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Review

Specific Bifunctionalization on the Surface of Phosphorus Dendrimers Syntheses and Properties

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Abstract: Dendrimers are highly branched macromolecules possessing, in most cases, identical terminal functions. However, it is sometimes desirable to have two types of surface functions in order to fulfil specific properties. The stochastic functionalization is frequently used for such purposes, but the presence of an uncontrolled number of each type of terminal function, albeit acceptable for research purposes, has no practical use. Thus, it is highly desirable to find strategies suitable for the precise grafting of two different functional groups on the surface of dendrimers. The easiest way, and the most widely used, consists in using a bifunctional monomer to be grafted to all of the surface functions of the dendrimers. Two other strategies are known but are rarely used: the modification of an existing function, to generate two functions, and the sequential grafting of one function then of a second function. The three methods are illustrated in this review with polyphosphorhydrazone (PPH) dendrimers, together with their properties as catalysts, for materials, and as biological tools.

Keywords: dendrimer; phosphorus; bifunctionalization; polyphosphorhydrazone; properties

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1. Introduction

Dendrimers [1] are highly branched three-dimensional macromolecules, which properties are essentially dependent on the type of their terminal functions. Numerous properties have been explored already, most of them being related to catalysis, materials, or biology/nanomedicine [2]. Dendrimers are synthesized by iterative processes, which afford a new generation at the end of each sequence, characterized by a multiplication of the number of terminal functions, most generally by two [3] or three [4], depending on the branching motives. Such processes generate identical terminal functions on the surface of the dendrimers, of course depending on the type of dendrimers, and on the synthetic process used. Such terminal functions can be modified uniformly to bring new properties. However, it is desirable in some cases to have two types of terminal functions, each type of functions affording eventually its own properties (for instance, one function for the solubility, the other affording properties for catalysis or biology, or one type of function for the grafting (for instance to materials), with the other functions bringing another property).

In most cases, the presence of two (or even more) functions on the surface of dendrimers is carried out using a stochastic approach (i.e., an uncontrolled number and location of each type of functions). However, this approach is contradictory with the aim of having a perfectly controlled and reproducible structure for the dendrimers, contrarily to classical polymers. Even if efforts have been carried out to increase the purity of compounds issued from the stochastic approach [5], batch-to-batch inconsistencies are unavoidable,

and induce in particular undesirable varying biological activities [6]. To solve this type of problem, it is highly desirable to synthesize dendrimers precisely bifunctionalized on their surface. Figure 1 displays the difference between both approaches.

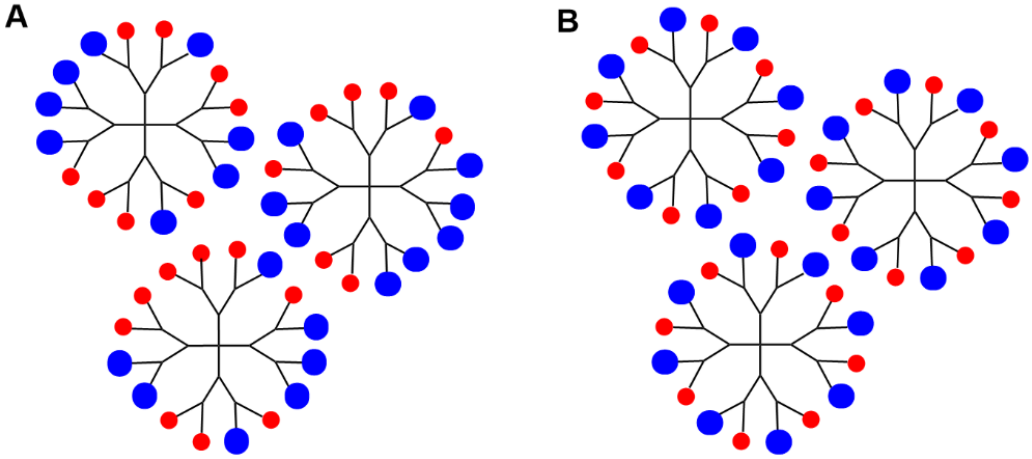
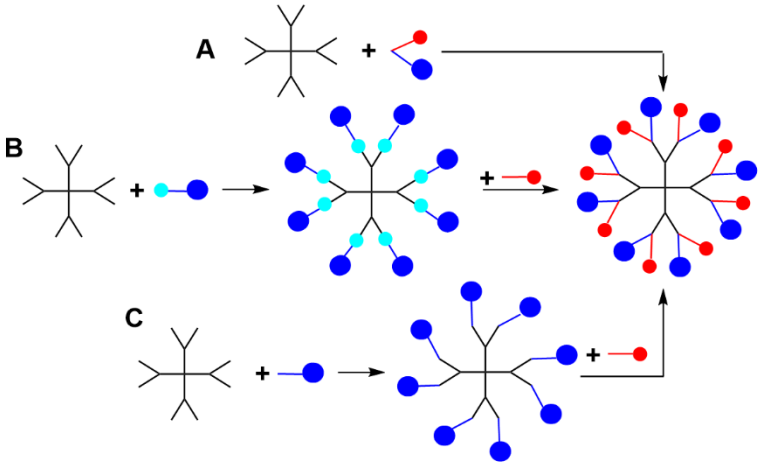


Figure 1. Examples of batches of bifunctionalized dendrimers. (**A**) Stochastic functionalization on the surface of dendrimers. (**B**) Precise bifunctionalization on the surface of dendrimers.

The easiest way to get dendrimers specifically bifunctionalized on their surface consists in grafting on each terminal function a compound bearing already both desired functions (Scheme 1A). Such a method has been applied to different types of dendrimers and functions. One can cite for instance as an early example the presence of both a phenyl and a pyrene on the surface of a series of dendrimers built on an arylether scaffold, and used for studying charge-transfer processes from the core to the surface [7]. More recent examples concern PAMAM (polyamidoamine) dendrimers functionalized with different aminoacids, to have NH_2 groups together with either OH, SH, or other functional groups, and tested for drug delivery [8]. Polyester dendrimers functionalized with both OH and azide, used later on in click chemistry to afford biosensors [9], or functionalized with both azide and alkyne, as a multipurpose platform, in particular to afford implant adhesives in bone fracture applications [10] are other more recent examples. Azide alkyne monomeric compounds have been used for synthesizing by click chemistry multifunctional nanocarriers bearing as terminal functions a model drug (R-lipoic acid), a fluorescent dye (BODIPY), and a poly(ethylene glycol) (PEG) chain [11]. Other recent examples of grafting directly two functions concern PPI (polypropyleneimine) dendrimers functionalized with both an electroactive carbazole and a mesogenic unit, all dendrimers of this family being liquid crystalline [12], and also Newkome-type polyamide dendrimers, functionalized with both one azide and two olefins [13]. A series of bifunctional dendrimers has been obtained from either a polyester-polyamide, or polyester-lysine, or polyamine-lysine hybrid internal structure functionalized on the surface with orthogonally protected aspartic acid [14]. The selective and sequential deprotection of the amine and of the carboxylic acid of the protected aspartic acid was carried out to graft a long PEG (115 units in average), and either a gadolinium complex [15,16] or diverse other lanthanide complexes (Dy, Yb [17], Eu, and Sm [18]) for magnetic resonance imaging (MRI), or two synthetic tubulysin analogues against C26 colon carcinomas [19]. Lysine derivatives protected by two different protecting groups, were grafted on the surface of lysine dendrimers and dendrons. Selective deprotection afforded dendrimers bearing both gadolinium complexes and PEG as MRI contrast agents [20]. The same process was applied to a series of dendrons having a carboxylic acid at the core and both a gadolinium complex and galactosyl moieties on the surface, as liver targeting imaging probes [21]. Another lysine-dendron bearing a long PEG chain at the core (114 units in average) and both a porphyrin analogue and cholic acid, was used for near-infrared fluorescence imaging (NIRFI), magnetic resonance imaging (MRI), positron emission tomography (PET) and dual modal PET-MRI [22].



Scheme 1. Schematization of the different methods used for having precisely two types of different functions on the surface of dendrimers. (**A**) grafting on each terminal function a compound bearing already both desired functions. (**B**) modifying one function already on the surface, to generate two functions. (**C**) sequential grafting of one function, followed by the grafting of the second one.

Other methods to get two types of terminal functions have been very rarely used. One can cite the possibility to modify one function already on the surface, to generate two functions (Scheme 1B). Such type of reaction has been illustrated with functionalized amines used for opening cyclic carbonates on the surface of polyester dendrimers [23].

The last method concerns the sequential grafting of one function, followed by the grafting of the second one, as illustrated in Scheme 1C. Such a type of reaction is rare, and has been used essentially with dendrimers having dichlorotriazine as terminal functions, reacted in sequential nucleophilic aromatic substitution with two different amines [24]. MRI (Magnetic Resonance Imaging) contrast agents have been obtained in this way, one amine bearing a ligand suitable for complexing gadolinium, the other an alcohol [25].

Besides the different types of dendrimers indicated above, another type of dendrimer is known for the versatility of its chemistry, namely phosphorus dendrimers, and particularly polyphosphorhydrazone (PPH) dendrimers, which possess a phosphorus atom at each branching point [26]. They are generally built from either $P(S)Cl_3$ or hexachlorocyclotriphosphazene as core [27]. Their structure is illustrated in Figure 2 with the first and second generations. Both generations are displayed as the full chemical structure, but also in a linear form with parentheses after each layer of branching points. The presence of either $P(S)Cl_2$ or aldehyde terminal functions, depending on the step considered, enables a versatile reactivity to fulfil the desired properties. In this review, we will display the different methods used for the bifunctionalization of phosphorus dendrimers, carried out using the three methods shown in Scheme 1. Besides the synthesis, the particular properties of such specifically bifunctionalized dendrimers in different fields such as catalysis, materials, and biology will be also emphasized.

As for other types of dendrimers, the stochastic grafting of two different terminal functions was carried out in a few cases on PPH dendrimers. One can cite the stochastic grafting of a julolidine fluorophore to mannose-capped dendrimers, able to prevent acute lung inflammation in vivo [28], or of fluorescein isocyanate grafted to a dendrimer bearing azabisphosphonate terminal functions, able to positively influence the human immune system [29]. Such method was also used for grafting different ratios of copper complexes [30], gold complexes and polyethylene glycol as terminal functions of PPH dendrimers having anti-cancer properties [31], bearing eventually fluorophores inside the structure to decipher the biological mechanism of action [32]. However, the precise number of terminal functions is an important criterium, in particular for biological purposes.

