tetracationic xantphos-type diphosphines with ammonium and guanidinium groups attached directly to the \textit{meta} position of the phosphorus aryl groups.

3.3.1 Tetracationic diphosphines with various binding motifs

The tetrakis(\textit{m}-aniline)-xantphos ligand \( \text{d} \) is prepared by the reaction of the commercially available Grignard reagent 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride with 2,7-di-
tert-butyl-4,5-bis(dichlorophosphino)-9,9-dimethylxanthene in 25% yield (Scheme 6a). This reaction requires the use of a dichlorophosphine as the phosphorus electrophile because a diphosphonite is not sufficiently electrophilic to react with the Grignard reagent, which in turn is less nucleophilic than the organolithium compounds. To our surprise, the N-protecting trimethylsilyl groups were removed during the workup procedure, which involved excess of diethylamine, hence no methanolysis step was required. In a subsequent step, the tetrakis(m-aniline)-xantphos ligand was selectively N-protonated by HCl in diethyl ether to yield the corresponding tetrakis(m-anilinium)-xantphos D-HCl in a quantitative yield (Scheme 6b).

Stelzer and co-workers have previously reported the synthesis of 4,5-bis[(m-N,N-dimethylguanidiniumphenyl)phosphino]-9,9-dimethylxanthene by palladium catalyzed P–C coupling of m-iodophenylguanidine with the corresponding highly toxic, diprimary phosphine. We have prepared tetrakis(m-N,N-dimethylguanidiniumphenyl)-xantphos E-HCl in 89% yield by reacting tetrakis(m-anilinium)-xantphos D-HCl with excess dimethylcyanamide (Scheme 6b). The same procedure is described by Stelzer and co-workers for m-guanidinium phenylphosphines. The electronic effect of the cationic groups of D-HCl and E-HCl on the phosphorus atoms is negligible as is suggested by their similar 31P NMR chemical shifts, see Scheme 6b.

3.3.2 Self-assembly and characterization of the diphosphine capsules

Self-assembly of capsules D·2 and E·2 is achieved by mixing methanol or dmso solutions of the corresponding pre-charged building blocks. The 1H NMR spectra of the xantphos-anilinium based capsule D·2 in CD3OD and dmso-d6 show sharp resonances. In contract to e.g. capsule C·2, no significant upfield shifts are observed upon capsule formation (Δδ ≤ 0.07 ppm),
because no side chains are present in D that change their environment by filling the capsule. The xantphos-guanidinium based capsule E·2 show sharp resonances and significant upfield shifts for the guanidinium substituents, with respect to those of the corresponding free diphosphine E: \( \Delta \delta((N(CH_3)_2) = 0.51 \text{ ppm in } CD_3OD \) and \( \Delta \delta(NH) = 0.55 \text{ ppm in dms}-d_6 \). The upfield shifts point to partial inclusion of the guanidinium moiety’s inside the hydrophobic cavity of the capsule. A single set of proton resonances for the free and bound building blocks was observed for capsules D·2 and E·2. This indicates a fast exchange process on the NMR time scale between the building blocks that are in the monomeric form (free) and those that are part of the capsule (bound).

The ESI-MS spectra of capsules D·2 and E·2 in CH₃OH show prominent ion peaks of the capsules at e.g. \( m/z \) 914.98 for \([D·2 + 2Na]^{2+}\) and at \( m/z \) 711.07 for \([E·2 + 3Na]^{3+}\) (Figure 7). These results support capsule formation and demonstrate their stability in the gas-phase.

![Figure 7 ESI-MS spectrum of capsule (E-HCl)·2 in CH₃OH (inset: measured isotope pattern).](image)

Capsule stability against bases and acids is important for their further applications in catalysis and therefore a few preliminary NMR experiments were performed. The addition of cesium carbonate (20 equiv.) to a methanol solution of capsule (C)·2 results in the precipitation of the calix[4]arene 2 and deprotonation of the ammonium-based diphosphine C. We assume that the cesium cation is encapsulated within the calix[4]arene.\(^{19}\) A similar experiment using capsule E·2 also results in the precipitation of 2, but the guanidinium-based diphosphine E remains protonated. This is in line with the strong basicity of guanidine (the conjugate base of guanidinium). Upon addition of p-toluenesulfonic acid (20 equiv.) to capsule E·2 no precipitation appears, but judging from the NMR spectra we conclude that the presence of an acid slightly destabilizes the ionic capsule: \( \Delta \delta((N(CH_3)_2) = 0.51 \text{ ppm decreased to } 0.42 \text{ ppm.} \)
3.3.3 Structure of the diphosphine capsules

The four positive charges of the xantphos-anilinium ligand D are located directly at the meta position of the phosphorus aryl groups. The modeled structure (PM3-level) of capsule D·2 shows a highly symmetrical capsular structure with the four aryl groups situated perpendicular to the capsule equator (Figure 8a). In addition, the ammonium groups are pointing down and each one is situated between two sulfonato groups of the calix[4]arene and interacts with both sulfonato groups. According to molecular modeling studies, moving the ammonium groups from meta to the para position is less favorable because the corresponding capsule enforces a twist in the phosphorus aryl groups. Introducing a methylene spacer between the aryl-ring and the cationic group does result in stable capsules, as was shown for capsule C·2. Hence, a careful design of the building blocks is important.4a,4h,16a-b,20 Unlike the diethylammonium-xantphos ligand C, the xantphos-anilinium ligand D lacks alkyl substituents on the ammonium groups and still forms a capsule. Hence, the presence of side chains are not a prerequisite for capsule formation.

The planar Y-shaped guanidinium group, [NHC(NH$_2$)$_2$]$^+$, is known for its ability to form directed hydrogen-bonds as well as non-directed ionic interactions, i.e. ionic-hydrogen bonds, with e.g. complementary oxoanions such as carboxylates.4c,21a The four [NHC(NH$_2$)(NMe$_2$)]$^+$ guanidinium groups of the xantphos-guanidinium ligand E are located directly on the meta position of the phosphorus aryl groups. The modeled structure of capsule E·2 shows that each guanidinium group is located between two sulfonato groups of the calix[4]arene and interacts with both sulfonato groups (Figure 8b).2c,21b-c As a result of the large size of the guanidinium groups, capsule E·2 is less symmetrical than capsule D·2.

![Figure 8](image)

**Figure 8** Modeled and molecular structures of diphosphine capsules D·2 (a) and E·2 (b). The NH hydrogen atoms are visible.
3.4 Encapsulation of a palladium species

Encapsulation of a transition metal within capsules A·2 and B·2 is achieved by using palladium dichloride complexes containing tetracationic ligands, i.e. cis-PdCl₂(A) (1A) and cis-PdCl₂(B) (1B).

3.4.1 Palladium complexes containing tetracationic diphosphines

**Tetraamine-diphosphine PdCl₂-complexes.** Palladium dichloride complexes cis-PdCl₂(a) (1a) and cis-PdCl₂(b) (1b) containing the tetraamine-diphosphine ligands a (dppe) and b (DPEphos), were prepared in a straightforward manner by the reaction of the metal precursor (1,5-COD)PdCl₂ with the corresponding tetraamine-diphosphine in dichloromethane (Scheme 7). The two Pd-complexes are stable in common organic solvents such as chloroform and acetonitrile, but 1b is not stable in methanol and decomposes rapidly as is also evident from a color change from yellow to deep brown-purple. Phosphorus NMR display at least four multiplets at –8.0, 15.7, 20.1 and 29.7 ppm. The deep brown-purple color suggests that Pd(I) clusters are formed, probably due to the ligand’s basic amine groups and methanol.

**Scheme 7 Synthesis of (tetraamine-diphosphine)PdCl₂-complexes 1a (a) and 1b (b).**

**Tetraammonium-diphosphine PdCl₂-complexes.** The positive charges on the tetraamine-diphosphine ligands of 1a and 1b are created by N-quaternization by protonation or methylation. Selective N-protonation of 1a and 1b is achieved by a reaction with p-toluenesulfonic acid (PTSA) to give 1(A-HOTs) and 1(B-HOTs), respectively (Scheme 8a). N-methylation is preferred over N-protonation, because an acidic proton is more labile than an alkylammonium group, because deprotonation or even oxidative addition of HX to the metal can take place. We have previously shown that the tetraamine-xantphos ligand c can be selective N-protonated by the addition of HCl in diethyl ether, but selective N-methylation was not successful because the phosphorus atoms are also quaternized under these conditions. The phosphines in the palladium
complexes 1a and 1b are protected by the metal which enables selective N-methylation with methyl triflate and methyl tosylate to yield the tetracationic-diphosphine Pd-complexes 1(A-MeOTf), 1(B-MeOTf) and 1(A-MeOTs) (Scheme 8b-c). Methyl triflate is an extremely reactive methylating agent and is about 10^4 more reactive than methyl tosylate. 25 Indeed, we have observed that N-methylation of 1a and 1b with methyl triflate occurs instantaneously at room temperature, while N-methylation with methyl tosylate was only successful for 1a and required a longer reaction time and higher temperatures to reach completion. Interestingly, after protection of the amines by N-quaternization, the Pd-complexes 1(B-HOTs) and 1(B-MeOTs) are stable in methanol, in contrast to their neutral (i.e. basic) analogue 1b.

