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Synthesis of Ferrocenyl Phosphorhydrazone Dendrimers

Subjects: [Chemistry, Inorganic & Nuclear](#) | [Polymer Science](#)

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The discovery of ferrocene is often associated with the rapid growth of organometallic chemistry. Dendrimers are highly branched macromolecules that can be functionalized at will at all levels of their structure. The functionalization of dendrimers with ferrocene derivatives can be carried out easily as terminal functions on the surface, but also at the core, or at one or several layers inside the structure. Depending on the desired location of the ferrocenes in the structure of phosphorhydrazone dendrimers, the ferrocenes should be functionalized differently. For the grafting to the surface, the ferrocene should bear a phenol group, suitable to react in substitution reactions with the $P(S)Cl_2$ terminal groups of the dendrimers. To be used as core, the ferrocene should have two aldehyde functions, from which the synthesis of the dendrimer will be carried out. To be introduced in the branches, at all layers or within a single layer, the ferrocene should replace hydroxybenzaldehyde; thus, it should bear both a phenol and an aldehyde.

ferrocene

dendrimer

catalysis

electrochemistry

1. Introduction

Thousands of publications concern ferrocene derivatives, and their discovery represented a turning point in organometallic chemistry, as the leading member of the metallocene family. Ferrocene consists of two cyclopentadienyl rings bound on opposite sides of a central Fe^{2+} atom. It has been shown to have excellent thermal and photochemical stability, and to undergo a facile and reversible one-electron oxidation to ferrocenium cation. The functionalization of one or both cyclopentadienyl units has led to their grafting to numerous types of molecules, and to polymers and to dendrimers. Dendrimers are a very special class of polymers, constituted of repetitive branching units but not synthesized by polymerization reactions. Their step-by-step synthesis ensures a perfectly defined and highly reproducible structure ^[1]. Among the diverse types of dendrimers, phosphorhydrazone dendrimers, which possess one phosphorus atom at each branching point ^[2], occupy a special place among “inorganic” dendrimers ^[3] thanks to their easy and versatile functionalization, in particular on their periphery ^[4], and to the numerous properties that have been already demonstrated with them. Figure 1 displays the chemical structure of phosphorhydrazone dendrimers of generation 2, built either from $P(S)Cl_3$ (**1-G2**) or cyclotriphosphazene $N_3P_3Cl_6$ (**2-G2**) ^[5].