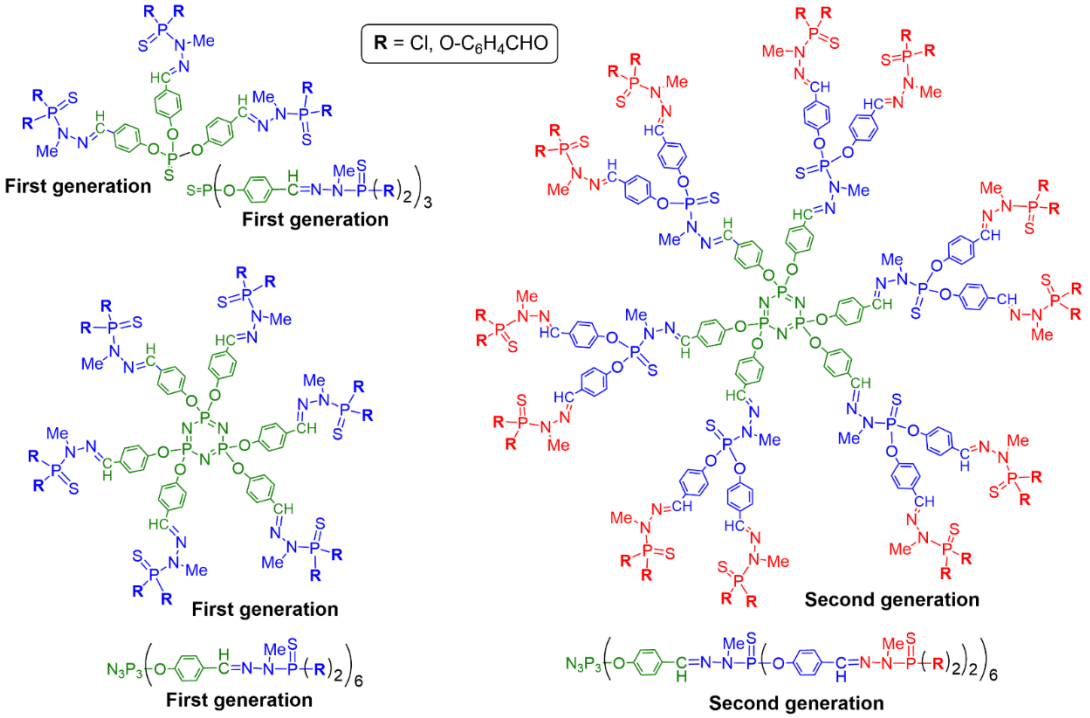
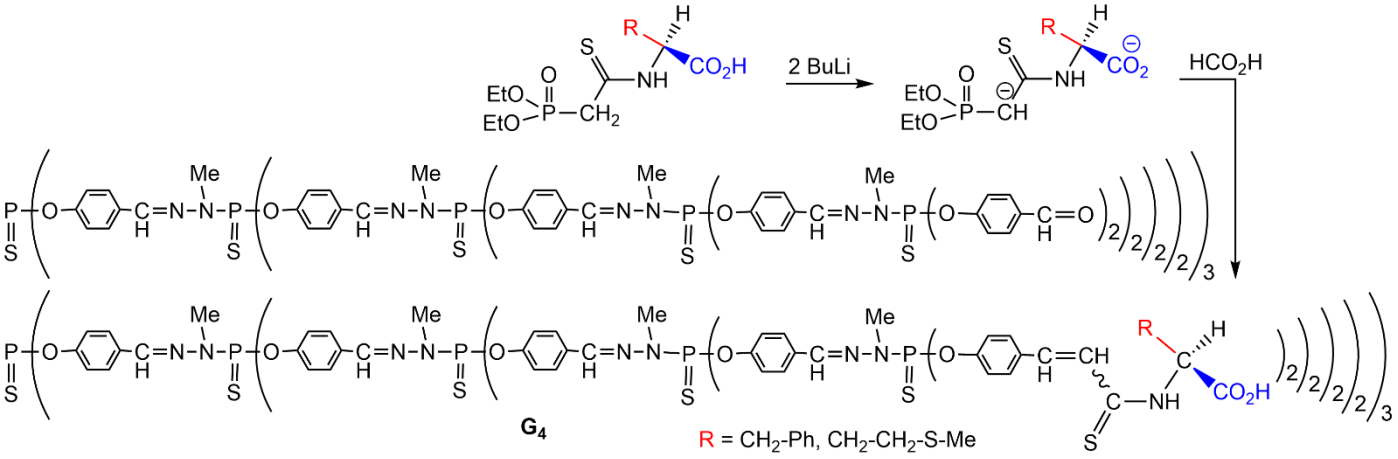


Figure 2. Two ways for drawing the 1st and 2nd generations of polyphosphorhydrazone dendrimers: full chemical structure, and linear structure with parenthesis after each layer of branching points.

2. Bifunctional Monomers Grafted to the Surface of PPH Dendrimers

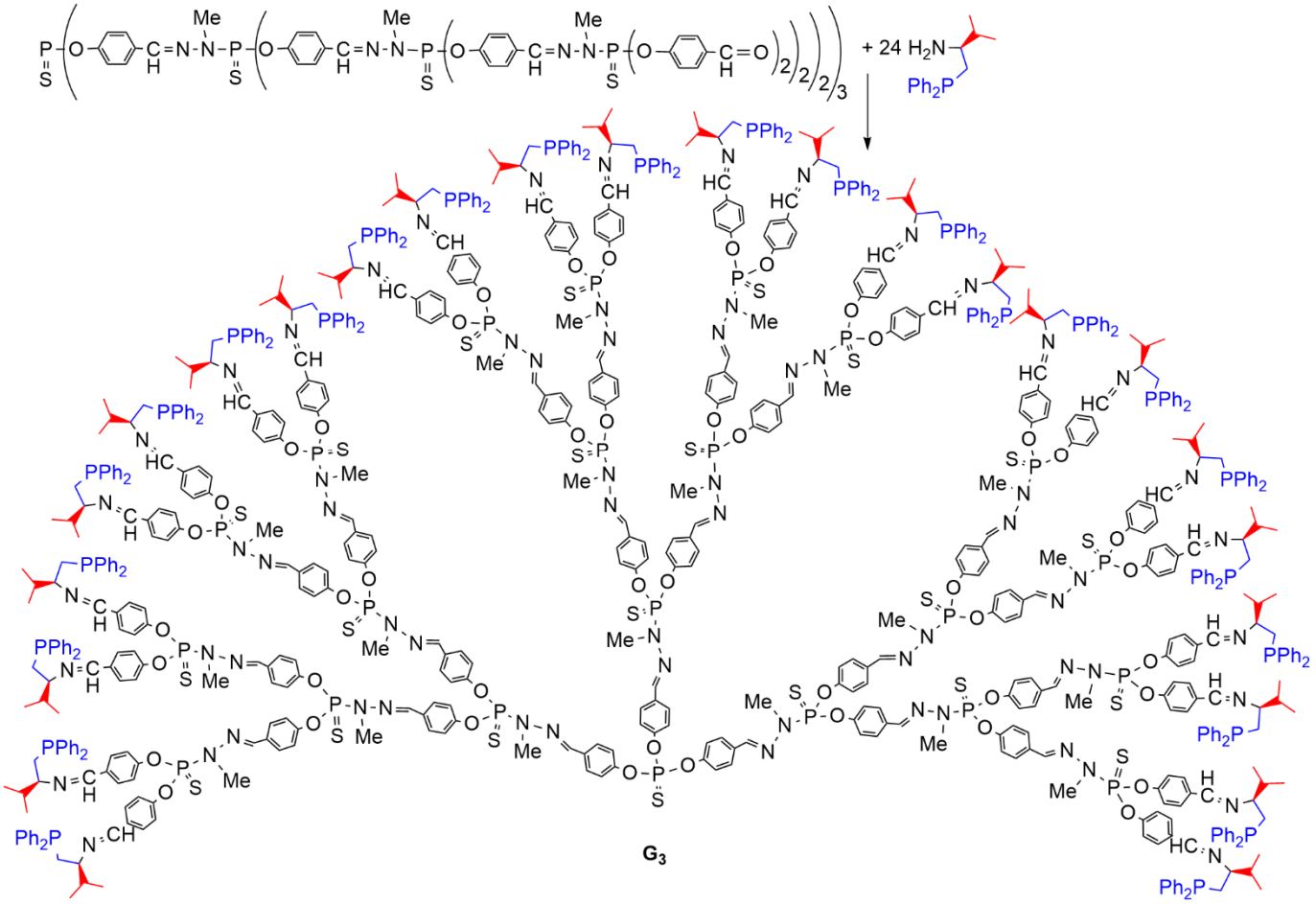
As for the other types of dendrimers, the grafting of a bifunctional monomer on the surface of polyphosphorhydrazone dendrimers is easy to carry out (way A in Scheme 1). The first attempts concerned only fundamental researches. For instance, the Horner-Wadsworth-Emmons reaction was applied to aldehyde terminal functions for the grafting of diverse amino acids, up to generation 4 (Scheme 2) [33].



Scheme 2. Generation 4 PPH dendrimer functionalized with amino acid terminal functions, obtained by Horner-Wadsworth-Emmons reactions on aldehyde terminal groups.

However, the use of bifunctional units was essentially applied in the fields of catalysis and biology. In the case of catalysis, many examples of phosphine complexes as terminal functions of dendrimers are known [34]. In a first example of PPH dendrimers, the terminal phosphines were used to complex gold, to facilitate imaging of single molecules with high-resolution transmission electron microscopy (HRTEM) [35]. Later on, dendritic complexes were used as catalysts for instance in Stille couplings [36], to dramatically

decrease palladium leaching in Suzuki couplings [37], to increase enantioselectivity in Rhodium-catalyzed [2+2+2] cycloadditions [38], to be efficiently recycled using a magnet in Pd-catalyzed couplings [39], and to switch on and off the catalytic efficiency through a redox control [40]. In all cases of catalysis, the efficiency of different generations is compared using the same number of catalytic sites (i.e., for instance the efficiency of 4 equiv. of the 1st generation is compared with that of 1 equiv. of the 3rd generation). An example of catalysis with bifunctionalized monomeric phosphines concerned a 3rd generation dendrimer decorated with chiral iminophosphines derived from (2*S*)-2-amino-1-(diphenylphosphinyl)-3-methylbutane, obtained by condensation reactions on the aldehydes (Scheme 3). The Pd complex of this dendrimer was used as catalysts in asymmetric allylic alkylation of *rac*-(E)-diphenyl-2-propenyl acetate or pivalate, using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as base and either LiOAc or KOAc as co-catalyst to produce the nucleophile from dimethylmalonate, and to afford 2-(1,3-diphenylallyl)-malonic acid dimethylester. Conversions were almost quantitative in all cases, with isolated yields up to 97% in the best cases, and ee (enantiomeric excess) up to 94–95%. Contrarily to the monomeric catalysts, this dendritic catalyst could be recovered and reused with the same efficiency at least 3 times (Figure 3) [41].



Scheme 3. Synthesis of the 3rd generation of a PPH dendrimer decorated with chiral iminophosphine end groups. The Pd complex was used as catalysts in asymmetric allylic alkylation.