Scheme 8 Selective N-quaternization of the (tetraamine-diphosphine)PdCl2-complexes 1a and 1b by toluenesulfonic acid (a), methyl triflate (b) and methyl tosylate (c) to give the (tetraammonium-diphosphine)PdCl2-complexes 1A and 1B.

3.4.2 Self-assembly of the palladium-diphosphine capsules

Self-assembly of the metallo-diphosphine capsules was observed upon mixing methanol solutions of the pre-charged building blocks: (tetraammonium-diphosphine)PdCl2-complex e.g. 1(A-MeOTf), and tetr sulfonato-calix[4]arene tetrasodiumsalt 2-SO3Na (Scheme 9a). The palladium capsules 1(A-MeOTf)-2, 1(A-MeOTs)-2 and 1(B-MeOTf)-2 are formed instantaneously and contain four equivalents of the corresponding NaOTf or NaOTs salts. Capsule formation was also accomplished by mixing methanol or dichloromethane solutions of the neutral building blocks (tetraamine-diphosphine)PdCl2-complex (1a or 1b), and tetr sulfonicacid-calix[4]arene 2-SO3H (Scheme 9b). After protonation of the tetraamine-diphosphine by the acidic calix[4]arene, the now charged building blocks self-assemble into capsules 1(A)-2 respectively 1(B)-2 without salt formation. The palladium capsules 1(A)-2 and
1(B)-2 hardly dissolve in methanol, unlike the palladium capsules assembled from the pre-charged building blocks. Addition of 5–10% (v) of the co-solvents dichloromethane or water did result in better solubility of the capsules. The four equivalents of salt and the NMe+ groups of capsules 1(A-MeOTf)-2, 1(A-MeOTs)-2 and 1(B-MeOTf)-2 probably facilitate capsule solubility in methanol compared to the salt free capsules 1(A)-2 and 1(B)-2.

Scheme 9 Self-assembly of palladium-diphosphine capsules 1A·2 and 1B·2 by the use of a pre-charged (a) and neutral (b) building blocks (schematic picture).

3.4.3 Characterization of the palladium-diphosphine capsules

The 1H NMR spectra of the palladium-diphosphine capsules 1A·2 and 1B·2 show upfield shifts for the diethylammoniummethyl substituents, CH2N(H/CH3)+(CH2CH3)2, with respect to those of the corresponding free palladium complexes 1A respectively 1B: \( \Delta \delta(\text{CH}_2\text{CH}_3)_2 = 0.28–0.37, \Delta \delta(\text{CH}_2\text{N}) = 0.06–0.12 \) and \( \Delta \delta(\text{NCH}_3) = 0.07–0.13 \) ppm (Figure 9 and Figure 10). The upfield shifts point to partial inclusion of the diethylammoniummethyl substituents inside the capsule’s hydrophobic cavity. The observed upfield shifts of the palladium capsules 1A·2 and 1B·2 are smaller than those of the diphosphine capsules A·2 and B·2 and of the previously reported palladium capsule [Pd(trans-C)(p-C6H4-CN)(Br)]·2 (\( \Delta \delta(\text{CH}_2\text{CH}_3) = 0.58, \Delta \delta(\text{CH}_2\text{H}_2) = 0.39, \Delta \delta(\text{H}_2\text{N}) = 0.17 \) ppm).\(^{5,8a}\) Even though the amount of \( \Delta \delta \) depends on the exact nature of the metal complex, our observations may indicate that the conformational rigid cis-PdCl2-complexes 1A and 1B experience less side chain encapsulation and are somewhat “less complementary” to calix[4]arene compared to the
corresponding free ligands and to the Pd-complex [Pd(C)(p-C_6H_4-CN)(Br)]. In addition, as the capsule is also occupied by the palladium dichloride species, less space is available to accommodate side chains.

![Figure 9](image_url)

Figure 9 1H NMR spectra of palladium capsule 1(A)·2 self-assembled from neutral building blocks. (a) 1(A-HOTs) in CD_3OD at 20 °C; (b) capsule 1(A)·2 in CD_3OD/D_2O (90/10 v) at 20 °C, [1A] = [2] = 2mM; (c) capsule 1(A)·2 at 40 °C; (d) 2-SO_3Na in CD_3OD at 20 °C. Asterisks indicate solvent signals.

A single set of proton resonances for the free and bound building blocks was observed in the temperature window 0–60 °C for all the ionic-based palladium capsules. Variable temperature 1H NMR spectra of the palladium capsules show line-broadening at 20 °C, in particular for the palladium building blocks, and sharper resonances at higher temperatures (40 and 60 °C) (Figure 9).\(^\text{16b}\) The observed line-broadening indicate that the phosphorus substituents of the rigid palladium complex are not equivalent anymore upon capsule formation because they experience different environments. At higher temperatures the exchange process between the free and bound building blocks and the bond-rotation rates are faster, resulting in sharper NMR spectra. The phosphorus chemical shifts of 1A and 1B in their capsular form 1A·2 and 1B·2 did not exhibit a noteworthy shift compared to the monomeric form (Δδ ≤ 0.8 ppm), indicating that the cis geometry around the phosphorus atoms did not change.\(^\text{26}\)

Additional support for the formation of the palladium capsules 1A·2 and 1B·2 comes from Job’s plot analysis of titration experiments carried in CD_3OD at 60 °C (at 20 °C, the proton signals were too broad to be accurate determined). The observed maximum at a mol fraction of 0.5 proves the 1:1 stoichiometry between 1(A-MeOTf) and 2-SO_3Na, and between 1(B-MeOTf) and 2-SO_3Na (Figure 11).
Figure 10 $^1$H NMR spectra of palladium capsule 1(B-MeOTf)·2 self-assembled from pre-charged building blocks in CD$_3$OD. (a) 1(B-MeOTf) at 20 °C; (b) capsule 1(B-MeOTf)·2 at 60 °C, [1B] = 2mM, [2] = 4mM; (c) 2-SO$_3$Na at 20 °C. Asterisks indicate solvent signals.

Figure 11 Job plot for 1(A-MeOTf) with calix 2-SO$_3$Na (Y = ($\Delta$δ$_{1A}$)∗(mol fraction 1A) in CD$_3$OD at 60 °C. Data points represent the absolute upfield shifts ($\Delta$δ$_{1A}$) of CH$_2$NH+(CH$_2$C$_3$H$_5$)$_2$ protons of 1A·2 relative to the chemical shifts of free 1A, ▲ CH$_2$CH$_3$, ■ CH$_2$CH$_3$.

Just like the guanidinium-based capsule E·2, NMR studies show that addition of cesium carbonate (20 equiv.) to a methanol solution of the palladium capsule 1(A-MeOTf)·2 results in precipitation of calix[4]arene 2 while the N-methylated Pd-complex 1(A-MeOTf) remains intact. Upon addition of p-toluenesulfonic acid (20 equiv.) to 1(A-MeOTf)·2 no precipitation appears, however, judging from the NMR studies, the presence of an acid destabilizes the ionic-based capsule: $\Delta$δ of N(CH$_2$C$_3$H$_5$)$_2$+ decreased from 0.35 to 0.09 ppm at 60 °C.

The ESI-MS spectra confirm the formation of the palladium capsules 1A·2 and 1B·2. Prominent doubly and triply charged ion peaks are observed for the capsules in CH$_3$OH at m/z 957.30 for [1(A)·2 – Cl + H]$^{2+}$, at m/z 652.60 for [1(A-MeOTf)·2 – 2Cl + Na]$^{3+}$, at m/z 645.27
for \([\text{1(A-MeOTs)·2 – 2Cl + H}]^3+\), at \(m/z\) 1023.37 for \([\text{1(B)·2 – 2Cl}]^2+\) and at \(m/z\) 701.28 for \([\text{1(B-MeOTf)·2 – 2Cl + H}]^3+\) (Figure 12 and Figure 13). The charge on the capsules is created by loss of one or two chlorides from the palladium complex and/or by addition of protons or sodium cations from the solution. All capsule’s ion peaks correspond to 1:1 complexes and no ion peaks for higher aggregates were detected. Comparison of the measured isotope patterns of the capsules with the calculated ones confirms the elemental composition and charge state. The palladium dichloride complexes contain a tetracationic diphosphine and four tosylate or triflate counterions. Interestingly, the ESI-MS spectra of the Pd-complexes show that one to three out of their four tosylate or triflate counterions remain attached to the ammonium groups during the ionization process. Examples are ion peaks at \(m/z\) 694.21 for \([\text{1(A-MeOTf) – Cl – OTf}]^2+\), at \(m/z\) 659.27 for \([\text{1(A-MeOTs) – 2OTs}]^2+\) and at \(m/z\) 778.22 for \([\text{1(B-MeOTf) – Cl – OTf}]^2+\). None of the ion peaks of the palladium capsules contain counterions, indicating that the palladium capsules do not encapsulate counterions. The absence of the counterions also indicates that the palladium complexes prefer to associate with one calix[4]arene rather than with one to three tosylate or triflate counterions.13