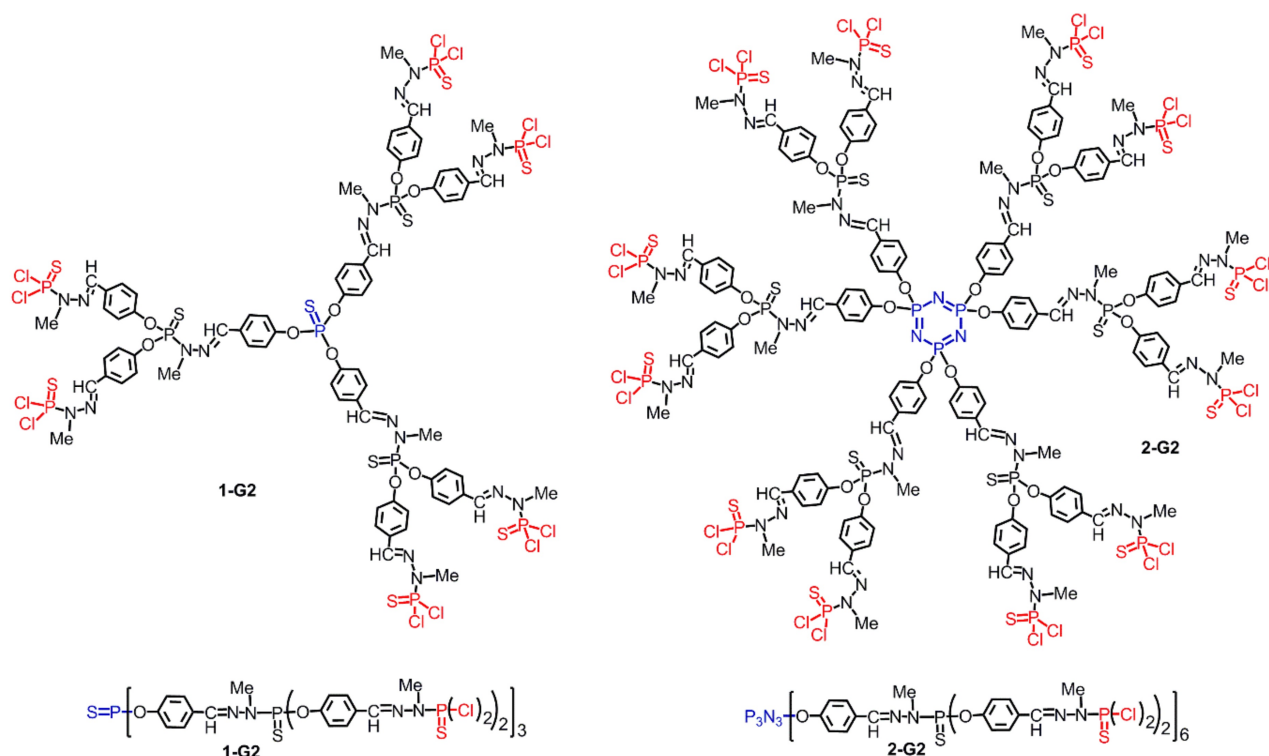


Figure 1. Structure of second generation phosphorhydrazone dendrimers. Left: built from $P(S)Cl_3$ as core; right: built from $N_3P_3Cl_6$ as core. Upper part: full structure; lower part: linear structures with parentheses to draw the same dendrimers.

Depending on the desired location of the ferrocenes in the structure of phosphorhydrazone dendrimers, the ferrocenes should be functionalized differently.

2. Ferrocenes on the Periphery of Dendrimers

The functionalization of ferrocene was carried out thanks to several efficient syntheses [6], [7], [8], [9]. All the ferrocenes that have been linked to the surface of phosphorhydrazone dendrimers are functionalized by a phenol, and possibly by another function, in particular a phosphine. The different types of these ferrocenes are shown in **Figure 2**. The ferrocene derivative **3** was linked to the surface of dendrimers of type **1-Gn** ($P(S)Cl_3$ as core), up to generation 9 (**3-G9**, 1536 ferrocenyl groups) [10]. The chiral ferrocene derivative **4** (planar chirality) was linked to the surface of the same type of dendrimers, up to generation 3 (**4-G3**, 24 ferrocenyl groups), whereas the chiral ferrocene derivative **5** was linked to the eleventh generation (**5-G11**, 6144 ferrocenyl groups) [11]. The chiral phosphino ferrocene **6** was also linked to the surface of the same dendrimers, up to generation 9 (**6-G9**, 1536 ferrocenyl groups) [11]. The chiral phosphino ferrocene **7** was linked to the surface of dendrimers of type **2-Gn** ($N_3P_3Cl_6$ as core), up to generation 4 (**7-G4**, 96 ferrocenyl groups) [12]. The phosphino ferrocenes **8**, **9**, and **10** have been linked to the surface dendrimers **2-Gn**, up to generation 3 (**8-G3**, **9-G3**, and **10-G3**, respectively, 48 ferrocenyl groups in all cases) [13].

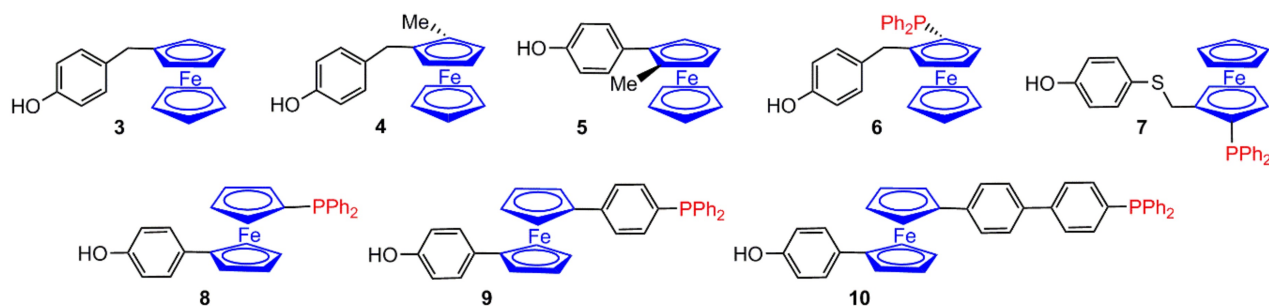


Figure 2. Ferrocenylphenols that have been linked to the surface of phosphorhydrazone dendrimers.