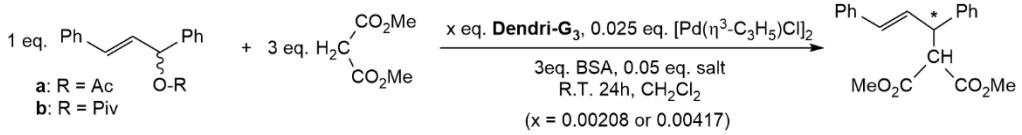
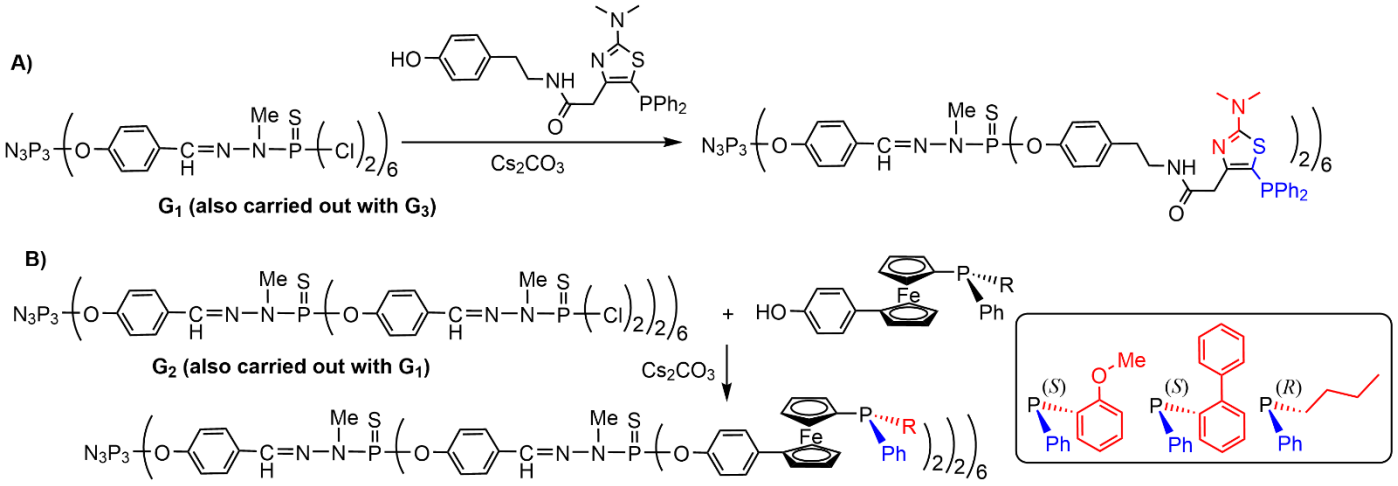


Figure 3. Allylic alkylation catalyzed by the Pd complex of the G_3 dendrimer shown in Scheme 3.

Another example of bifunctional monophosphine concerns a thiazolyldiphenylphosphine grafted on the surface of generations 1 and 3 of PPH dendrimers (Scheme 4A). These dendrimers were able to complex palladium, and were used as catalysts in Suzuki couplings (Figure 4A). It was possible to recover and reuse even the first generation at least four times with the same efficiency, contrarily to a dendrimer having triphenylphosphine as terminal functions. Interestingly, palladium leaching could not be detected with the dendrimer bearing the thiazolyldiphenylphosphines, whereas it was found to be 173 (±3) ppm with the dendrimer bearing the triphenylphosphine [37]. Recently, a series of dendrimers (generations 1 and 2) functionalized with chiral ferrocenylphosphines was synthesized (Scheme 4B). These dendrimers were used as catalysts in the ruthenium-catalyzed redox-switchable transfer hydrogenation of a ketone, yielding a slighlty enantioenriched alc ohol (Figure 4B). It has been shown previously that, thanks to the presence of the ferrocene, adding a chemical oxidant or reductant, modified the catalytic activity of the complexes, which was reversibly switched off, and back on again [40]. The same phenomenon was observed with the chiral ferrocenylphosphines shown in Scheme 4B. The first generation was more active than the second, but practically no difference in activity was observed depending on the type of substituents on the phosphine [42].



Scheme 4. Synthesis of dendrimers functionalized with thiazolyldiphenylphosphine for which the Pd complex was used in Suzuki couplings (**A**) and chiral ferrocenylphosphines for which the Ru complexes were used in switchable transfer hydrogenations (**B**).

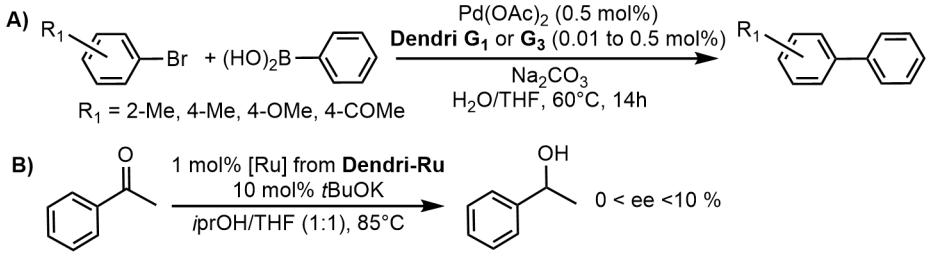
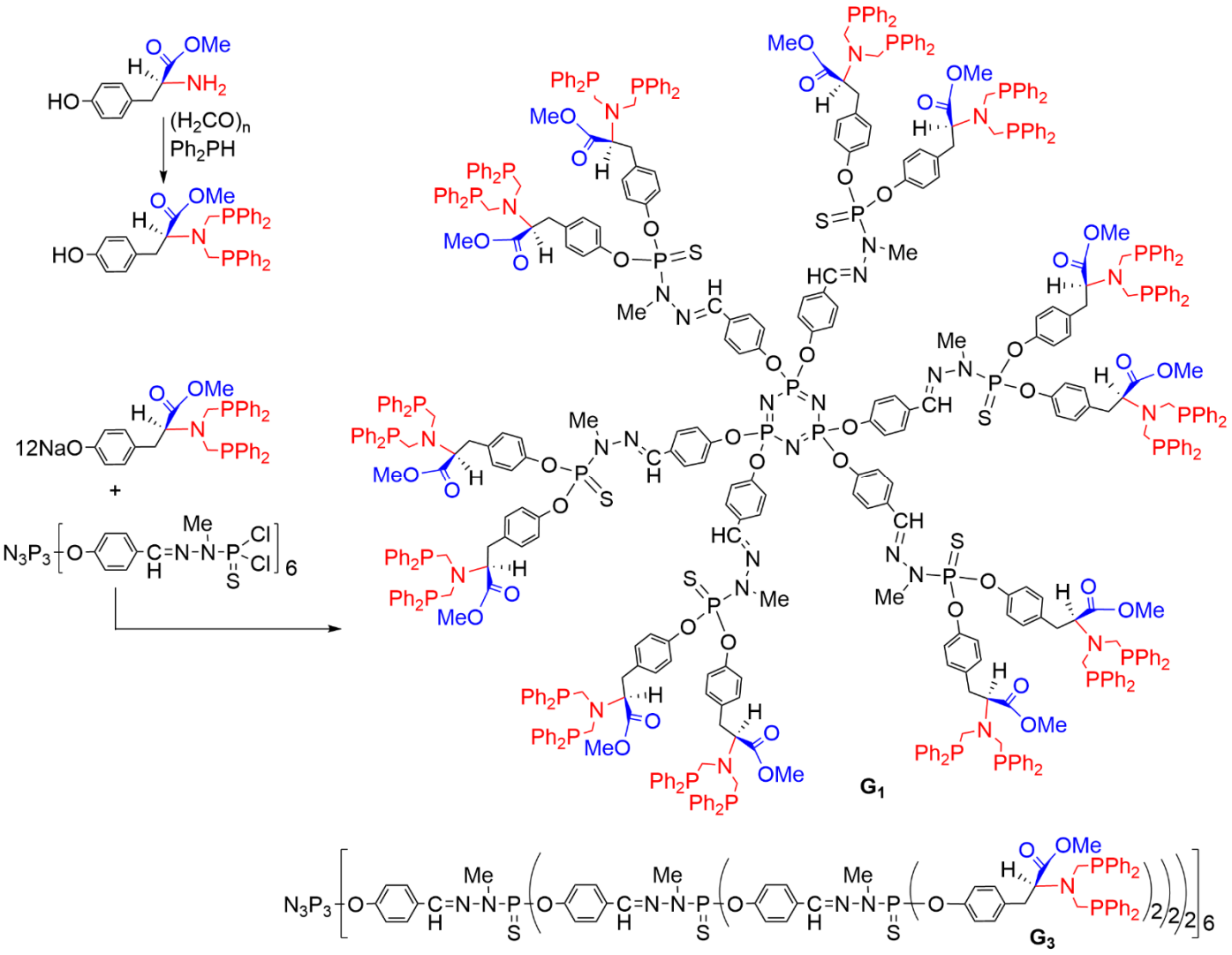


Figure 4. (**A**) Suzuki coupling catalyzed by Pd complexes of the dendrimers shown in Scheme 4A. (**B**) Transfer hydrogenation catalyzed by Ru complexes of the dendrimers shown in Scheme 4B.

Besides monophosphines, symmetrical diphosphine derivatives grafted on the surface of phosphorhydrazone dendrimers have been proposed for the complexation of palladium, platinum, rhodium [43], and ruthenium [44]. The Pd complexes were used as catalysts in Stille couplings, whereas the Ru complexes were used as catalysts in Knoevenagel condensations and diastereoselective Michael additions [45]. There is also an example of a diphosphine bearing a chiral substituent based on L-tyrosine methyl ester, as shown in Scheme 5 for the first and third generations of the polyphosphorhydrazone dendrimers. The catalytic properties of this series of dendrimers complexing palladium were compared

with that of the corresponding diphosphine dendritic ligands not bearing the L-tyrosine derivative, but derived from tyramine. Both families of dendrimers were studied in C-C cross-coupling reactions, namely, Suzuki, Sonogashira, and Heck reactions, all of them being carried out in the presence of water (Figure 5). In all cases, the series built from L-tyrosine is less efficient than the series built without it, showing the negative influence of the local hindrance on the catalytic efficiency. However, in all cases, the dendritic catalysts are more efficient than the corresponding monomeric complexes, of course considering the same number of catalytic entities in all experiments. Indeed, the efficiency of 12 equivalents of monomeric catalyst is compared with that of 1 equivalent of the 1st generation dendrimer, which bears 12 catalytic entities in a single molecule [46].



Scheme 5. Synthesis of the 1st generation of PPH dendrimer bearing diphosphine derivatives of L-tyrosine methyl ester as terminal functions, and linear representation of the corresponding third generation. The palladium complexes were used as catalysts in C-C cross-coupling reactions.