Figure 12 ESI-MS spectrum of a palladium capsule 1(A-MeOTf)·2 self-assembled of pre-charged building blocks (insets: measured isotope patterns).
3.4.4 Structure of the palladium-diphosphine capsules

After characterizing the metallo-diphosphine capsules 1A·2 and 1B·2, we studied their capsular structures by molecular modeling (PM3-level). The modeled structures of the d⁸ palladium complexes 1A and 1B, containing the dppe and DPEphos type ligands, show that they both adopt a square planar geometry with the diphosphine ligand chelated in a cis fashion (Scheme 10). The four aryl groups of 1A are pointing slightly more into the same direction than the aryl groups of 1B, i.e. they are better preorganized for capsule formation. The reported X-ray structures of related Pd(dppe) and Pd(DPEphos) complexes illustrate that the relative spatial arrangement of the four aryl groups and the diphenyl ether backbone can vary to some extent.¹⁰a,¹⁷b,²²,²⁷a-b The resemblance between the modeled structure and the related X-ray structures is better for 1A than for 1B. The palladium complexes 1A and 1B might be rigid compared to their corresponding free ligands, but they can still rotate around some bonds, i.e. around the Pd–P, P–Ar and Ar–CH₂ bonds and around the diphenyl ether backbone (Figure 14). In this way, they can adopt the proper conformation needed for capsule self-assembly. We assume that the transition metal complexes will adopt higher-energy conformations only if the energy gain achieved upon capsule formation will compensate the energy loss. The modeled structures of the palladium capsules 1A·2 and 1B·2 illustrate that the capsules have a proper capsular structure with the two chlorides pointing into the capsule’s interior. Noteworthy, the calculated bite angles (P–Pd–P) of 1A and 1B are comparable to the literature values and do not change significantly upon capsule formation (Table 2).
Scheme 10 Self-assembly of metallo-diphosphine capsules 1A·2 (a) and 1B·2 (b): modeled and molecular structures.

Figure 14 Possible bond rotations in the Pd-complexes 1A and 1B.

Table 2 Bite angles (P–Pd–P) for the Pd-complexes 1A and 1B, the Pd-capsules 1A·2 and 1B·2, and related Pd-complexes.

<table>
<thead>
<tr>
<th></th>
<th>P–Pd–P</th>
<th></th>
<th>P–Pd–P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>86° (calc.)</td>
<td>1B</td>
<td>107° (calc.)</td>
</tr>
<tr>
<td>1A·2</td>
<td>86° (calc.)</td>
<td>1B·2</td>
<td>111° (calc.)</td>
</tr>
<tr>
<td>Pd(dppe)Cl2</td>
<td>86° (X-ray)</td>
<td>Pd(DPEphos)Cl2</td>
<td>101° (X-ray)</td>
</tr>
<tr>
<td>Pd(dppe)b</td>
<td>85° (70° - 95°)</td>
<td>(flexibility range)</td>
<td>102° (86° - 120°)</td>
</tr>
</tbody>
</table>

a see reference 27a
b see reference 27c
3.5 Attempts to synthesize biscationic palladium species

We have tried to synthesize biscationic-palladium complexes by chloride abstraction with silver triflate from the palladium dichloride complexes and capsules described in section 3.4, which is a prerequisite to obtained catalysis for alkene and CO type substrates. Chloride abstraction from the tetraamine-diphosphine PdCl₂-complexes 1a and 1b by silver triflate in DCM/MeCN resulted in complex decomposition probably initiated by coordination of silver to the ligand functions of 1a and 1b. Chloride abstraction from the tetraammonium-dppe complex 1(A-MeOTf) with silver triflate in MeOH or MeCN resulted in a non-complete chloride abstraction according to ESI-MS analysis. Chloride abstraction from the tetraammonium-DPEphos 1(B-MeOTf) in MeOH by silver triflate led to complex decomposition. Apparently, the cationic 1(B-MeOTf)-complex is not stable in MeOH in the presence of silver salts. Chloride abstraction from 1(B-MeOTf) by silver triflate in MeCN was not complete after 16 h and required excess silver triflate to reach completion. The product was not soluble in dichloromethane and therefore the excess of silver triflate could not be removed from the product.

Chloride abstraction from the dppe-based PdCl₂-capsule 1(A)·2 by silver triflate in MeOH/DCM 95/5 (v) resulted in non-complete chloride abstraction according to ESI-MS analysis. Interestingly, ¹H NMR and ESI-MS studies have shown that the ammonium functionalities of the diphosphine ligand 1(A) remained intact, but the capsule was not present anymore. We assume that silver has been encapsulated within the sulfonated calix[4]arene 2, which apparently interferes with capsule formation. Indeed, addition of two equivalents of 2-SO₃Na to the product did result in capsule formation according to the ¹H NMR spectra. The DPEphos-based PdCl₂-capsule 1(B)·2 was not soluble in DCM and required 5% of MeOH in order to dissolve. As could be expected, even 5% of MeOH was enough to decompose the 1(B)-complex due to the presence of silver salts.

3.6 Conclusions

In this Chapter we have demonstrated that the scope of capsules based on functionalized diphosphine ligands or metal complexes thereof can easily be extended. These capsules are formed by ionic interactions and are composed of a tetracationic diphosphine ligand and a complementary tetraanionic calix[4]arene. Encapsulation of a transition metal within the capsules is achieved successfully by self-assembly of a transition metal complex containing a tetracationic ligand, and a tetraanionic calix[4]arene. Diphosphine ligands with different flexibilities and shapes (i.e. different backbones and cationic binding motifs) assembled into (metallo) capsules with the proper capsular structure, as is indicated by ¹H NMR, 1D-NOESY, ESI-MS and modeling studies. The ionic capsules can disassemble under acidic and basic conditions or due to encapsulation of a metal cation within the calix[4]arene. This approach for
metal encapsulation opens up new opportunities to control the activity, stability and selectivity of the potential homogeneous catalysts. The compatibility of capsule formation and their application as catalysts, *i.e.* the encapsulated cationic Pd species, is an issue to be addressed in further studies.

### 3.7 Appendix

An overview is given of the notations and structures of the compounds used in this Chapter.

<table>
<thead>
<tr>
<th>Ligands:</th>
<th>Diphosphine</th>
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<tbody>
<tr>
<td>a</td>
<td>dppe</td>
<td>p-C_6H_4-CH_2NEt_2</td>
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<tr>
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<tr>
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<td>dppe-MeOTs</td>
<td>p-C_6H_4-[CH_2NMMeEt_2]OTs</td>
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<td>m-C_6H_4-[NHC(NH_2)(NMMe_2)]Cl</td>
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</table>

*a These ammonium-diphosphines are used in this Chapter only in the metal-complex form and not as free ligands.

### Diphosphine capsules:

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<td>Pre-charged BB</td>
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<td>(A-HCl)-2</td>
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<tr>
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<tr>
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<td>-</td>
<td>(E-HCl)-2</td>
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### Palladium-diphosphine capsules:

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<td>1A-2</td>
<td>1(A)-2</td>
<td>1(A-MeOTf)-2</td>
</tr>
<tr>
<td>1B</td>
<td>1B-2</td>
<td>1(B)-2</td>
<td>1(B-MeOTf)-2</td>
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</table>

*a General notation for the tetracationic diphosphines and their corresp. Pd-complexes, regardless to the nature of the ammonium groups. *b* General notation for ALL the capsules, regardless to the nature of their building blocks (neutral or pre-charged). *c* Capsules assembled from neutral building blocks. *d* Capsules assembled from pre-charged building blocks. 2 = Tetrasulfonatocalix[4]arene.
3.8 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), hexanes and pentane were distilled from sodium/benzophenone. TMEDA (N,N,N',N'-tetramethylethlenediamine) was distilled from sodium. Dichloromethane, methanol and acetonitrile were distilled from CaH₂. Deuterated solvents were distilled from the appropriate drying agents. Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. Bis(N,N-diethylamino)chlorophosphine,²⁹ 2,7-di-tert-butyl-4,5-bis(dichlorophosphino)-9,9-dimethylxanthene,¹⁷b-c 4,5-bis[(diethylamino)methyl]phenyl-phosphino]-9,9-dimethylxanthene ¹,₈a 4,5-bis[(diethylammoniumchloride)methyl]phenyl-phosphino]-9,9-dimethylxanthene C-HCl¹₈a and 5,11,17,23-tetrakis(sulfonato)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene tetraysodiumsalt ²⁵,²₆,²₇,²₈-²⁵,²₆,²₇,²₈-tetrakis(sulfonato)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene tetraysodiumsalt ²⁵,²₆,²₇,²₈ were synthesized according to reported procedures. NMR spectra were recorded on Varian Inova 500, Bruker Avance DRX 300 and Varian Mercury 300 NMR spectrometers. Chemical shifts are given relative to TMS (¹H and ¹³C NMR), 85% H₃PO₄ (³¹P NMR) and Cl₂CF (¹⁹F NMR). Chemical shifts are given in ppm. 1D-NOESY measurements (1D transient NOE) were carried out with a DFGSE excitation (double pulsed field gradient spin-echo). 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. 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. Molecular modeling calculations were performed using Spartan ’04 V1.0.3 software, on the semi-empirical PM3-level. Abbreviations used: Me-p-C₆H₄SO₃⁻ = OTs⁻ and CF₃SO₃⁻ = OTf⁻ and COD = cyclooctadiene. The PdCl₂(B) and PdCl₂(B) complexes containing the DPEphos-type ligand, give broad carbon resonances in their ¹³C NMR spectra and therefore could not be characterized by carbon NMR.