The synthesis of such functionalized ferrocenes is not trivial, and necessitates in all cases several steps from commercially available ferrocenes. Ferrocenes having a planar chirality (ferrocenes **4**, **5**, **6**, and **7**) are all synthesized starting from a common precursor, ferrocene carboxaldehyde, as illustrated in **Figure 3**. The first steps are also identical for all compounds. The aldehyde is quantitatively converted to the acetal using neat trimethylorthoformate. Trans acetalization was carried out with (S)-(-)-1,2,4-butanetriol, to provide another acetal, having the cis-1,3-dioxane structure. Methylation of the hydroxyl group is then carried out using NaH and MeI. Ortho-deprotonation was carried out using t-BuLi. The lithium derivative is the last common precursor, which is reacted with diverse electrophiles [14]. The electrophile used is MeI for the synthesis of ferrocene **4** (way A), $\text{ICH}_2\text{CH}_2\text{I}$ for ferrocene **5** (way B), and Ph_2PCI for ferrocenes **6** and **7** (way C) (**Figure 3**). The deprotection of the acetal to recover the aldehyde is carried out in all cases using p-toluene sulfonic acid (PTSA) and water.

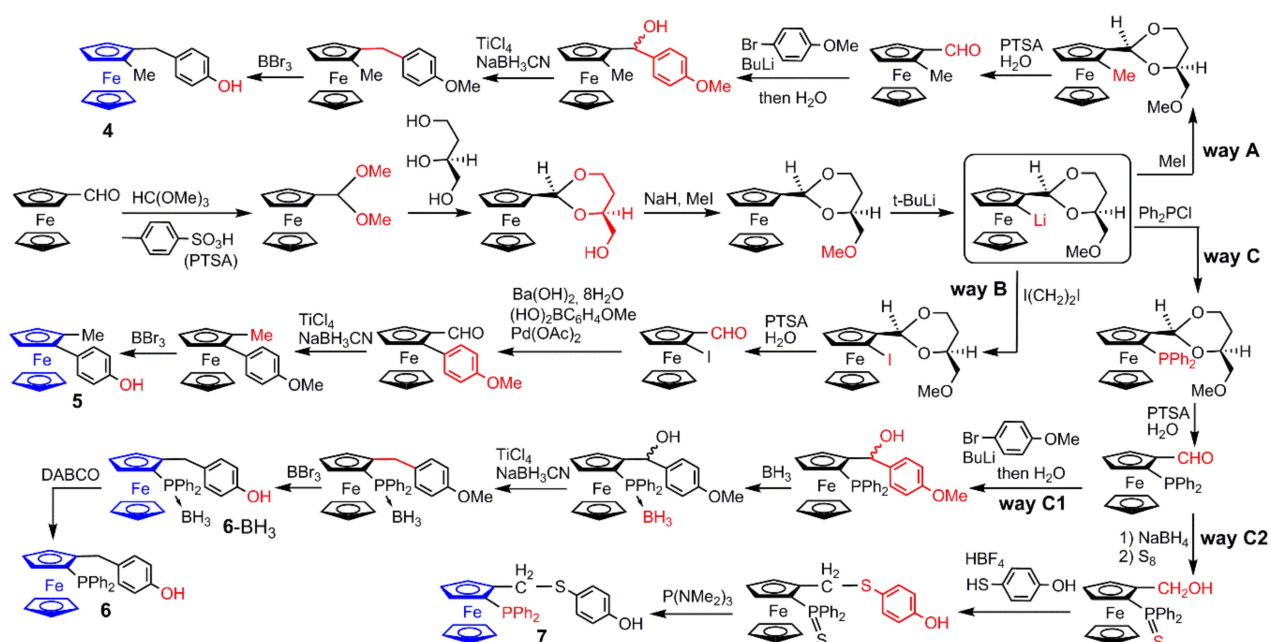


Figure 3. Synthesis of ferrocenes **4**, **5**, **6**, and **7**, starting from the common precursor ferrocene carboxaldehyde.