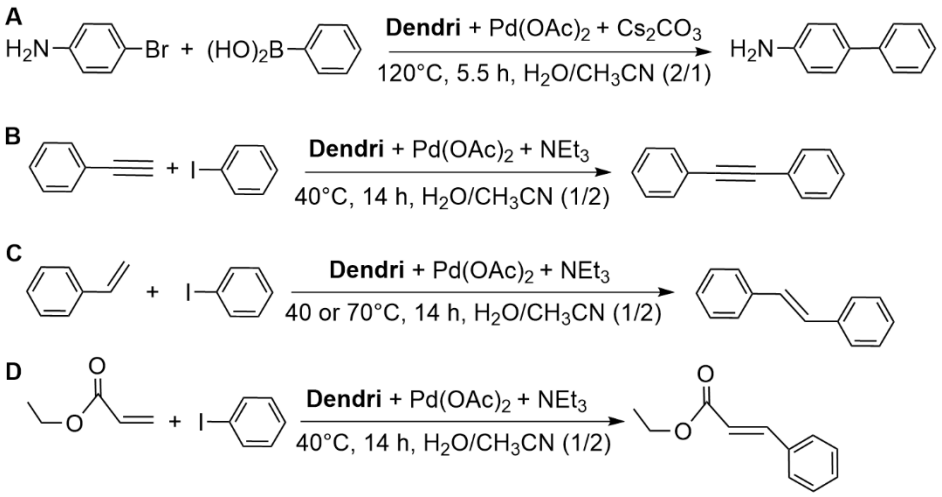


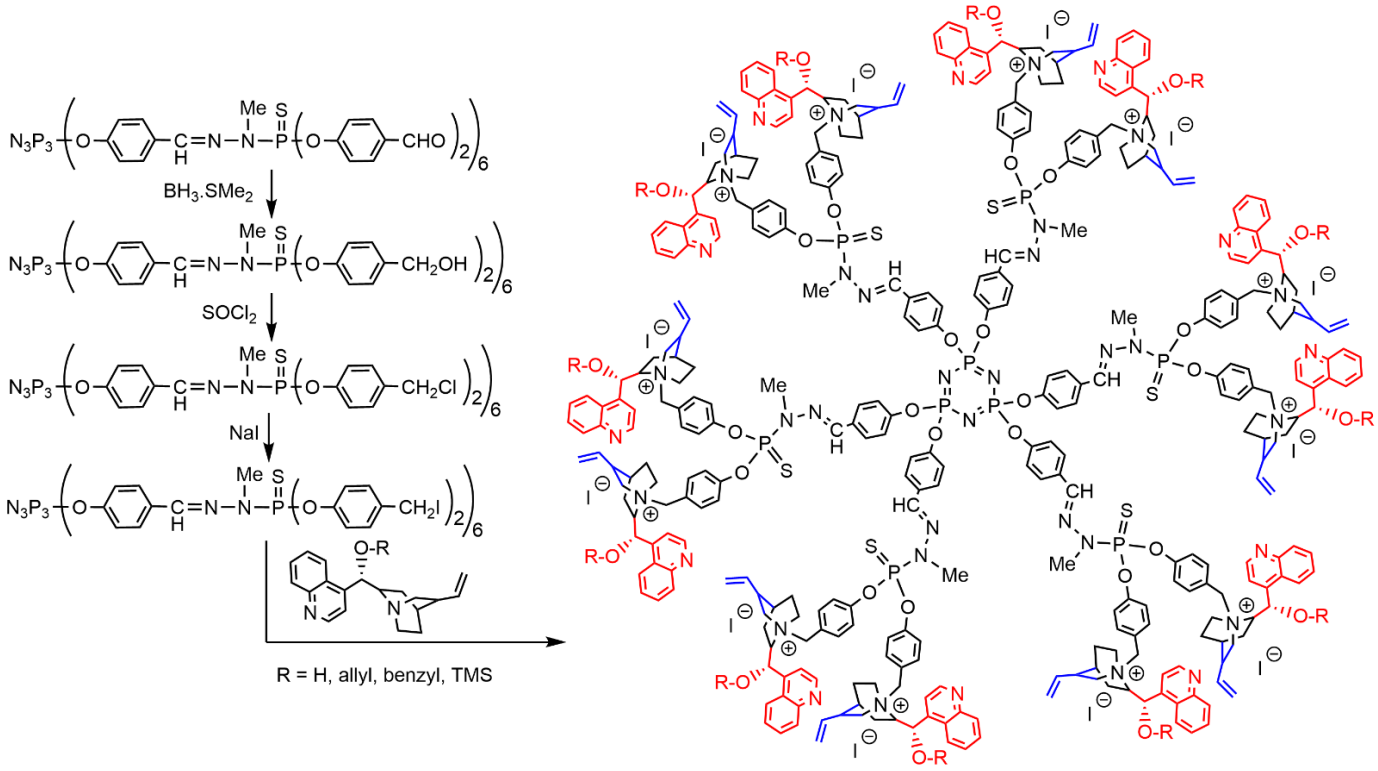
Figure 5. Catalytic reactions carried out with Pd complexes of the dendrimers shown in Scheme 5. (**A**) Suzuki coupling; (**B**) Sonogashira coupling; (**C**,**D**) Heck couplings.

Even if the use of dendrimers can enable a large decrease of metal leaching as indicated above [37], organocatalysis has been recognized as an interesting alternative to avoid metals, including in the field of dendrimeric catalysts [47]. For instance, polyphosphorhydrazone dendrimers of first- and fourth-generations were decorated with (+)-cinchonine moieties, and used as efficient organocatalysts in the α-amination of several types of β-dicarbonyl compounds. It was possible to recover and reuse the dendritic organocatalyst 10 times without loss of activity [48]. Another example concerned a bifunctional derivative of (+)-cinchonine. In that case, the dendrimer of the first generation had to be modified in three steps from the aldehyde terminal functions, to obtain iodine surface functions. This dendrimer was found suitable for the quaternization of the quinuclidinic N atom of several types of (+)-cinchonine (variation of the OR group, see Scheme 6). These compounds were used as organocatalysts in the asymmetric alkylation of a glycinate Schiff base with different types of bromides, in particular benzyl bromide derivatives (Figure 6). The case where R is an allyl group was found the most efficient. Recovery and reuse of the catalysts was carried out five times without a loss of efficiency and with only a minor decrease in enantioselectivity [49].

The grafting of 15-membered tri-olefinic triazamacrocycles on PPH dendrimers was carried out in different ways, one of them consisting in the grafting of a diamine on the $P(S)Cl_2$ terminal functions from generations 1 to 4. This reaction creates a five-membered non-symmetrical heterocycle on each terminal function (Scheme 7), suitable for complexing $Pt_2(dba)_3$. Instead of discrete complexes, platinum nanoparticles were generated in very mild conditions [50], which organized as unprecedented branched supramolecular assemblies of dendrimers and coalesced Pt nanoparticles. Both the size and the degree of branching vary with the generation of the dendrimer, with the G_4 dendrimer producing longer networks than smaller dendrimers [51]. These 15-membered macrocycles were also condensed onto the aldehyde terminal functions of dendrimers, followed by reduction of the imine, and affording palladium complexes or palladium nanoparticles, suitable for catalyzing Heck reactions [52]. Analogous compounds bearing long alkyl chains on the aryl groups of the sulfonamides displayed columnar liquid crystal properties [53].

Besides these examples as catalysts, all of the other bifunctional PPH dendrimers synthesized by grafting bifunctional derivatives were synthesized for biological purposes. A series of dendrimers having labile hydrogen atoms (carboxylic acid or phosphonic acid terminal functions) were used for electrostatic interactions with galactosylceramide analogs, potentially suitable against HIV [54]. Within this series, several compounds having a pendant alkyl chain were synthesized, especially in the case of phosphonic acids as terminal groups (Scheme 8). They were synthesized by grafting the bifunctional phenols based on tyramine onto the $P(S)Cl_2$ terminal functions. These compounds alone were

found non-toxic, but displayed interesting anti-HIV properties in vitro in the 10^{-5}–10^{-6} M range [55]. The galactosyl ceramide analogues were associated with all of these dendrimers in a second step, and were found efficient, but also toxic, inducing a low safety index [56]. Investigations about the stability of the self-associations demonstrated a partial segregation of the different partners, which could explain the cytotoxicity [57]. The use of a fluorescent analog of galactosylceramide, having a coumarine derivative in replacement of the alkyl chain, confirmed the ion pair disassembly hypothesis [58].



Scheme 6. Modification of the surface of a first generation PPH dendrimer for enabling the alkylation of the quinuclidinic N atom of several types of (+)-cinchonine, used as organocatalysts.

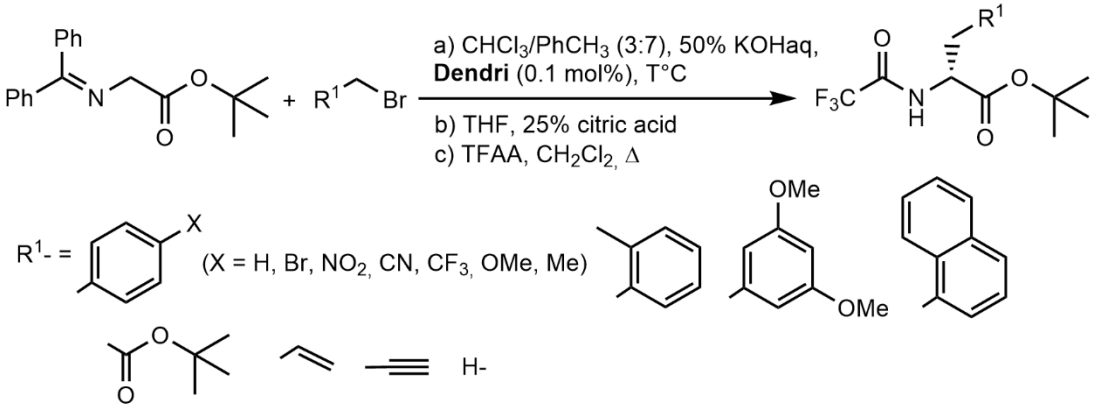
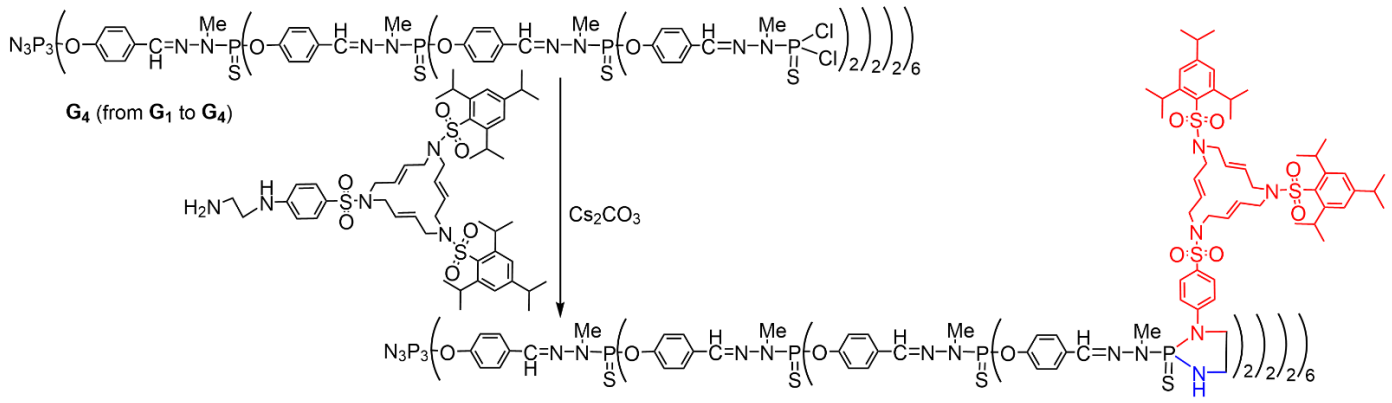
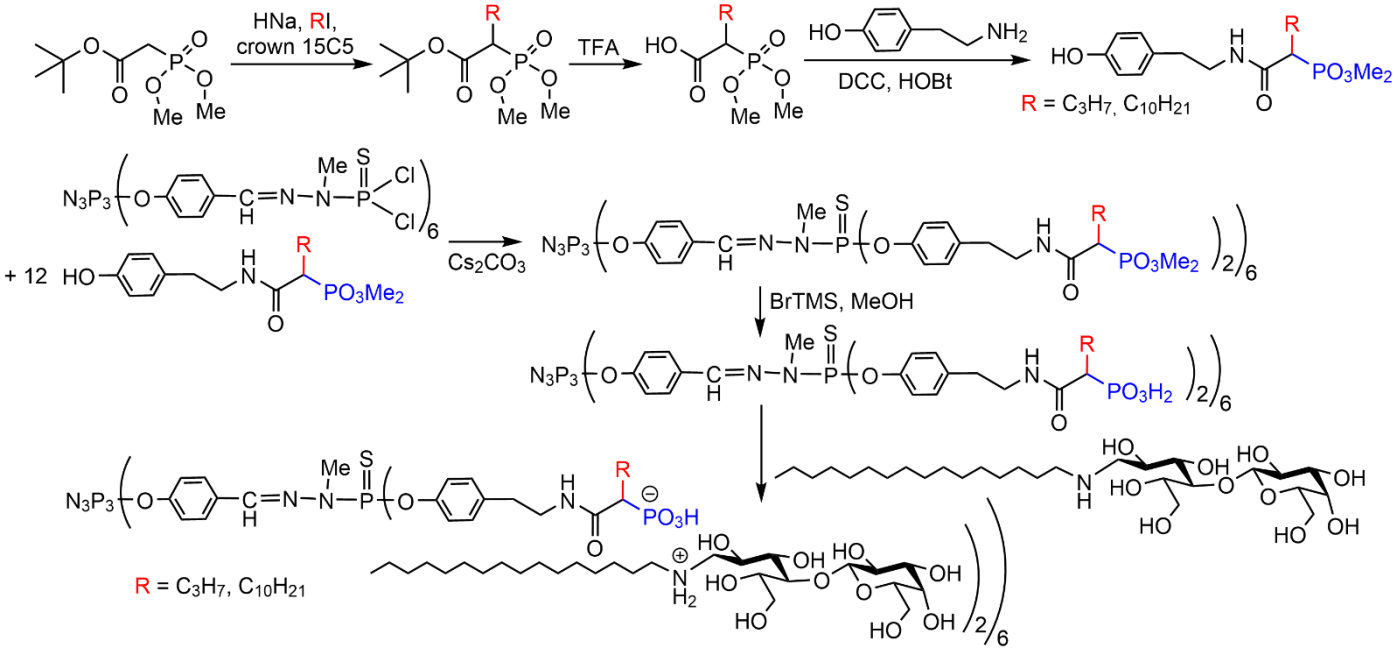