**Synthesis**

1,2-Bis[(diethylamino)methyl]phenylphosphino|ethane: a

\[
\text{P} \quad \text{P} \quad \text{P} \quad \text{P} \quad \text{P} \\
\mid \mid \mid \mid \mid \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl}
\]

\(n\)-Butyllithium (2.5 M in hexanes, 15.09 ml, 37.72 mmol) was added to 100 ml THF at 0 °C, and the solution was further cooled to −65 °C. A yellow solution of (4-bromobenzyl)diethylamine (9.14 g, 37.72 mmol) in 40 ml THF was added to the \(n\)-butyllithium solution in 1 h. The resulting pink reaction mixture was stirred for another 30 min at −45 °C. After cooling the resulting yellow reaction mixture to −65 °C, a solution of 1,2-bis(dichlorophosphino)ethane (1.99 g, 8.57 mmol) in 30 ml THF was added in 30 min. The resulted green reaction mixture was allowed to warm to room temperature overnight. The yellow 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 yellow viscous oil was purified by column chromatography (silica gel: 95-65% PE 40-60, 0-30% EtOAc, 5% NEt3). The product \( a \) was obtained as a white solid (3.80 g, 5.14 mmol, 60 %). \( ^1H \) NMR (300 MHz, CDCl\(_3\), 293 K): \( \delta = 7.25 \) (s, 16H, PC\(_6\)H\(_4\)), 3.52 (s, 8H, CH\(_2\)N), 2.48 (q, \( J = 7.0 \) Hz, 16H, CH\(_2\)CH\(_3\)), 2.02 (t, \( J = 3.8 \) Hz, 4H, CH\(_2\)CH\(_2\)), 1.01 (t, \( J = 7.1 \) Hz, 24H, CH\(_2\)C\(_3\)H\(_3\)), \( ^{31}P\)\({}^{1}H\) NMR (121.5 MHz, CDCl\(_3\), 293 K): \( \delta = -12.7 \) (s); \( ^{13}C\)\({}^{1}H\) NMR (76 MHz, CDCl\(_3\), 293 K): \( \delta = 141.1 \) (s, Cq, PC\(_6\)H\(_4\)), 136.6 (s, Cq, PC\(_6\)H\(_4\)), 133.0 (s, CH, PC\(_6\)H\(_4\)), 129.3 (s, CH, PC\(_6\)H\(_4\)), 57.6 (s, CH\(_2\)N), 47.1 (s, CH\(_2\)CH\(_3\)), 24.4 (s, CH\(_2\)CH\(_3\)), 12.1 (s, CH\(_2\)C\(_3\)H\(_3\)); HRMS (FAB+): found 739.4990, calcd. for [C\(_{46}\)H\(_{68}\)N\(_4\)P\(_2\) + H]\(^+\) 739.4998.

2,2’-[Bis(bis-diethylamino)phosphonito]-4,4’-dimethyl-diphenylether

This compound is synthesized according to a reported procedure.\(^{10}\) A solution of \( p \)-tolylether (5.10 g, 25.72 mmol) and TMEDA (8.54 ml, 56.59 mmol) in 20 ml hexanes was stirred and cooled to –45 °C giving a white suspension. Subsequently \( n \)-butyllithium (2.5 M in hexanes, 22.64 ml, 56.59 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight resulting in a yellow suspension. The dilithiosalt was isolated from excess \( n \)-butyllithium by leaving the salt to precipitate at –20 °C for 7 h and subsequently removing the orange supernatant liquid with a syringe (this step is not necessary). Subsequently, a solution of bis(diethylamino)chlorophosphine (11.38 g, 54.01 mmol) in 40 ml hexanes/diethyl ether (1/1) was stirred and cooled to –78 °C. The off-white dilithiosalt was dissolved in 40 ml diethyl ether and was slowly added to the solution of ClP(NEt\(_2\))\(_2\) via a Teflon canula. The reaction mixture was allowed to warm to room temperature overnight. The salts were filtered off from the yellow solution and washed twice with diethyl ether. Evaporation of the solvents in vacuo yielded 2,2’-[bis(bis-diethylamino)phosphonito]-4,4’-dimethyl-diphenylether as a yellow oil. \( ^{31}P\)\({}^{1}H\) NMR (121.5 MHz, 293 K): \( \delta = 93.53 \) (s).

2,2’-Bis(dichlorophosphino)-4,4’-dimethyl-diphenylether

This compound is synthesized according to a reported procedure.\(^{10}\) A solution of 2,2’-[bis(bis-diethylamino)phosphonito]-4,4’-dimethyl-diphenylether in 600 ml hexanes was stirred and cooled down to –78 °C. HCl-gas was bubbled into the reaction mixture during 1.5 h which resulted immediately in large amounts of white precipitation. Subsequently the reaction mixture was allowed to warm to room temperature. The salts were filtered off and washed with 100 ml of diethyl ether. Evaporation of the solvents resulted in a white powder. Crystallization from 35 ml hexanes at –20 °C yielded 2,2’-bis(dichlorophosphino)-4,4’-dimethyl-diphenylether as an off-white powder (52 %, 5.34 g, 13.35 mmol). \( ^1H \) NMR (500 MHz, CDCl\(_3\), 293 K): \( \delta = 7.85 \) (bs, 2H, H\(_{Ar}\)), 7.30 (dd, \( J = 1.5 \) Hz, \( J = 8.5 \) Hz, 2H, H\(_{Ar}\)), 6.81 (dt, \( J = 3.0 \) Hz, \( J = 8.5 \) Hz, 2H, H\(_{Ar}\)), 2.44 (s, 6H, CH\(_3\)); \( ^{31}P\)\({}^{1}H\) NMR (202 MHz, CDCl\(_3\), 293 K): \( \delta = 159.12 \) (s).

2,2’-Bis[bis(p-((diethylamino)methyl)phenyl)phosphino]-4,4’-dimethyldiphenylether: \( n \)-Butyllithium (2.5 M in hexanes, 11.39 ml, 24.47 mmol) was added to 75 ml THF at 0 °C, and the solution was further cooled to –65 °C. A yellow solution of (4-bromobenzyl)diethylamine (6.89 g, 28.47 mmol) in 30 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 pale orange reaction mixture to –65 °C, a solution of 2,2’-bis(dichlorophosphino)-4,4’-dimethyl-diphenylether (2.28 g, 5.69 mmol) in 20 ml THF was added in 30 min. The resulted green reaction mixture was allowed to warm to room temperature overnight. The 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 yellow viscous oil was purified by column chromatography (silica gel: 97-45% hexanes, 0-50% EtOAc, 3-5% NEt₃). The product was obtained as a white solid (3.12 g, 3.43 mmol, 60 %). 1H NMR (300 MHz, CDCl₃, 293 K): δ = 7.19 (d, J = 7.6 Hz, 8H, PC₆H₄), 7.13 (m, 8H, PC₆H₄), 6.87 (d, J = 8.1 Hz, 2H, OC₆H₃), 6.56 (bs, 2H, OC₆H₃), 6.42 (m, 2H, OC₆H₃), 3.51 (s, 8H, CH₂N), 2.47 (q, J = 6.9 Hz, 16H, CH₂CH₃), 2.09 (s, 6H, CH₃), 0.99 (t, J = 7.2 Hz, 24H, CH₂C₆H₃); 31P{¹H} NMR (121.5 MHz, CDCl₃, 293 K): δ = –16.4 (s); 13C{¹H} NMR (76 MHz, CDCl₃, 293 K): δ = 157.8 (bs, Cq, CAr), 140.5 (s, Cq, CAr), 135.5 (s, Cq, CAr), 134.6 (s, Cq, CAr), 134.3 (s, CH, OC₆H₃), 134.0 (s, CH, PC₆H₄), 132.8 (s, Cq, CAr), 131.0 (s, CH, OC₆H₃), 129.2 (s, CH, PC₆H₄), 118.1 (s, CH, OC₆H₃), 57.7 (s, CH₂N), 47.1 (s, CH₂CH₃), 21.2 (s, CH₃), 12.2 (s, CH₂CH₃); HRMS (FAB+): found 907.5588, calcd. for [C₅₈H₇₆ON₄P₂ + H]+ 907.5573; Anal. calcd. for C₅₈H₇₆N₄OP₂: C 76.79, H 8.44, N 6.18, found: C 76.67, H 8.40, N 6.11.