The next step in way A is the reaction of 4-lithioanisole obtained by transmetalation of 4-bromoanisole by n-butyllithium on the aldehyde, followed by deoxygenation with sodium cyanoborohydride in presence of titanium tetrachloride. Finally, the methoxy group is transformed to hydroxyl group by reaction with boron bromide, to provide the ferrocene **4**, after 9 steps from ferrocene carboxaldehyde [11]. The ferrocene derivative functionalized with both an aldehyde and an iodine (way B) is reacted in a Suzuki coupling reaction with 4-methoxyphenylboronic acid to yield enantiomerically pure 4-methoxyphenyl group on the 2 position of ferrocenecarboxaldehyde. The aldehyde is then converted to a methyl group using sodium cyanoborohydride in presence of titanium tetrachloride. Finally, the methoxy group is deprotected to provide compound **5** after 9 steps, as was obtained ferrocene **4** [11]. The (S)-2-(diphenylphosphino) ferrocene carboxaldehyde obtained in way C is the precursor of both ferrocenes **6** (way C1) and **7** (way C2). In way C1, 4-lithioanisole is first reacted on the aldehyde; then, the phosphine is protected with BH_3 . Reactions with sodium cyanoborohydride in presence of titanium tetrachloride and then with boron bromide are carried out as in way A, to provide compound **6-BH₃**. The phosphine is finally deprotected using DABCO (1,4-diazabicyclo[2.2.2]octane) to provide the ferrocene **6** after 11 steps [11]. In way C2, the aldehyde is reduced to alcohol and the phosphine is oxidized to thiophosphine using sulfur. In a second step, 4-hydroxythiophenol is reacted on the alcohol, providing directly a phenol. The

last step is the reduction of the thiophosphine with tris (dimethylamino)phosphine, providing the ferrocene **7** in 9 steps (**Figure 3**) [12].

The ferrocenes functionalized on both cyclopentadienyl rings (compounds **8**, **9**, and **10**) are easier to synthesize, as shown in **Figure 4**. The common precursor in these cases is 1,1'-dibromoferrocene, on which one bromine is treated with 4-bromoanisole in a Negishi cross-coupling reaction. The direct grafting of diphenylphosphine on the other cyclopentadienyl ring is carried out by lithiating the ferrocene, then quenching with diphenylchlorophosphine. The deprotection of the phenol using tetrabutylammonium fluoride provides the ferrocene **8** after only three steps (**Figure 4**) [13]. A slightly different procedure is used for introducing a linker between the ferrocene and the phosphine (compounds **9** and **10**) [15]. The lithiated ferrocene in presence of ZnCl_2 and $[\text{Pd}(\text{PPh}_3)_4]$ is treated with either 4-bromophenyl-diphenylphosphane sulfide or 4'-bromobiphenyl diphenylphosphane sulfide. The corresponding phenol is obtained as previously using tetrabutylammonium fluoride. The last step is the deprotection of the thiophosphine, using Raney nickel, to provide ferrocenes **9** or **10** in only four steps, depending on the linker used (**Figure 4**) [13].

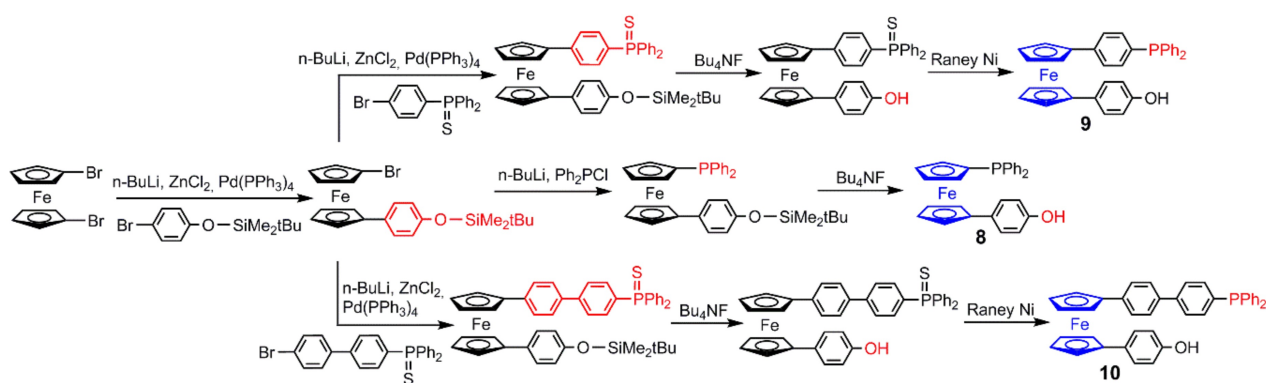


Figure 4. Synthesis of ferrocenes **8**, **9**, and **10**, starting from the common precursor 1,1'-dibromoferrocene.