Figure 6. Asymmetric alkylation of a glycinate Schiff base with different types of bromides, in particular benzylbromide derivatives, organocatalyzed with the dendrimer functionalized with (+)-cinchonine, as shown in Scheme 6.



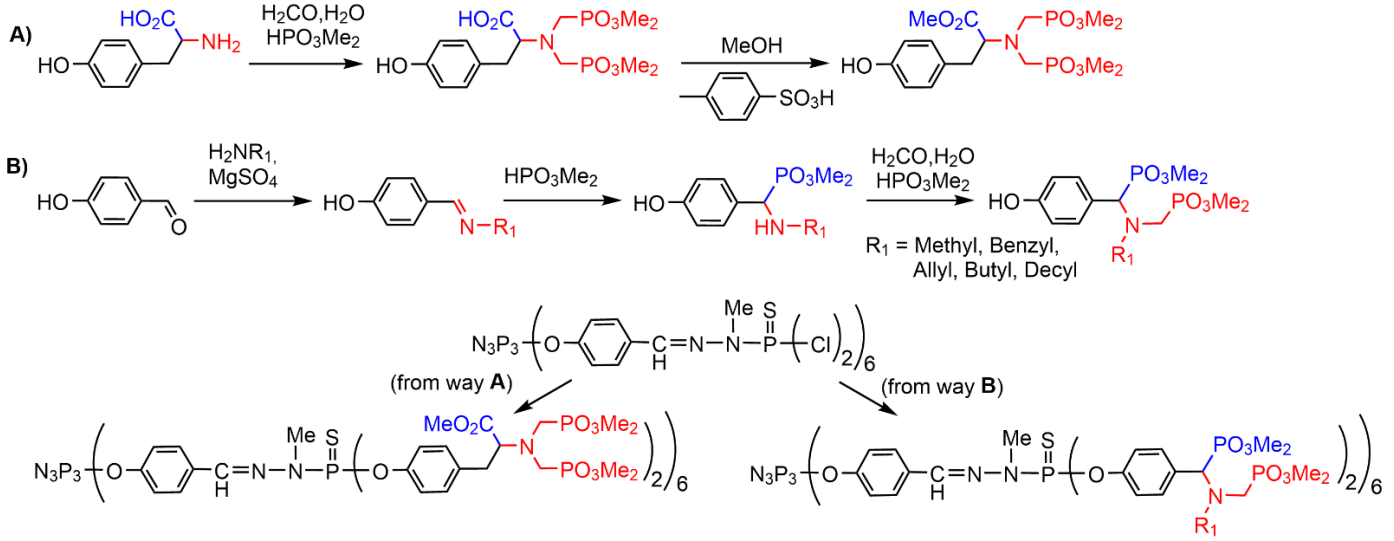
Scheme 7. Grafting of 15-membered macrocycles, suitable for creating branched supramolecular assemblies of Pt nanoparticles.



Scheme 8. Synthesis of phosphonate dendrimers bearing a pendant alkyl chain and a phosphonic acid, and their association with a derivative of galactosylceramide, having anti-HIV properties.

Other types of phosphonate terminal functions were obtained by synthesizing the appropriate phenol derivatives. (D-L) tyrosine was first reacted with formaldehyde and dimethylphosphite, then the carboxylic acid was protected with a methyl group, to be suitable to react with the $P(S)Cl_2$ surface functions of dendrimers, mostly of first generation (Scheme 9A). These dendrimers bearing azabisphosphonate terminal functions were then tested among others to activate human monocytes through an anti-inflammatory pathway [29,59], but also to multiply natural killer (NK) cells, which play in particular a key role against cancers [60]. These first properties then led to cure inflammation in mice models of rheumatoid arthritis [61], of multiple sclerosis [62], of Uveitis [63], and of psoriasis [64]. In view of all of these biological properties, a large study to decipher the structure/activity relationship has been carried out [65]. The synthesis of non-symmetrical azabisphosphonate terminal functions was carried out for this purpose. It started from 4-hydroxybenzaldehyde, to which diverse primary amines were condensed in the first step. Addition of dimethylphosphite induced the grafting of one phosphonate. A reaction with formaldehyde and dimethylphosphite induced the grafting of the second phosphonate, affording a series of non-symmetric azabisphosphonate monomers (Scheme 9B), also grafted to the 1st generation dendrimer. The primary amines used were, for the first time,

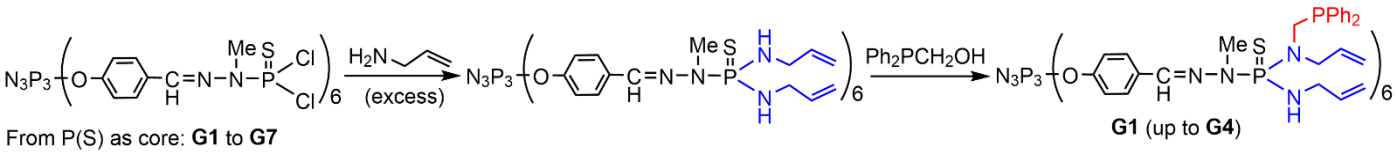
methylamine and benzylamine [29,60], then allyl, butyl, and decyl amines [66]. All of these compounds were tested, but they were found less efficient than the symmetrical azabisphosphonate functions for the anti-inflammatory activation of monocytes.



Scheme 9. Synthesis of bifunctional phenols from tyrosine (way **A**) and from 4-hydroxybenzaldehyde (way **B**), and structure of 1st generation of PPH dendrimers modified with them. The anti-inflammatory properties of these dendrimers were then tested.

3. Modification of a Function Already on the Surface of PPH Dendrimers

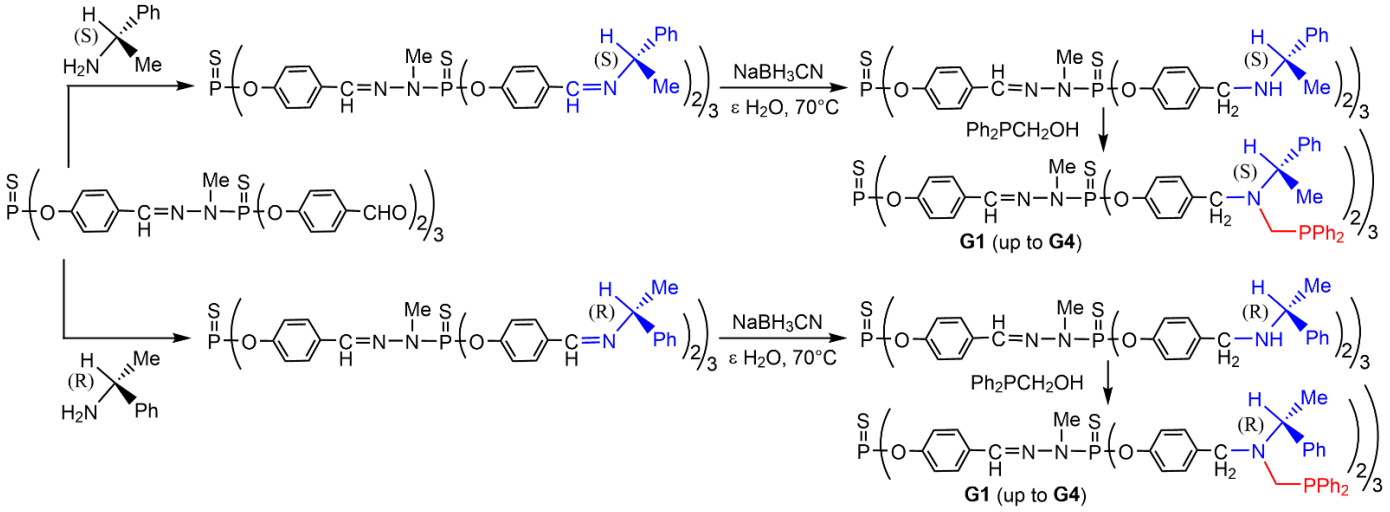
The generation of secondary amines induced by the grafting of functional groups on the surface of PPH dendrimers was the only way to obtain bifunctionalized dendrimers by a second modification after a first modification (related to way B of Scheme 1). In a first example, the reaction of Ph_2PCH_2OH, obtained from the reaction of diphenylphosphine with paraformaldehyde occurred on one among two allylamines previously grafted to the $P(S)Cl_2$ terminal functions of the dendrimers (Scheme 10). Such specific reaction was carried out from generation 1 to generation 7 of the PPH dendrimers built from a trifunctional core, and from generation 1 to generation 4 of the PPH dendrimers built from the hexafunctional N_3P_3 core. The phosphines were used for the complexation of either $Fe(CO)_4$ or $W(CO)_5$ [67].



Scheme 10. Grafting of diphenylphosphine as the second functional group to PPH dendrimers.