1,2-Bis[bis(p-(diethylammoniumchloride)methyl)phenyl)phosphino]ethane: A-HCl
A 2 M solution of HCl in diethyl ether (0.50 ml, 1.00 mmol) was added dropwise to a solution of a (85 mg, 114 μmol) in 10 ml diethyl ether, upon which a white precipitation appeared. After stirring for 30 min. the volatiles were removed in vacuo and A-HCl was obtained as a white powder in quantitative yield. 1H NMR (300 MHz, CD₃OD, 293 K): δ = 7.64 (d, J = 7.9 Hz, 8H, PC₆H₄), 7.46 (m, 8H, PC₆H₄), 4.40 (s, 8H, CH₂N), 3.23 (m, 16H, CH₂CH₃), 2.18 (t, J = 4.3 Hz, 4H, CH₂CH₂), 1.38 (t, J = 7.3 Hz, 24H, CH₂CH₃); 31P{¹H} NMR (121.5 MHz, CD₃OD, 293 K): δ = –12.7 (s); 13C{¹H} NMR (75 MHz, CD₃OD, 293 K): δ = 139.5 (br s, Cq, PC₆H₄), 133.2 (t, J = 9.3 Hz, CH, PC₆H₄), 131.1 (t, J = 3.3 Hz, CH, PC₆H₄), 130.7 (s, Cq, PC₆H₄), 55.3 (s, CH₂N), 46.7 (s, CH₂CH₃), 46.6 (s, CH₂CH₃), 23.0 (br s, CH₂CH₂), 7.7 (s, CH₂CH₃); HRMS (FAB+): found 775.4777, calcd. for [C₄₆H₇₂N₄P₂Cl₄ – 2H – 3Cl]+ 775.4764.

2,2’-Bis[bis(p-(diethylammoniumchloride)methyl)phenyl)phosphino]-4,4’-dimethyl-diphenylether: B-HCl
The compound B-HCl was prepared similarly to A-HCl. 1H NMR (300 MHz, CD₃OD, 293 K): δ = 7.62 (d, J = 7.3 Hz, 8H, PC₆H₄), 7.30 (m, 8H, PC₆H₄), 7.11 (d, J = 7.9 Hz, 2H, OC₆H₃), 6.66 (d, J = 4.3 Hz, 2H, OC₆H₃), 6.53 (m, 2H, OC₆H₃), 4.41 (s, 8H, CH₂N), 3.22 (m, 16H, CH₂CH₃), 2.16 (s, 6H, CH₃), 1.37 (br t, 24H, CH₂CH₂); 31P{¹H} NMR (121.5 MHz, CD₃OD, 293 K): δ = –15.3 (s); 13C{¹H} NMR (75 MHz, CD₃OD, 293 K): δ = 156.9 (br s, Cq, CAr), 138.5 (br s, Cq, CAr), 134.4 (s, CH, CAr), 134.1 (s, CH, CAr), 133.1 (s, Cq, CAr), 131.4 (s, Cq, CAr), 130.9 (br s, CH, CAr), 130.4 (s, CH, CAr), 126.6 (br s, Cq, CAr), 117.7 (s, CH, CAr), 55.4 (s, CH₂N), 46.7 (s, CH₂CH₃), 46.6 (s, CH₂CH₃), 19.4 (s, CH₃), 7.7 (br s, CH₂CH₃); HRMS (FAB+): found 943.5336, calcd. for [C₅₈H₇₅ON₄P₂Cl₄ – 2H – 3Cl]+ 943.5339.
Chapter 3

2,7-Di-tert-butyl-4,5-bis[bis(3-aminophenyl)phosphino]-9,9-dimethylxanthene: d

The solution of 2,7-di-tert-butyl-4,5-bis(dichlorophosphino)-9,9-dimethylxanthene (3.95 g, 7.57 mmol) in 60 ml THF was added slowly to 1.0 M THF solution of 3-[N,N-bis(trimethylsilyl)amino]phenylmagnesium chloride (37.83 ml, 37.83 mmol) at –25 °C. The resulted yellow reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was hydrolyzed with 5 ml degassed water and the solvent was removed in vacuo. Next, in order to receive the crude product as a powder, it was dissolved in dichloro methane and the solvent was removed in vacuo. Subsequently, the product was extracted and N-deprotected by solid-liquid extraction with diethylamine (4x, 250 ml, 30 min., filtration over a glass filter (Por 4). The product d was purified by column chromatography (basic alumina: dichloromethane/methanol). The product was obtained as an orange powder (1.40 g, 1.86 mmol 25%).

\[ \text{1H NMR (300 MHz, CDCl}_3, 293 K): \delta = 7.31 (br s, 2H, PC}_6\text{H}_2), 6.97 (t, J = 7.3 Hz, 4H, PC}_6\text{H}_4), 6.66 (br s, 2H, PC}_6\text{H}_2), 6.57 (m, 12H, PC}_6\text{H}_4), 3.52 (br s, 8H, NH}_2), 1.62 (s, 6H, C(CH}_3}_2), 1.10 (s, 18H, C(CH}_3}_3); \]

\[ \text{31P}_1{1H} \text{ NMR (121.5 MHz, CDCl}_3, 293 K): \delta = -15.1 (s); \]

\[ \text{13C}_1{1H} \text{ NMR (75 MHz, CDCl}_3, 293 K): \delta = 146.4, 139.3, 134.5, 134.3, 131.1, 130.1, 129.3, 128.3, 127.7, 127.2, 124.8, 123.6, 34.5, 34.1, 31.7, 30.3); \]

\[ \text{HRMS (FAB+): found 751.3678, calcd. for [C}_47\text{H}_52\text{ON}_4\text{P}_2 + H]^{+} 751.3695. \]

2,7-Di-tert-butyl-4,5-bis[bis((3-ammoniumchloride)phenyl)phosphino]-9,9-dimethylxanthene: D-HCl

A 2 M solution of HCl in diethyl ether (3.20 ml, 6.40 mmol) was added dropwise to a solution of d (600.7 mg, 800.0 μmol) in 20 ml dichloromethane, upon which a fine pink precipitation appeared. After stirring for 30 min. the volatiles were removed in vacuo and D-HCl was obtained as a pink powder in quantitative yield. \[ \text{1H NMR (300 MHz, CD}_3\text{OD, 293 K): \delta = 7.54 (m, 6H, PC}_6\text{H}_2 + PC}_6\text{H}_4), 7.41 (d, J = 7.4 Hz, 4H, PC}_6\text{H}_4), 7.31 (br t, J = 7.3 Hz, 4H, PC}_6\text{H}_4), 7.24 (s, 2H, PC}_6\text{H}_2), 6.38 (s, 2H, PC}_6\text{H}_2), 1.68 (s, 6H, C(CH}_3}_2), 1.08 (s, 18H, C(CH}_3}_3); \]

\[ \text{31P}_1{1H} \text{ NMR (121.5 MHz, CD}_3\text{OD, 293 K): \delta = -13.7 (s); \]

\[ \text{13C}_1{1H} \text{ NMR (75 MHz, CD}_3\text{OD, 293 K): \delta = 146.4, 139.3, 134.5, 134.3, 131.1, 130.1, 129.3, 128.3, 127.7, 127.2, 124.8, 123.6, 34.5, 34.1, 31.7, 30.3); \]

\[ \text{HRMS (FAB+): found 751.3687, calcd. for [C}_47\text{H}_56\text{Cl}_4\text{N}_4\text{OP}_2 – 3H – 4Cl]^{+} 751.3695. \]

2,7-Di-tert-butyl-4,5-bis[bis((3-N,N-dimethylguanidiniumchloride)phenyl)phosphino]-9,9-dimethylxanthene: E-HCl

An orange suspension of D-HCl (300 mg, 269 μmol) in degassed dimethylcyanamide (48.9 μl, 6.00 mmol) was heated at 110 °C for 24 h. Subsequently, the clear brown solution was cooled to room temperature upon which a fine brown precipitation appeared. After washing the precipitation with diethyl ether (4x), the product E-HCl was obtained as an orange powder (314 mg, 267 μmol, 89%). \[ \text{1H NMR (300 MHz, CD}_3\text{OD, 293 K): \delta = 7.56 (d, J = 2.1 Hz, 2H, PC}_6\text{H}_2), 7.47 (t, J = 7.8 Hz, 4H, PC}_6\text{H}_4), \]

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7.30 (d, J = 6.6 Hz, 4H, PC₆H₄), 7.20 (br t, 4H, PC₆H₄), 7.12 (br s, 4H, PC₆H₄), 6.60 (q, J = 2.4 Hz, 2H, PC₆H₂), 3.07 (s, 24H, N(CH₃)₂), 1.67 (s, 6H, C(CH₃)₂), 1.13 (s, 18H, C(CH₃)₃); 31P{1H} NMR (121.5 MHz, CD₃OD, 293 K): δ = –14.5 (s); 13C{1H} NMR (75 MHz, CD₃OD, 293 K): δ = 155.9 (s, Cq, CN₃), 149.7 (br s, Cq, C Ar), 146.1 (s, Cq, C Ar), 138.8 (t, J = 7.0 Hz, Cq, C Ar), 136.7 (t, J = 3.7 Hz, Cq, C Ar), 132.1 (t, J = 10.7 Hz, CH, C Ar), 129.7 (br s, CH, C Ar), 129.4 (s, Cq, C Ar), 129.0 (br t, CH, C Ar), 128.7 (s, CH, C Ar), 124.5 (s, CH, C Ar), 124.1 (s, CH, C Ar), 37.9 (s, NMe₂), 34.6 (s, C(CH₃)₃), 31.2 (s, C(C₆H₃)₂), 30.3 (s, C(C₆H₃)₃); HRMS (FAB⁺): found 1031.5829, calcd. for [C₅₉H₆₇ON₁₂P₂Cl₄ – 3H – 4Cl]⁺ 1031.5819.