3. Ferrocene at the Core of Dendrimers

Ferrocene derivatives usable as core should have at least two identical functions. The commercially available 1,1'-ferrocene dicarboxaldehyde **11** was used as core to grow the dendrimer up to generation 4 (**11-G4**, 64 aldehyde terminal functions) (**Figure 5**) [10].

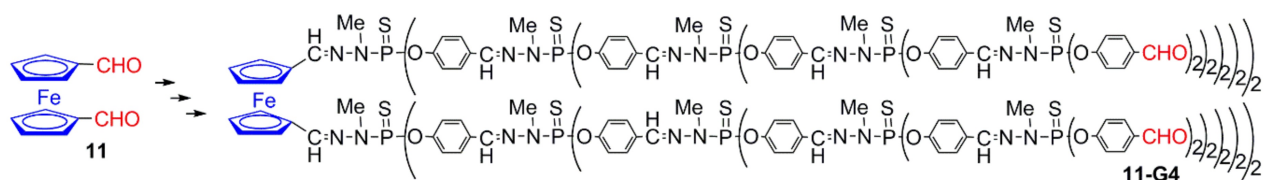


Figure 5. 1,1'-ferrocene dicarboxaldehyde used as core of dendrimer **11-G4**.

4. Ferrocenes as Branches of Dendrimers at one or Several Layers

The functionalization of ferrocenes usable as branches of phosphorhydrazone dendrimers necessitates one to have a phenol on one side and an aldehyde on the other side. Several ferrocene derivatives have been synthesized bearing both suitable functions, and have been used either at several layers of small dendrimers (ferrocenes **12** and **13**, **Figure 6**) or at a single layer

inside the structure of large dendrimers (ferrocenes **14** and **15**, **Figure 6**). The methods of synthesis are relatively similar to those shown in **Figure 3**. In particular, the ferrocene **14** is obtained by transformation of the methoxy to hydroxyl group in the final step, after seven steps shown in **Figure 3** [11]. The main difference between the reactions in **Figure 3** and **Figure 6** concerns the reaction of ferrocene carboxaldehyde with the lithium salt of N-methylpiperazine, which, after additional reaction with t-BuLi, generates the lithiation of the other cyclopentadienyl ring [6]. Reaction with electrophiles such as ICH₂CH₂I or Bu₃SnCl are then carried out. The iodoferrocene is first reacted in a Suzuki coupling reaction with 4-methoxyphenylboronic acid, and then the methoxy group is deprotected with BBr₃ to provide the ferrocene **12** [10]. The stannyl derivative is first reacted on the aldehyde with 4-lithioanisole, and then the alcohol is reduced with BH₃,SMe₂. The tributylstannyl group is converted to an aldehyde using butyl lithium, dimethylformamide, and then water. The final step for the synthesis of compound **15** is the cleavage of the methoxy group to provide the phenol, as done previously for compound **12**.