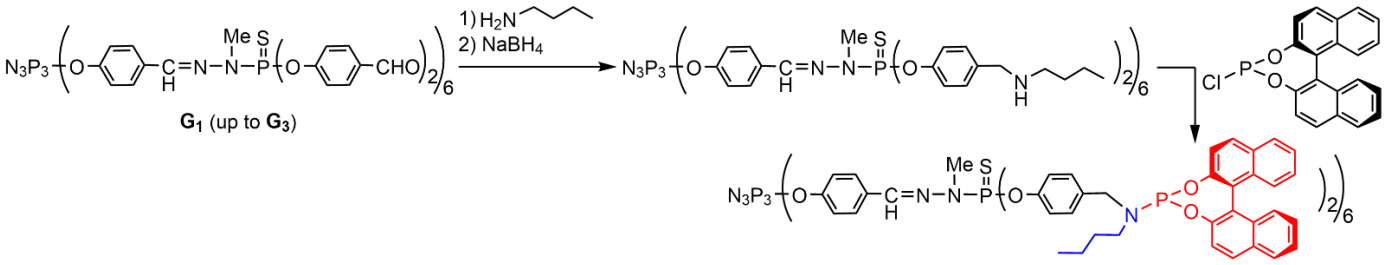
An easy way to get secondary amines as terminal functions consists in the condensation of a primary amine on the aldehyde terminal functions of the dendrimers, followed by the reduction of the imine, to generate a secondary amine. It must be noted that this reduction occurs only on the imine functions on the surface, and not on the hydrazone linkages constituting the internal structure of the PPH dendrimers. Such reaction was carried out first with (*S*)-(–)-α-methylbenzylamine and (*R*)-(+)-α-methylbenzylamine (both separated enantiomers), followed by the reduction of the imine bonds with $NaBH_3CN$. In that case, the reaction of diphenylphosphine and paraformaldehyde occurred on all of the NH groups on the surface of the dendrimer (Scheme 11), contrarily to the example shown in Scheme 10. The reactions were carried out on generations 1 to 4, built from a trifunctional core. Study of the chiroptical properties of all of these families of chiral dendrimers allowed to demonstrate for the first time that the value of the molar specific

rotation of dendrimers with stereogenic end groups linearly increased with the increase of the number of stereogenic groups [68].



Scheme 11. Two-step method for the grafting of two terminal groups from aldehydes.

This process was applied for the grafting of a phosphoramidite ligand. In the first step, butylamine was condensed onto the aldehydes, followed by the reduction of imines with $NaBH_4$. The last step was the reaction of the secondary amine with the chlorophosphite derived from (S)-BINOL. The synthesis was carried out on the first, second and third generations of PPH dendrimers (Scheme 12). Complexation with rhodium provided dendrimers suitable for catalyzing [2+2+2] cycloaddition reactions (Figure 7). All dendrimers afforded the highest yields (up to 99%) and the highest enantioselectivities (up to 98%), whereas the corresponding monomer afforded poor yields (maximum 49%), with a very poor enantioselectivity (<5%) [38].



Scheme 12. Grafting of an aminophosphoramidite ligand on the surface of PPH dendrimers. The Rh complexes efficiently catalyzed [2+2+2] cycloadditions.

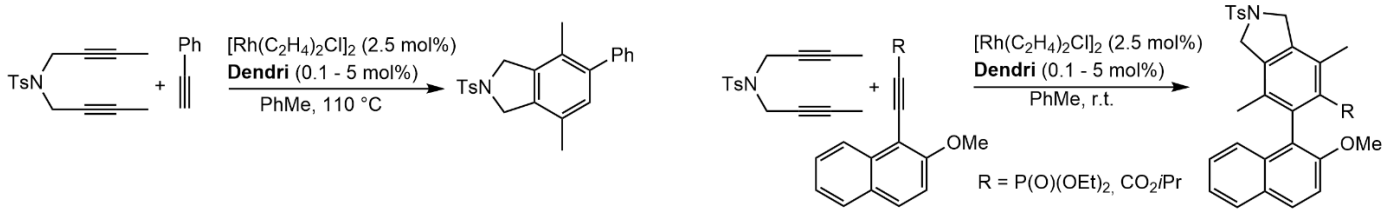
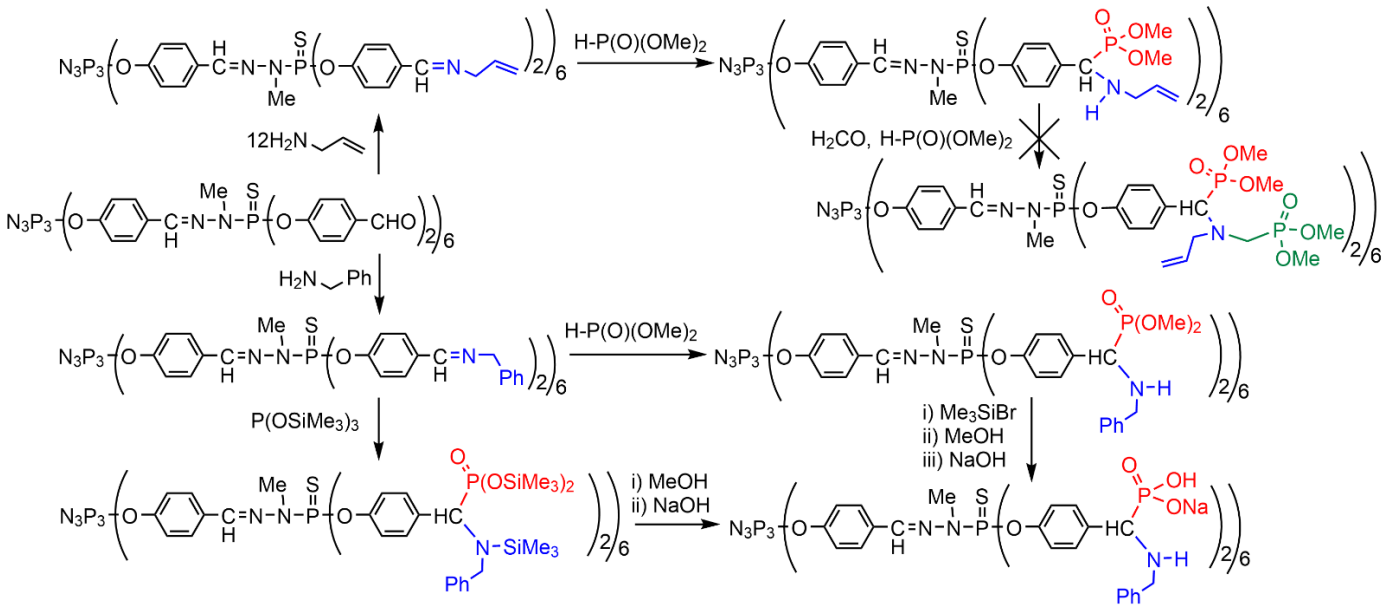


Figure 7. [2+2+2] cycloaddition reactions catalyzed by the Rh complex of the dendrimers shown in Scheme 12.

Related two-step processes were applied in particular to the 1st generation dendrimers ended with aldehyde groups, to afford phosphonate terminal functions, using different primary amines in the first step. This work is related to the one shown in Scheme 9 concerning the synthesis of dendrimers having anti-inflammatory properties. In the first

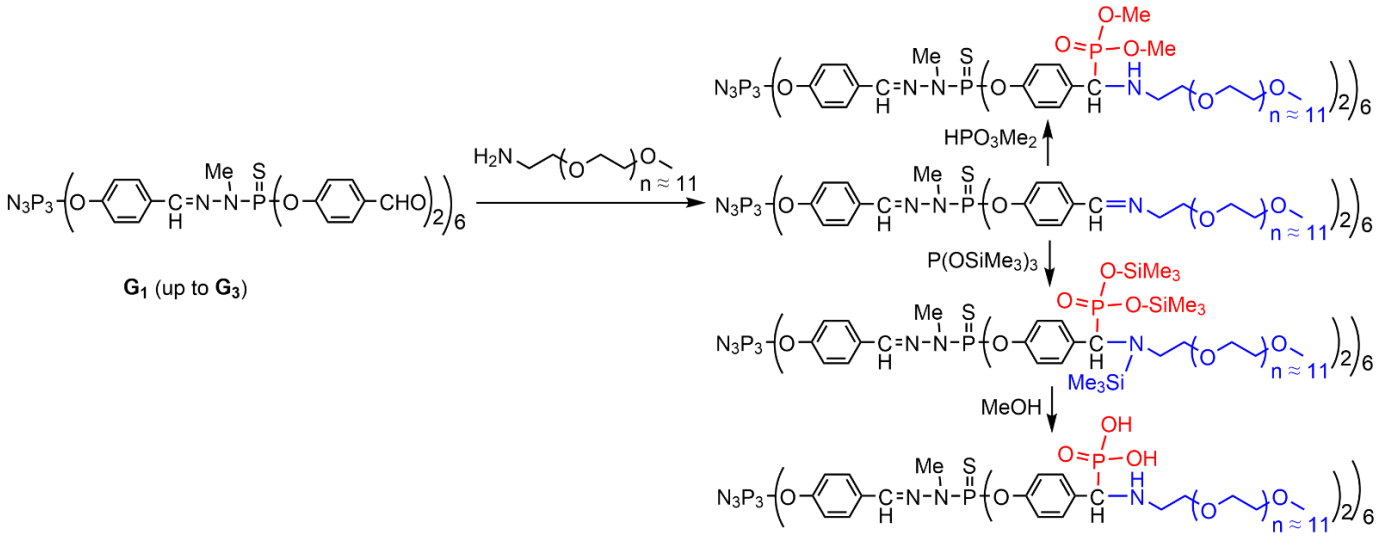
example, condensation with allylamine was followed by the addition of dimethylphosphonate ($HP(O)(OMe)_2$) onto the imine bonds. Such a reaction induced the presence of a phosphonate and a secondary amine on each terminal function. Attempts to graft another phosphonate on the N-H function failed (Scheme 13), whereas such reaction was possible on the corresponding monomer (as already shown in Scheme 9) [66]. A similar reaction was carried out with benzylamine. In this case also, it was not possible to react the secondary amine, but the phosphonate could be transformed into phosphonic acid sodium salt. The same bifunctional dendrimer was also obtained in another way, by adding $P(OSiMe_3)_3$ on the imine (Scheme 13) [60]. However, all of these non-symmetrical compounds were found poorly or non-active for the activation of monocytes.



Scheme 13. Two-step processes from aldehydes, affording phosphonate and secondary amines as terminal functions of PPH dendrimers. They display poor anti-inflammatory properties.

An analogous strategy, involving the formation of imino-PEG terminated dendrimers, which were subsequently hydrophosphorylated led to a series of amino-PEG-phosphonate-terminated PPH dendrimers from $\mathbf{G_1}$ to $\mathbf{G_3}$, using two different ways (Scheme 14). Theoretical and experimental size measurements revealed an efficient surface capping with PEG chains. A favorable effect of PEG-capping on cytotoxic properties was also evidenced [69]. An analogous work was carried out with PPH dendrimers grafted to silica nanoparticles. These materials were suitable for hosting Ag and Ag_2O nanoparticles (Figure 8). The resulting composites exhibited antibacterial activity [70].

The addition of dimethylphosphonate ($HP(O)(OMe)_2$) was also carried out directly on aldehyde terminal functions, instead of on imines, on generations 2 to 4 of PPH dendrimers. An alcohol and a phosphonate were directly generated, the latter can be converted to a phosphonic acid salt, as shown in Scheme 15. These dendrimers, reacted with titanium tetraisopropoxide, $Ti(OiPr)_4$, enabled its controlled mineralization. A new family of hierarchically porous dendrimer-bridged titanium dioxide materials was obtained in this way [71]. Further studies demonstrated that the dendritic medium provided at low temperature, discrete anatase nanocrystals (4.8 to 5.2 nm in size), whereas amorphous titanium dioxide phase is generally obtained in standard conditions. Furthermore, upon thermal treatment, the ring opening polymerization of the cyclophosphazene core prevented, up to 800 °C, the commonly observed anatase-to-rutile phase transformation [72].