cis-[PdCl₂(a)]: 1a

A solution of dppe-p-C₆H₄-CH₂NEt₂ a (0.915 g, 1.24 mmol) in 15 ml dichloromethane was added to a solution of (1,5-COD)PdCl₂ (0.354 g, 1.24 mmol) in 20 ml dichloromethane. The pale yellow reaction mixture was stirred for 1 h at room temperature. Subsequently, the solvent was evaporated and the precipitate was washed thoroughly three times with 20 ml pentane and dried in vacuo. The product 1a was obtained as a pale yellow powder (1.10 g, 1.20 mmol, 97%). 1H NMR (300 MHz, CDCl₃, 293 K): δ = 7.77 (m, 8H, PC₆H₄), 7.42 (d, J = 8.0 Hz, 8H, PC₆H₄), 3.56 (s, 8H, CH₂N), 2.50 (q, J = 7.2 Hz, 16H, C₂H₂CH₃), 2.37 (m, 4H, CH₂CH₂), 1.01 (t, J = 7.1 Hz, 24H, CH₂C₆H₃); 31P{1H} NMR (121.5 MHz, CDCl₃, 293 K): δ = 64.4 (s); 13C{1H} NMR (75 MHz, CDCl₃, 293 K): δ = 145.6 (s, Cq, PC₆H₄), 133.9 (s, CH, PC₆H₄), 129.7 (s, CH, PC₆H₄), 126.2 (s, Cq, PC₆H₄), 57.7 (s, CH₂N), 47.4 (s, CH₂CH₃), 28.9 (br s, CH₂CH₂), 12.2 (s, CH₂CH₃); HRMS (FAB⁺): found 879.3637, calcd. for [C₄₆H₆₈Cl₂N₄P₂Pd – Cl]⁺ 879.3656.

cis-[PdCl₂(b)]: 1b

The compound 1b was prepared similarly to 1a. The product was obtained as an orange powder (98%). 1H NMR (300 MHz, CDCl₃, 293 K): δ = 7.48 (m, 8H, PC₆H₄), 7.22 (m, 8H, PC₆H₄), 3.56 (s, 8H, CH₂N), 2.48 (q, J = 7.4 Hz, 16H, C₂H₂CH₃), 2.00 (s, 6H, CH₃), 1.00 (t, J = 7.0 Hz, 24H, CH₂CH₃); 31P{1H} NMR (121.5 MHz, CDCl₃, 293 K): δ = 19.2 (s); HRMS (FAB⁺): found 1047.4235, calcd. for [C₅₈H₇₆Cl₂N₄OP₂Pd – Cl]⁺ 1047.4235.

cis-[PdCl₂(A-HOTs)]: 1(A-HOTs)

p-Toluenesulfonic acid monohydrate (29.6 mg, 155.4 μmol) was added to a solution of 1a (35.6 mg, 38.9 μmol) in 3 ml methanol. The reaction mixture was stirred for 1 h at room temperature. Next, the solvent was evaporated and pentane was added to the solid precipitate. After evaporation of the solvent in vacuo the product 1(A-HOTs) was obtained as a yellow powder in quantitative yield. 1H NMR (300 MHz, CD₂OD, 293 K): δ = 8.00 (m, 8H, PC₆H₄), 7.69 (d, J = 6.8 Hz, 8H, PC₆H₄), 7.64 (d, J = 7.9 Hz, 8H, OTs⁻), 7.21 (d, J = 7.9 Hz, 8H, OTs⁻), 4.38 (s, 8H, CH₂N), 3.17 (m, 16H, CH₂CH₃), 2.81 (m, 4H, CH₂CH₂), 2.32 (s, 12H, CH₃), 1.29 (t, J = 6.9 Hz, 24H, CH₂CH₃); 31P{1H} NMR (121.5 MHz, CD₂OD, 293 K): δ = 68.3 (s); 13C{1H} NMR (75 MHz, CD₂OD, 293 K): δ = 142.2 (s, OTs⁻), 140.6 (s, OTs⁻), 134.4 (br s), 131.6 (br s), 129.8 (s), 129.1 (s), 128.7 (s, OTs⁻), 125.6 (s, OTs⁻), 55.1 (s, CH₂N), 46.9 (s, CH₂CH₃), 28.0 (br s, CH₂CH₂), 20.1 (s, CH₃), 7.7 (s, CH₂CH₃); HRMS (FAB⁺): found 879.3665, calcd. for...
cis-[PdCl₂(B-HOTs)]: 1(B-HOTs)

\[ \text{cis-[PdCl}_2\text{(B-HOTs)}] \]

\[ \text{cis-[PdCl}_2\text{(B-HOTs)}] \] was prepared similarly to \( \text{cis-[PdCl}_2\text{(A-MeOTf)}] \). The product was obtained as an orange powder in quantitative yield. \({}^1\)H NMR (300 MHz, CD₃OD, 293 K): \( \delta = 7.66 \) (d, \( J = 8.3 \) Hz, 8H, OTs –), 7.60 (m, 16H, PC₆H₄), 7.30 (d, \( J = 8.3 \) Hz, 2H, OC₆H₃), 7.20 (d, \( J = 7.9 \) Hz, 8H, OTs –), 6.95 (m, 2H, OC₆H₃), 6.50 (d, \( J = 10.0 \) Hz, 2H, OC₆H₃), 4.36 (dd, \( J = 13.3 \) Hz and 18.8 Hz, 2H, CH₂N), 3.17 (m, 16H, C₆H₂CH₃), 2.32 (s, 12H, CH₃, OTs –), 2.05 (s, 6H, CH₃), 1.28 (t, \( J = 7.3 \) Hz, 8H, CH₂CH₃); 31P\{¹H\} NMR (121.5 MHz, CD₃OD, 293 K): \( \delta = 20.3 \) (s); HRMS (FAB+): found 1047.4226, calcd. for \([\text{C}_86\text{H}_{108}\text{Cl}_2\text{N}_4\text{O}_{13}\text{P}_2\text{PdS}_4} - \text{C}_{28}\text{H}_32\text{S}_4\text{O}_{12}\text{Cl}]^+\) 1047.4235.

cis-[PdCl₂(A-MeOTf)]: 1(A-MeOTf)

\[ \text{cis-[PdCl}_2\text{(A-MeOTf)}] \]

Methyl trifluoromethanesulfonate (0.34 ml, 3.00 mmol) was added dropwise to a solution of \( \text{1a} \) (0.46 g, 0.50 mmol) in 20 ml dichloromethane resulting in some orange precipitation. The reaction mixture was stirred for 2 h at room temperature. Next, the solution was concentrated to 2 ml, and 10 ml of diethyl ether was added which resulted in more precipitation. The supernatant was removed and the crude product was washed twice with diethyl ether and dried in vacuo. The product \( \text{1(A-MeOTf)} \) was obtained as an off white fine powder (0.75 g, 0.48 mmol, 96%). \({}^1\)H NMR (300 MHz, CD₃OD, 293 K): \( \delta = 8.04 \) (m, 8H, PC₆H₄), 7.75 (d, \( J = 7.0 \) Hz, 8H, PC₆H₄), 4.56 (s, 8H, CH₂N), 3.39 (m, 16H, C₆H₂CH₃), 2.95 (s, 12H, NCH₃), 2.87 (m, 4H, CH₂CH₂), 1.41 (t, \( J = 7.2 \) Hz, 24H, CH₂CH₃); \(^{31}\)P\{¹H\} NMR (121.5 MHz, CD₃OD, 293 K): \( \delta = 69.3 \) (s); \(^{13}\)C\{¹H\} NMR (75 MHz, CD₃OD, 293 K): \( \delta = 133.9 \) (br s), 132.1 (s), 129.6 (s), 120.5 (q, \( J = 319 \) Hz, CF₃), 63.6 (s, NCH₃), 55.9 (s, CH₂N), 46.0 (s, CH₂CH₃), 27.8 (br s, CH₂CH₂), 6.9 (s, CH₂CH₂); \(^{19}\)F NMR (282 MHz, CD₃OD, 293 K): \( \delta = -77.8 \) (s); HRMS (FAB+): found 1423.2822, calcd. for \([\text{C}_{54}\text{H}_{80}\text{Cl}_2\text{F}_{12}\text{N}_4\text{O}_{12}\text{P}_2\text{PdS}_4} - \text{CF}_3\text{SO}_3]^+\) 1423.2832.

cis-[PdCl₂(B-MeOTf)]: 1(B-MeOTf)