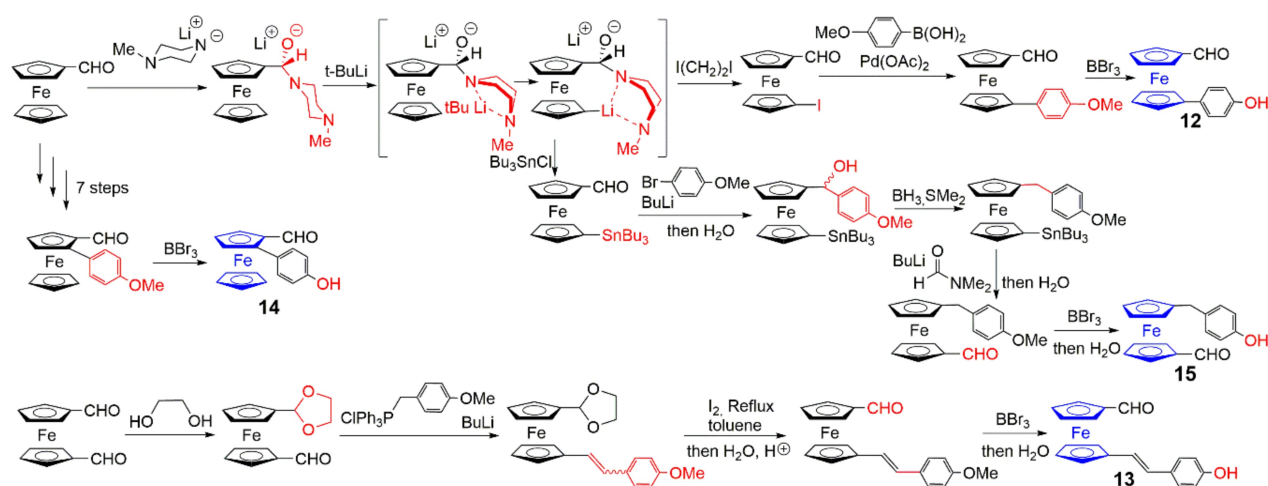


Figure 6. Methods of synthesis of ferrocenes functionalized by both a phenol and an aldehyde, which are suitable to be used as branches inside dendrimers. The seven steps for the synthesis of **14** are shown in **Figure 3**.

Ferrocene **13** is obtained in a different way, as the starting compound for its synthesis is the 1,1'-ferrocene dicarboxaldehyde. A first aldehyde is protected with ethylene glycol, then the second aldehyde is reacted with 4-methoxybenzyltriphenylphosphonium chloride in the presence of n-BuLi to yield a mixture of diastereoisomer (**E/Z** = 1) by a Wittig reaction. Reaction with iodine in refluxing toluene followed by an acidic hydrolysis provides a complete conversion to the E-isomer of the corresponding aldehyde. The last step to get ferrocene **13** is the deprotection of the methoxy group to hydroxyl, as carried out for many other ferrocenes.

4.1. Ferrocenes at all Layers of Dendrimers

The bifunctional ferrocene **12** was first reacted with the P(S)Cl₃ core; then, it was used alternately with the phosphorhydrazide H₂NNMeP(S)Cl₂, up to the second generation **12-G2** (21 ferrocene derivatives and 12 aldehyde terminal groups) (**Figure 7**) [10].

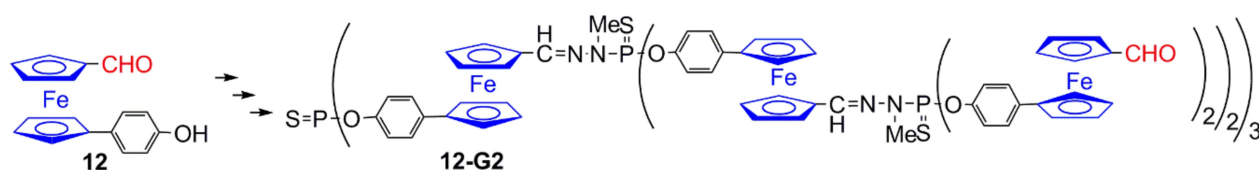


Figure 7. Bifunctional ferrocene **12** used at all layers of dendrimer **12-G2**.

The same process was applied to the other bifunctional ferrocene **13**, and was carried out up to

the first generation **13-G1** (9 ferrocene derivatives and 6 aldehyde terminal functions) (**Figure 8**) [16].

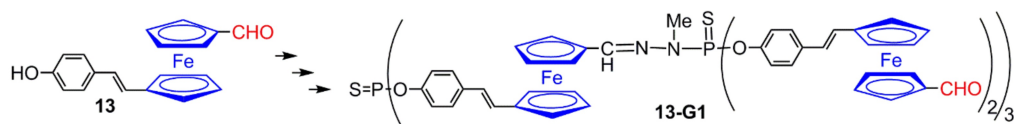


Figure 8. Bifunctional ferrocene **13** used at all layers of dendrimer **13-G1**.