Scheme 14. Two different routes for the synthesis of a series of α-amino-PEG-phosphonate-terminated PPH dendrimers, having very low cytotoxicity.

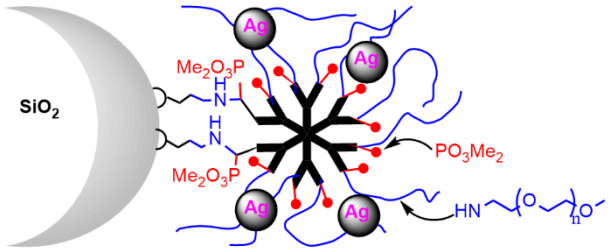
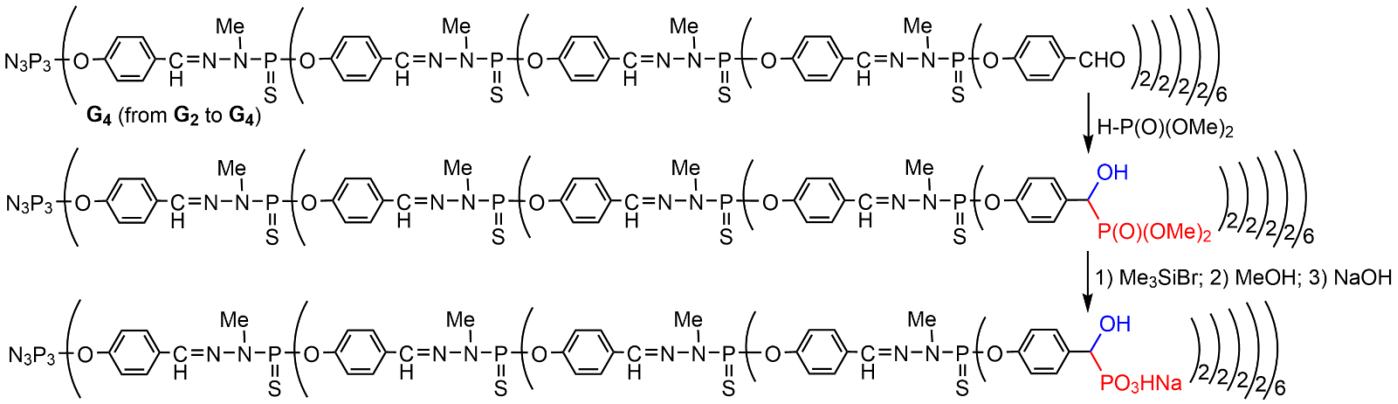


Figure 8. Dendrimers linked to SiO_2 NPs and hosting Ag/Ag_2O NPs exhibiting antibacterial activity.

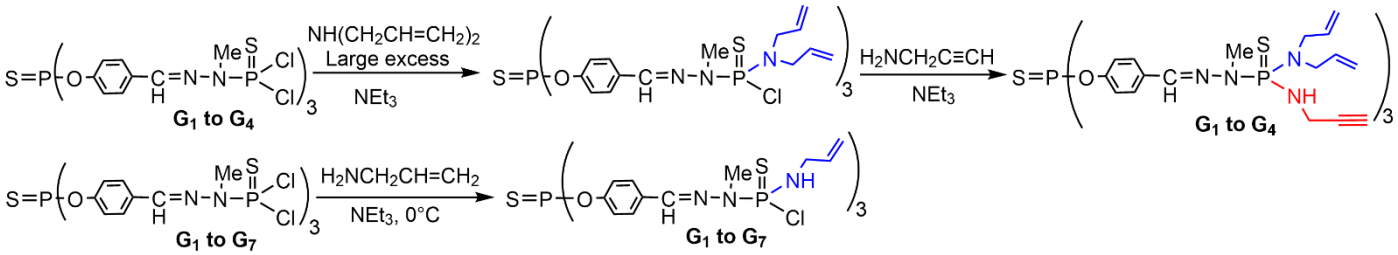


Scheme 15. Direct addition of H-P(O)$(OMe)_2$ on aldehyde terminal functions. These dendrimers efficiently controlled the mineralization of Ti$(OiPr)_4$.

4. Sequential Grafting of a First, then a Second Function on the Surface of PPH Dendrimers

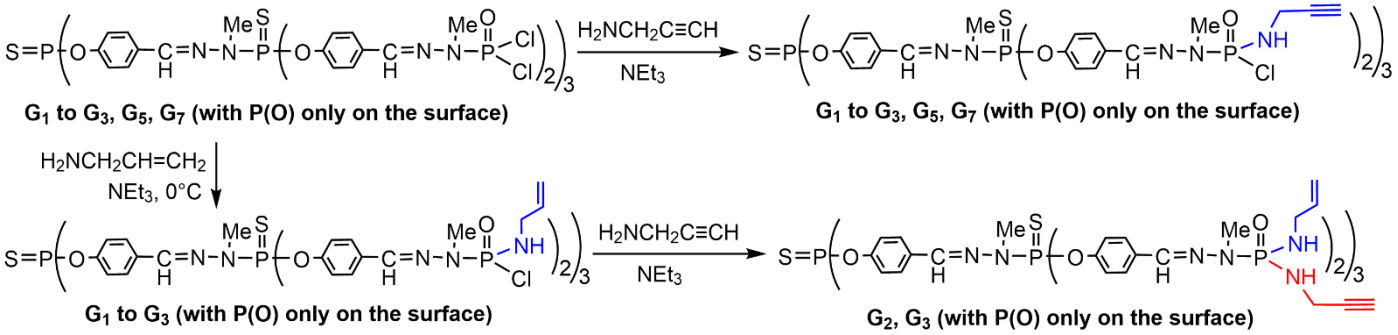
As indicated in the introduction, sequential grafting on the surface of dendrimers, as shown in Scheme 1C, is very rare, and has been carried out only and recently with triazine dendrimers [24,25]. On the contrary, such a type of reaction is carried out since a long time with polyphosphorhydrazone dendrimers, thanks to the specific reactivity of the P(S)Cl_2 terminal functions. The possibility of such sequential reaction was discovered first with secondary amines. Indeed, only one Cl of each P(S)Cl_2 terminal functions was able to react with diallylamine (even when used excessively). However, the remaining Cl was able to react with primary amines, such as propargylamine (Scheme 16). This sequential reaction is

not limited to secondary amines. Indeed, depending on the conditions used (temperature and quantity of amine), it is possible to react only one allylamine on each $P(S)Cl_2$ terminal function. Some reactions were carried out up to the seventh generation [73].



Scheme 16. Sequential addition of two different amines on the surface of PPH dendrimers.

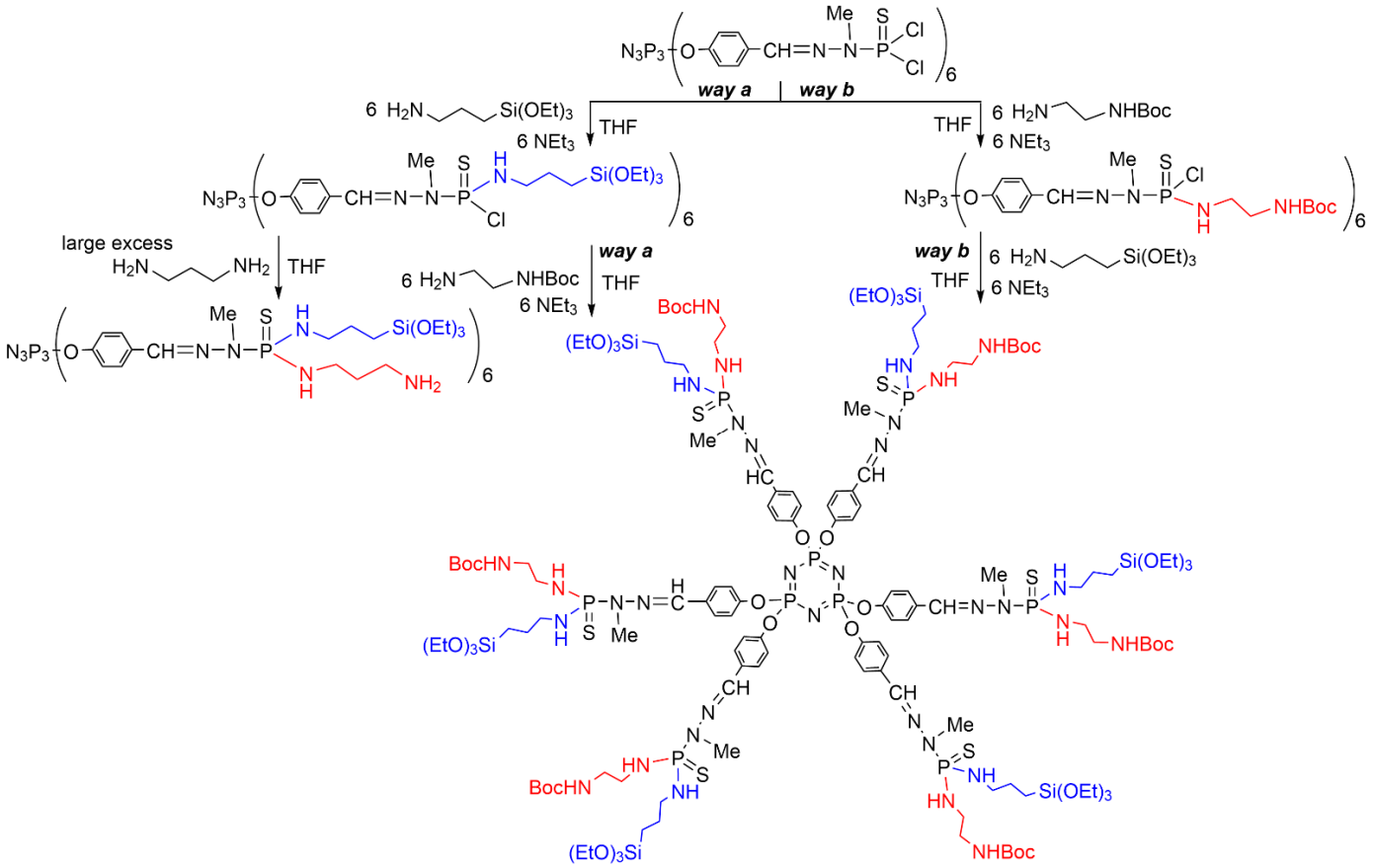
In some cases, the surface functions are $P(O)Cl_2$ instead of $P(S)Cl_2$, but they display the same specific reactivity. In particular, one propargylamine or one allylamine could be grafted on each $P(O)Cl_2$ function. As in the previous case, the second reaction can be carried out with propargylamine when allylamine was already grafted (Scheme 17) [73].