The compound \( \text{1(B-MeOTf)} \) was prepared similarly to \( \text{1(A-MeOTf)} \). The product was obtained as an off white fine powder (92%). \({}^1\)H NMR (300 MHz, CD₃OD, 293 K): \( \delta = 7.68 \) (m, 16H, PC₆H₄), 7.33 (d, \( J = 8.3 \) Hz, 2H, OC₆H₃), 6.99 (m, 2H, OC₆H₃), 6.58 (d, \( J = 10.5 \) Hz, 2H, OC₆H₃), 4.53 (dd, \( J = 12.9 \) Hz and 24.2 Hz, 8H, CH₂N), 3.63 (m, 16H, CH₂CH₃), 2.93 (s, 12H, NCH₃), 2.07 (s, 12H, CH₃), 1.40 (t, \( J = 6.7 \) Hz, 24H, CH₂CH₃); \(^{31}\)P\{¹H\} NMR (121.5 MHz, CD₃OD, 293 K): \( \delta = 21.2 \) (s); \(^{19}\)F NMR (282 MHz, CD₃OD, 293 K): \( \delta = -80.4 \) (s); HRMS (FAB+): found 1591.3403, calcd. for \([\text{C}_{66}\text{H}_{88}\text{Cl}_2\text{F}_{12}\text{N}_4\text{O}_{12}\text{P}_2\text{PdS}_4} - \text{CF}_3\text{SO}_3]^+\) 1591.3411.

cis-[PdCl₂(A-MeOTs)]: 1(A-MeOTs)

Methyl p-toluenesulfonate (222 µl, 1.464 mmol) was added to the yellow solution of \( \text{1a} \) (224 mg, 244 µmol) in 10 ml acetonitrile. The reaction mixture was stirred at 70 °C for three days. After cooling to
Design of Metallo Diphosphine Capsules

room temperature, the reaction mixture was filtered through Celite filter aid to remove the formed metallic palladium. The Celite filter aid was washed with methanol and the solvents were evaporated. Next, the crude product was dissolved in 2 ml of acetonitrile and the addition of 15 ml diethyl ether resulted in a fine precipitation. Removing the supernatant and drying of the precipitate in vacuo gave the product 1(A-MeOTs) as an orange microcrystalline solid (358 mg, 216 μmol, 88%).

$^1$H NMR (300 MHz, CD$_3$OD, 293 K): δ = 8.06 (m, 8H, PC$_6$H$_4$), 7.73 (d, J = 7.8 Hz, 8H, PC$_6$H$_4$), 7.63 (d, J = 8.1 Hz, 8H, OTs$^-$), 7.19 (d, J = 7.8 Hz, 8H, OTs$^-$), 4.52 (s, 8H, CH$_2$N), 3.33 (m, 16H, C$_4$H$_2$CH$_3$), 2.89 (s, 12H, NCH$_3$), 2.80 (m, 4H, CH$_2$CH$_2$), 2.32 (s, 12H, CH$_3$, OTs$^-$), 1.35 (t, J = 7.2 Hz, 24H, CH$_2$C$_2$H$_5$); $^{31}$P($^1$H) NMR (121.5 MHz, CD$_3$OD, 293 K): δ = 68.7 (s); $^{13}$C($^1$H) NMR (75 MHz, CD$_3$OD, 293 K): δ = 142.6 (s, OTs$^-$), 140.4 (s, OTs$^-$), 134.0 (br s), 129.7 (s), 128.7 (s, OTs$^-$), 125.6 (s, OTs$^-$), 63.5 (s, NCH$_3$), 55.9 (s, CH$_2$N), 46.0 (s, CH$_2$CH$_3$), 27.9 (br s, CH$_2$CH$_2$), 20.1 (s, CH$_3$, OTs$^-$), 7.1 (s, CH$_2$CH$_3$); HRMS (FAB+): found 1489.4620, calcd. for [C$_{78}$H$_{108}$Cl$_2$N$_4$O$_{12}$P$_2$PdS$_4$ – C$_7$H$_7$SO$_3$]+ 1489.4625.

General procedure for chloride abstraction attempts from 1a, 1b, 1A, 1B, 1(A)-2 and 1(B)-2
Silver triflate solution in dichloromethane, acetonitrile or methanol was added to the solution of the dichloride compounds. The reaction mixture was stirred in dark at room temperature for 1–16 h. Subsequently, the reaction mixture was filtered through Celite filter aid and evaporated to dryness in vacuo.

To a white suspension of tetraysulfonatocalix[4]arene tetrasodiumsalt 2-SO$_3$Na (2.02 g, 1.80 mmol) in 35 ml methanol was added 3.6 g of the strongly acidic Amberlyst$^\circledR$ 15 ion-exchange resin (macroreticular resin with sulfonic acid functionality). The reaction mixture was stirred for 1 h at room temperature. Subsequently, the clear pale yellow solution was filtered and upon evaporation of the solvent in-vacuo, the product 2-SO$_3$H was obtained as a brown sticky solid in quantitative yield. $^1$H NMR (300 MHz, CD$_3$OD, 293 K): δ = 7.38 (s, 8H, H$_{Ar}$), 4.74 (d, J = 12.8 Hz, 4H, CHH$'$), 4.31 (t, J = 5.0 Hz, 8H, OCH$_2$CH$_2$), 3.91 (t, J = 5.0 Hz, 8H, OCH$_2$CH$_2$), 3.56 (q, J = 7.0 Hz, 8H, OCH$_2$CH$_3$), 3.39 (d, J = 12.9 Hz, 4H, CHH$''$), 1.22 (t, J = 7.0 Hz, 12H, OCH$_2$CH$_3$); $^1$H NMR (300 MHz, CD$_2$Cl$_2$, 293 K): δ = 11.0 (bs, SO$_3$H); $^{13}$C($^1$H) NMR (75 MHz, CD$_3$OD, 293 K): δ = 158.8 (s, C$_q$, C$_{Ar}$), 136.7 (s, C$_q$, C$_{Ar}$), 135.0 (s, C$_q$, C$_{Ar}$), 126.4 (s, CH, C$_{Ar}$), 73.8 (s, CH$_2$), 69.6 (s, CH$_2$), 66.3 (s, CH$_2$), 30.8 (s, ArCH$_2$Ar), 14.8 (s, CH$_3$).

General procedure for the self-assembly of the diphosphine capsules by the use of pre-charged building blocks
Capsule self-assembly was done in situ. Equimolar methanol solutions of the tetracationic diphosphine (A-HCl or B-HCl or C-HCl) and the tetraanionic calix[4]arene 2-SO$_3$Na were mixed at room temperature, resulting in the immediate formation of the corresponding capsule ((A-HCl)-2, (B-HCl)-2 and (C-HCl)-2 respectively). Self-assembly of capsules (D-HCl)-2 and (E-HCl)-2 was done in a similar way.
General procedure for the self-assembly of the diphosphine capsules by the use of neutral building blocks
Methanol solution of the tetraacidic calix[4]arene 2-SO₃H (1 equiv.) was slowly added to a methanol solution of the tetraamine diphosphine (a or b or c) (1 equiv.). The solution was stirred for 30 min. at room temperature and subsequently the solvent was evaporated resulting in the corresponding capsule ((A)·2, (B)·2 and (C)·2 respectively).

General procedure for the self-assembly of Pd-capsules by the use of pre-charged building blocks
Capsule self-assembly was done in situ. Equimolar methanol solutions of the palladium tetracationic-diphosphine complex (1(A-MeOTf) or 1(A-MeOTs) or 1(B-MeOTf)) and the tetraanionic calix[4]arene 2-SO₃Na were mixed at room temperature, resulting in the immediate formation of the corresponding capsule (1(A-MeOTf)·2, 1(A-MeOTs)·2 and 1(B-MeOTf)·2 respectively).

Self-assembly of Pd-capsules by the use of neutral building blocks: Capsule 1(A)·2
Equimolar methanol solution of the tetraacidic calix[4]arene 2-SO₃H (1 equiv.) was slowly added to a methanol solution of 1a (1 equiv.) upon which some precipitation appeared. The reaction mixture was stirred for 30 min. at room temperature and subsequently the solvent was evaporated resulting in capsule 1(A)·2.

Self-assembly of Pd-capsules by the use of neutral building blocks: Capsule 1(B)·2
Equimolar dichloromethane solution of the tetraacidic calix[4]arene 2-SO₃H (1 equiv.) was slowly added to a dichloromethane solution of 1b (1 equiv.) upon which precipitation appeared. The reaction mixture was stirred for 30 min. at room temperature and subsequently the solvent was evaporated resulting in capsule 1(B)·2. Note: self-assembly of capsule 1(B)·2 was done in dichloromethane because of the instability of 1b in methanol. After the capsule was formed the capsule was stable and soluble in MeOH/CH₂Cl₂ or MeOH/H₂O mixtures.