4.2. Ferrocenes at a Single Layer Inside Dendrimers

The chiral ferrocene **14** was introduced at a single layer in phosphorhydrazone dendrimers. It was used first on the surface of dendrimer **1-G3**, providing dendrimer **14-G3** [11], then the growing of the dendritic shell was carried out to obtain **14-G3+1**, then **14-G3+2**, as illustrated in **Figure 9** (24 ferrocenyl groups for all). The same type of experiment was carried out starting from **1-G5** and **1-G9**, providing **14-G5+2** (96 ferrocenyl groups) and **14-G9+2** (1536 ferrocenyl groups), respectively [17].

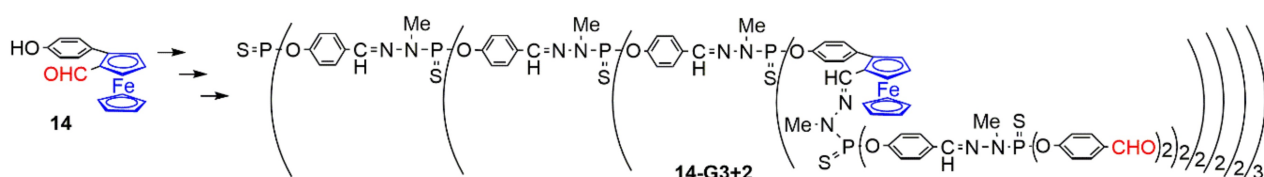


Figure 9. Bifunctional ferrocene **14** used at a single layer of dendrimer, and dendrimer **14-G3+2**.

Other dendrimers bearing a single layer of ferrocenes were also obtained, starting from the dendrimer **2-G2**, onto which 24 ferrocenyl derivatives **15** were grafted. The growing of the dendrimer was continued in order to get water-soluble ferrocenyl dendrimers. Ammonium derivatives have been linked to the surface, providing the positively charged dendrimer **15-G3⁺**, whereas carboxylates have been used to provide the negatively charged dendrimer **15-G3⁻** (**Figure 10**) [18].

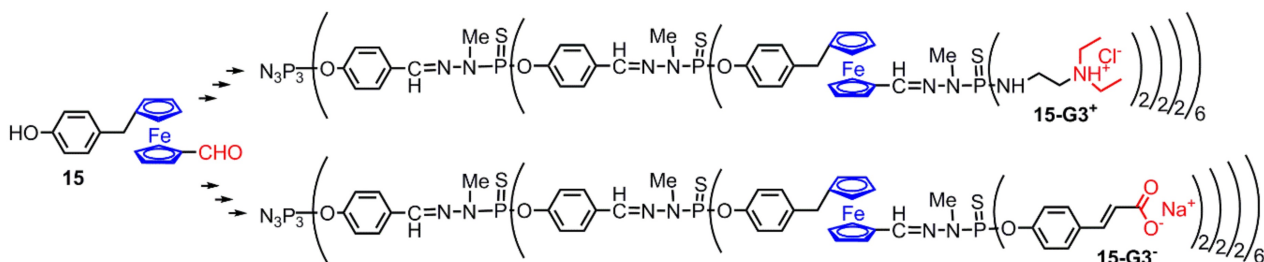


Figure 10. Bifunctional ferrocene **15** used at a single layer of water-soluble dendrimers **15-G3⁺** and **15-G3⁻**.

In conclusion, the marriage between dendrimers and ferrocene derivatives is indeed fruitful, with each component providing its specificities. The presence of ferrocenes inside the structure of dendrimers induces a detrimental influence on the electrochemical properties, as the ferrocene's burial in the structure increases. On the contrary, the presence of ferrocenes on the surface of dendrimers provides clean electrochemical data, even for very high generations, such as the eleventh generation. The presence of a phosphine in close proximity of the ferrocene on the surface provides additional properties after the complexation with a metal, in particular for carrying catalysis experiments. Several examples have been already proposed, such as the complexation of palladium for catalyzing asymmetric allylic substitution reaction, and the complexation of ruthenium for the catalytic isomerization of the allylic alcohol 1-octen-3-ol to 3-

octanone. In the latter case, the oxidation of the ferrocene induces a strong decrease of the catalytic properties, which are recovered upon reduction of the ferrocenium to ferrocene. This is the very first example of a switch ON/OFF/ON of a dendritic catalyst. Work is in progress to expand the scope of the catalytic properties of ferrocenyl dendrimers, as shown by a recent example with P-chiral dendritic ferrocenyl phosphine complexes [\[19\]](#).

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