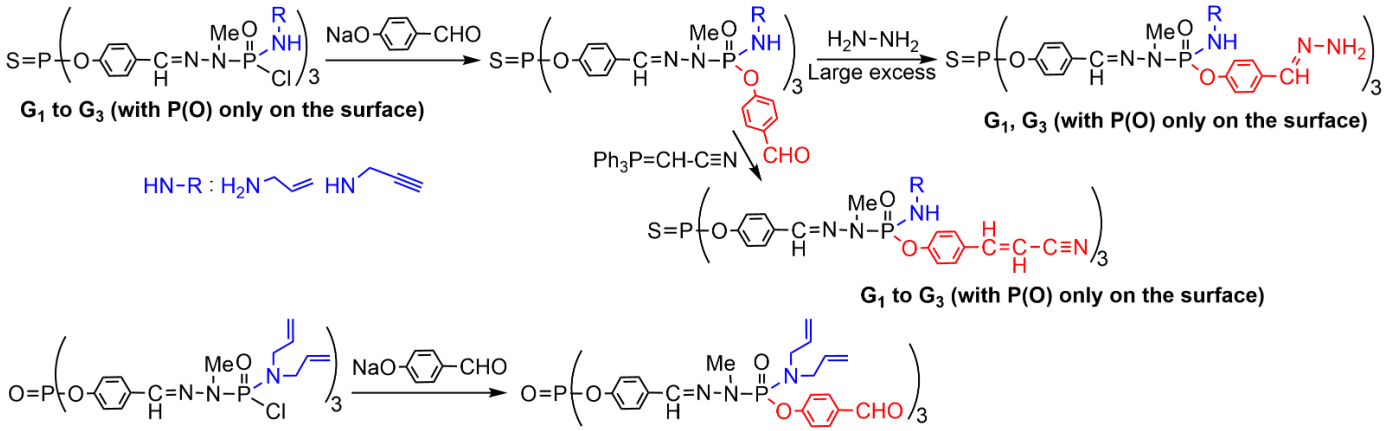
Scheme 17. Sequential addition of two different amines on the surface of polyphosphorhydrazone dendrimers having $P(O)Cl_2$ terminal functions.

The same type of reaction was carried out more recently to obtain compounds bearing both a triethoxysilane and a primary amine. Boc-monoprotected ethylene diamine as the amino part, and 3-(triethoxysilyl) propylamine as the silyl part were chosen. The first step was the grafting of one of the two amines (way a or way b, Scheme 18), followed by the grafting of the other amine in the second step, affording the same compound in both cases. Besides, a large excess of 1,3-diaminopropane can be used as the second amine, to directly afford a free amine as terminal function (Scheme 18) [74]. These compounds were tested among other dendritic structures possessing both types of functions for the grafting to silica, followed by attempts for trapping CO_2, after deprotection of the Boc-protected amine, to form a carbamate. These compounds having both types of functions on the surface were not the most efficient. Indeed, dendrons possessing a single triethoxysilyl group at the core and several primary amines on the surface were found to be more efficient [75].

Besides the grafting of two amines, it is also possible to graft both an amine and a phenol. Such type of reaction was carried out up to now only on $P(O)Cl_2$ terminal functions. After the grafting of either allyl amine or propargylamine, the second step was the grafting of 4-hydroxybenzaldehyde, in basic conditions. The aldehydes were then used for the condensation with hydrazine in large excess, or for Wittig reactions with the ylide $Ph_3P{=}CH{-}C{\equiv}N$ (Scheme 19) [73]. Hydroxybenzaldehyde could react also when bulky diallylamine was grafted in the first step [76].

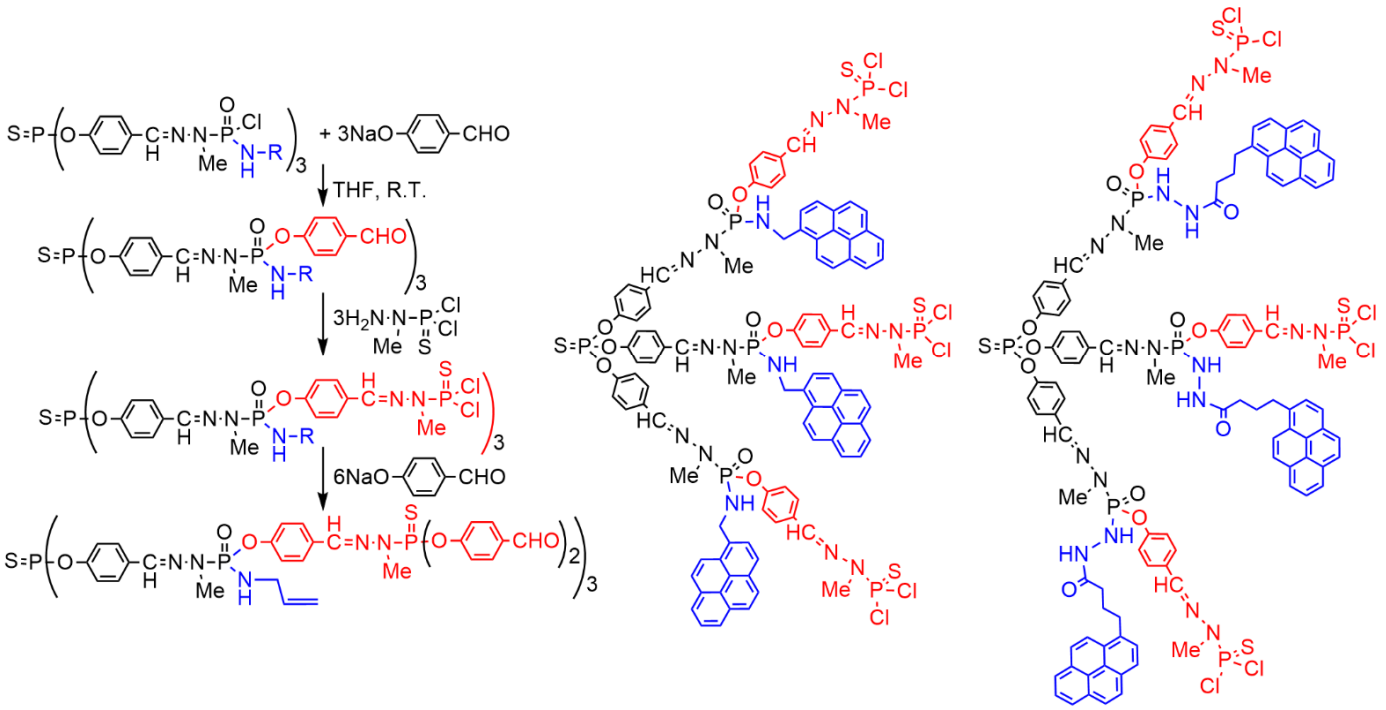


Scheme 18. Other examples of sequential addition of two different amines on PPH dendrimers, to be grafted to silica, and used for trapping CO_2.



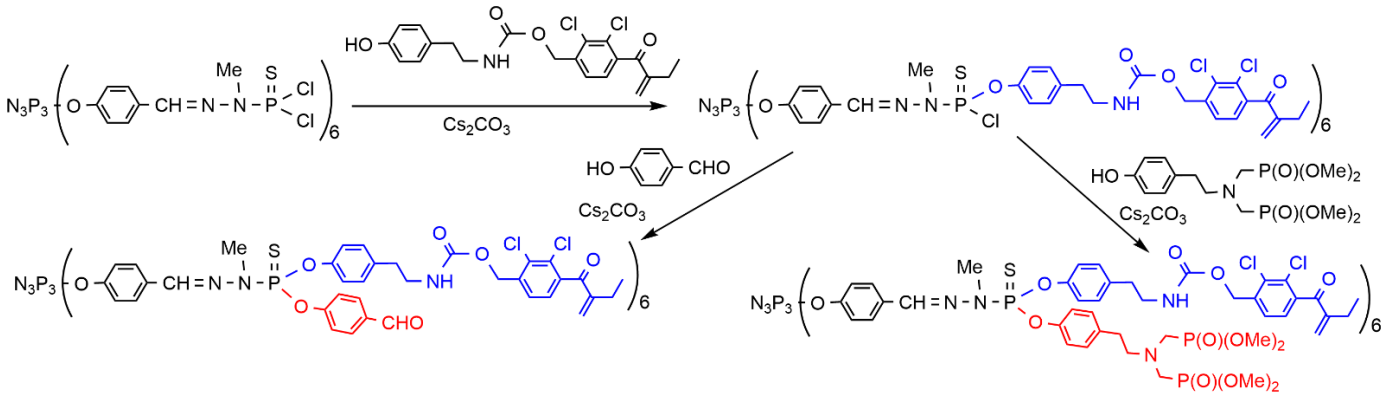
Scheme 19. Sequential addition of an amine and of 4-hydroxybenzaldehyde on the surface of PPH dendrimers.

The presence of the aldehydes as shown in Scheme 19 enabled the continuation of the synthesis of dendrimers having pendant internal functions inside the structure. These pendant groups were either an allylamine, or 1-aminomethylpyrene, or 1-pyrenebutanoic hydrazide. The aldehydes were reacted with $H_2NNMeP(S)Cl_2$, as in the classical synthesis of PPH dendrimers (Scheme 20) [77].



Scheme 20. Amino derivatives of allyl or pyrene as pendant functions inside polyphosphorhydrazone dendrimers.

Besides the sequential use of two amines, or of an amine and a phenol shown in the previous Schemes, the sequential use of two phenols was also attempted on the surface of polyphosphorhydrazone dendrimers. The reaction is less clean than with amines, as it is difficult to avoid a small percentage (less than 5%) of either homodisubstitution, or unreacted $P(S)Cl_2$. The grafting of a phenol derivative of ethacrynic acid, followed by the grafting of either 4-hydroxybenzaldehyde or the phenol of the azabisphosphonate were carried out (Scheme 21). Ethacrynic acid grafted on the entire surface of phosphorhydrazone dendrimers was shown to display strong anti-proliferative activities against both liquid and solid tumors [78]. However, these unsymmetrical compounds were not tested [79].



Scheme 21. Grafting of a phenol derivative of ethacrynic acid and other phenols on the surface of PPH dendrimers having anticancer properties.

5. Conclusions

The specific bifunctionalization on the surface of dendrimers is still an ongoing challenge. Among the three different ways that have been already proposed, the easiest and most widely used with all types of dendrimers is the grafting of a monomer possessing already both desired functions. The other two methods (i.e., the modification of a first function by a second one, and the sequential grafting of the first and then the second func-

tion) have been rarely used on dendrimers in general, but relatively more frequently with polyphosphorhydrazone dendrimers than with other types of dendrimers. For example, the condensation of primary amines with the aldehyde terminal functions affords imines, which can be either reduced, for further reactivity on the NH, or directly reacted with compounds such as phosphonates or $P(OSiMe_3)_3$. The sequential grafting of two functions on $P(X)Cl_2$ (X = S, O) terminal functions was carried out essentially with two different amines, but also in some cases with an amine and a phenol, or with two different phenols. Besides the pioneering works with polyphosphorhydrazone dendrimers which were carried out for purely fundamental researches, the presence of two different functions was also used for catalysis, for materials, and for biological purposes. Despite being challenging, the specific presence of two functions on the surface of dendrimers offers new opportunities for the future, in particular for increasing the solubility in specific media such as water and for dendrimers having catalytic or biological properties. In this regard, efforts should be engaged to develop efficient new strategies leading to sophisticated and highly controlled multifunctional dendrimeric architectures.

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Conflicts of Interest: Cédric-Olivier Turrin is co-founder and CEO of IMD-Pharma. Anne-Marie Caminade is a shareholder of IMD-Pharma.

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