NMR characterization of the capsules
Upfield shifts (ΔδH) of the CH₂N(+/CH₃⁺)(CH₂CH₃)₂ protons of the bound PP- or Pd(PP)-building blocks upon capsule formation are given, with respect to those of the corresponding free building blocks (for capsules assembled from neutral building blocks ΔδH is calculated with respect to the corresponding protonated building blocks) (Table 3). Some of the proton resonances were not visible because they overlap with other signals or are very broad, or because of H–D exchange with CD₃OD. Capsule (D-HCl)·2 did not show significant upfield shifts upon capsule formation (ΔδH ≤ 0.07 ppm). Capsule (E-HCl)·2: Δδ(N(CH₃)₂) = 0.51 ppm in CD₃OD and Δδ(NH) = 0.55 ppm in dms-o-d₆. The phosphorus chemical shifts of the diphosphines A-E and the Pd-diphosphines 1A and 1B in their capsular form (A-F)·2 or 1(A-B)·2 did not exhibit a noteworthy shift compared to the monomeric form (Δδ ≤ 0.8 ppm).
Table 3 Observed upfield shifts (ΔδH) of the CH2N(CH3)2 protons upon capsule formation.a

<table>
<thead>
<tr>
<th>Capsule</th>
<th>Solvent/ temp</th>
<th>PP/2</th>
<th>Δδ(CH2CH3) (ppm)</th>
<th>Δδ(CH2CH3) (ppm)</th>
<th>Δδ(CH2N) (ppm)</th>
<th>Δδ(NCH3) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A-HCl)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/3</td>
<td>0.46</td>
<td>0.31</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
<td>(B-HCl)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/3</td>
<td>0.42</td>
<td>0.32</td>
<td>0.20</td>
<td>-</td>
</tr>
<tr>
<td>(C-HCl)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/3</td>
<td>0.43</td>
<td>0.33</td>
<td>0.25</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(A)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/1</td>
<td>0.43</td>
<td>0.33</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(B)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/1</td>
<td>0.39</td>
<td>0.32</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>(C)-2</td>
<td>CD3OD / 20 °C</td>
<td>1/1</td>
<td>0.40</td>
<td>0.35</td>
<td>0.27</td>
</tr>
<tr>
<td>(A)-2</td>
<td>CD3OD / 60 °C</td>
<td>1/2</td>
<td>0.35</td>
<td>0.16</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td>(B)-2</td>
<td>CD3OD / 60 °C</td>
<td>1/2</td>
<td>0.35</td>
<td>n.o.</td>
<td>n.o.</td>
<td>0.10</td>
</tr>
<tr>
<td>(A)-2</td>
<td>CD3OD / 40 °C</td>
<td>1/2</td>
<td>0.28</td>
<td>n.o.</td>
<td>n.o.</td>
<td>0.07</td>
</tr>
<tr>
<td>(A)-2</td>
<td>CD3OD/D2O 8/2 mol% 40 °C</td>
<td>1/1</td>
<td>0.33</td>
<td>0.22</td>
<td>0.11</td>
<td>-</td>
</tr>
<tr>
<td>(B)-2</td>
<td>CD3OD/D2O 8/2 mol% 40 °C</td>
<td>1/1</td>
<td>0.37</td>
<td>0.23</td>
<td>0.12</td>
<td>-</td>
</tr>
</tbody>
</table>

a [PP] or [Pd(PP)] = 2 mM, n.o. = not observed.

Job Plot
Equimolar solutions (2 mM) of 1(PP) and 2-SO3Na in CD3OD were prepared and mixed in various ratios. In this way the total concentration of 1(PP) and 2 was kept constant at 2 mM and only the 1(PP)/2 ratio was varied. 1H NMR spectra of the mixtures were recorded at 60 °C, and the chemical shifts of 1(PP) 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 2.30 1(PP) = 1(A-MeOTf) or 1(B-MeOTf).

1H NMR titrations
The 1H NMR titrations of 2-SO3Na with A-HCl and of 2-SO3Na with B-HCl 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 A-HCl and B-HCl were varied from 0 to 3 mM. The chemical shifts of the diphosphine protons CH2NH+(CH2CH3)2 of (A-HCl)-2 and (B-HCl)-2, relative to the chemical shifts of A-HCl respectively B-HCl were followed and fitted to a 1:1 binding model using a least-squares fitting procedure.21b 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.31 The association constants from different runs were then averaged. The association constant found for capsule (A-HCl)-2 is KA2 = 3·104 M–1 and for capsule (B-HCl)-2 is KB2 = 8·104 M–1. Lines in the titration curves are best-fit curves calculated by nonlinear regression.

ESI-MS measurements
Samples of the capsules (PP/calix = 1/1 – 1/3) with initial concentrations of 100-250 μM were diluted in MeOH to a final concentration of 1%. Comparison of the measured isotope patterns of the capsules 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 capsule’s building blocks. The reported \( m/z \) correspond to the 100% ion peak (isotope with the highest intensity).

**Capsule (A-HCl)·2** (C90H124N4O20P2S4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([A·2 + 2Na]^{2+}\) found 908.95, calcd. 908.85; \([A·2 + Na + H]^+\) found 897.93, calcd. 897.86; \([A·2 + 2H]^2+\) found 886.42, calcd. 886.37.

**Capsule (B-HCl)·2** (C102H132N4O21P2S4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([B·2 + H + Na]^{2+}\) found 981.99, calcd. 981.89; \([B·2 + 2H]^2+\) found 970.97, calcd. 970.90; \([B·2 + 2H + Na]^{3+}\) found 654.99, calcd. 654.93; \([B·2 + 3H]^{3+}\) found 647.66, calcd. 647.60.

**Capsule (C-HCl)·2** (C103H132N4O21P2S4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([C·2 + 3H]^{3+}\) found 651.263, calcd. 651.265; \([C·2 + 2H + 1Na]^{3+}\) found 658.602, calcd. 658.593; \([C·2 + 1H + 2Na]^{3+}\) found 665.921, calcd. 665.920; \([C·2 + 3Na]^{3+}\) found 673.251, calcd. 673.247; \([C·2 + 2H]^2+\) found 976.354, calcd. 976.394; \([C·2 + 1H + 1Na]^{2+}\) found 987.327, calcd. 987.385; \([C·2 + 2Na]^{2+}\) found 998.325, calcd. 998.375.

**Capsule (D-HCl)·2** (C91H108N4O21P2S4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([D·2 + 2Na]^{2+}\) found 914.98, calcd. 914.78; \([D·2 + Na + H]^+\) found 903.99, calcd. 903.79; \([D·2 + 2H]^2+\) found 893.00, calcd. 892.80.

**Capsule (E-HCl)·2** (C103H132N4O21P2S4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([E·2 + 2Na]^{2+}\) found 967.41, calcd. 967.34; \([E·2 + 3Na]^{3+}\) found 711.07, calcd. 710.92; \([E·2 + 2Na + H]^{3+}\) found 703.77, calcd. 703.60; \([E·2 + Na + 2H]^2+\) found 696.44, calcd. 696.27.

**Capsule 1(A-MeOTf)·2** (C94H112N4O20P2PdS4Cl2) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([1(A-MeOTf)·2 – 2Cl]^{2+}\) found 967.38, calcd. 967.34; \([1(A-MeOTf)·2 – 2Cl + Na]^+\) found 652.60, calcd. 652.56; \([1(A-MeOTf)·2 – 2Cl + H]^+\) found 645.24, calcd. 645.23.

**Capsule 1(A-MeOTs)·2** (C94H112N4O20P2PdS4Cl2) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([1(A-MeOTs)·2 – 2Cl]^{2+}\) found 967.41, calcd. 967.34; \([1(A-MeOTs)·2 – 2Cl + Na]^+\) found 691.27, calcd. 691.20; \([1(A-MeOTs)·2 – 2Cl + Na]^{2+}\) found 652.59, calcd. 652.56; \([1(A-MeOTs)·2 – 2Cl + H]^{3+}\) found 645.27, calcd. 645.23.

**Capsule 1(A)·2** (C90H124Cl2N4O20P2PdS4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([1(A)·2 – Cl + H]^+\) found 957.30, calcd. 957.30; \([1(A)·2 – Cl]^{2+}\) found 938.31, calcd. 938.31; \([1(A)·2 – 2Cl + H]^{3+}\) found 625.88, calcd. 625.88. **Capsule 1(B-MeOTf)·2** (C106H140Cl2N4O21P2PdS4) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([1(B-MeOTf)·2 – Cl + 2H]^{3+}\) found 713.26, calcd. 713.24; \([1(B-MeOTf)·2 – 2Cl + H]^{3+}\) found 701.28, calcd. 701.25. **Capsule 1(B)·2** (C102H132N4O21P2PdS4Cl2) ESI-MS (\( m/z, \text{CH}_3\text{OH} \)): \([1(B)·2 – Cl + H]^{3+}\) found 1041.36, calcd. 1041.33; \([1(B)·2 – 2Cl]^{2+}\) found 622.37, calcd. 622.34; \([1(B)·2 – Cl + 2H]^{3+}\) found 694.58, calcd. 694.55; \([1(B)·2 – 2Cl + H]^{3+}\) found 682.58, calcd. 682.56.

### 3.9 Acknowledgments

Dr. Christian Müller and Dr. Maria Caporali are kindly acknowledged for providing the synthetic procedures of bisdiethylamo-DPEphos and bisdichloro-DPEphos. Henk Dekker is gratefully acknowledged for the ESI-MS measurements. Han Peeters is gratefully acknowledged for the high resolution mass spectra measurements.
3.10 References and notes


[23] Pd(II) and base in methanol will generate Pd methoxy species, which via β-hydrogen elimination give palladium hydrides. The latter with base give Pd(0) which dimerizes with Pd(II) to give strongly colored dimers (or trimers).


