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Alkyne-functionalized phosphorus dendrimers and dendrons: Syntheses and properties

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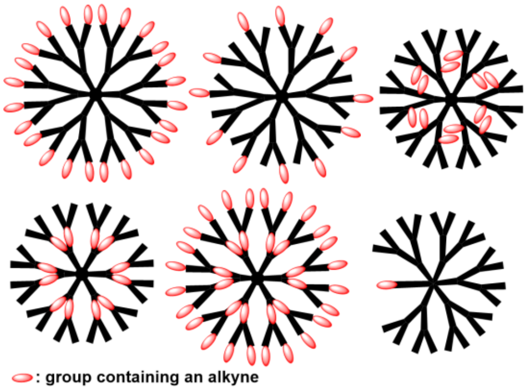
Abstract

Phosphorus-containing dendrimers and dendrons are highly-tunable, hyper-branched macromolecules, displaying numerous properties depending on their functionalization. Alkyne-functionalized phosphorus dendrimers and dendrons represent powerful platforms for precision macromolecular engineering. This review summarizes the functionalization of such macromolecules with alkynes, either on the surface, within the internal structure or at the core. Different uses of such functionalities have been proposed, in particular for click reactions with copper (CuAAC, copper-catalyzed azide-alkyne cycloaddition) or even without copper (SPAAC, strain-promoted azide-alkyne cycloadditions). Some of these alkyne-functionalized or alkyne-reacted dendritic structures displayed properties for two-photon-absorption (TPA)-induced fluorescence, for bio-imaging, including *in vivo*, for photodynamic therapy (PDT), for the functionalization of materials such as graphene-oxide, and for treating orphan diseases and inflammations.



Keywords: Dendrimer, dendron, alkyne, click reaction

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1. Introduction

Dendrimers are highly branched macromolecules, synthesized step-by-step to ensure a perfect radial structure.[1] Each time the number of terminal functions increases, a new generation is created. Among the different types of dendrimers,[2] phosphorus-containing dendrimers and dendrons are two unique classes of hyper-branched macromolecules,[3,4] characterized by their well-defined architecture, high functionality, and tunable properties.[5] Figure 1 displays the chemical structure of a dendrimer built from a trifunctional core (A),[6] which has been synthesized up to generation 12,[7] and from a hexa-functional core (B),[8] which has been synthesized up to generation 8.[9] These phosphorus dendrimers have either P(S)Cl_2 or aldehyde terminal functions, depending on the step considered during the synthesis. The resulting phosphorhydrazone linkage (CH=NN(Me)P) is iconic for this super-family of dendrimers, namely the poly(phosphorhydrazone) (PPH) dendrimers. Dendrimers can be represented both as a full structure, and in a linear form with parentheses after each branching level. Such linear forms will be used in most of Schemes and Figures in this review, as they are more convenient, especially for large compounds.

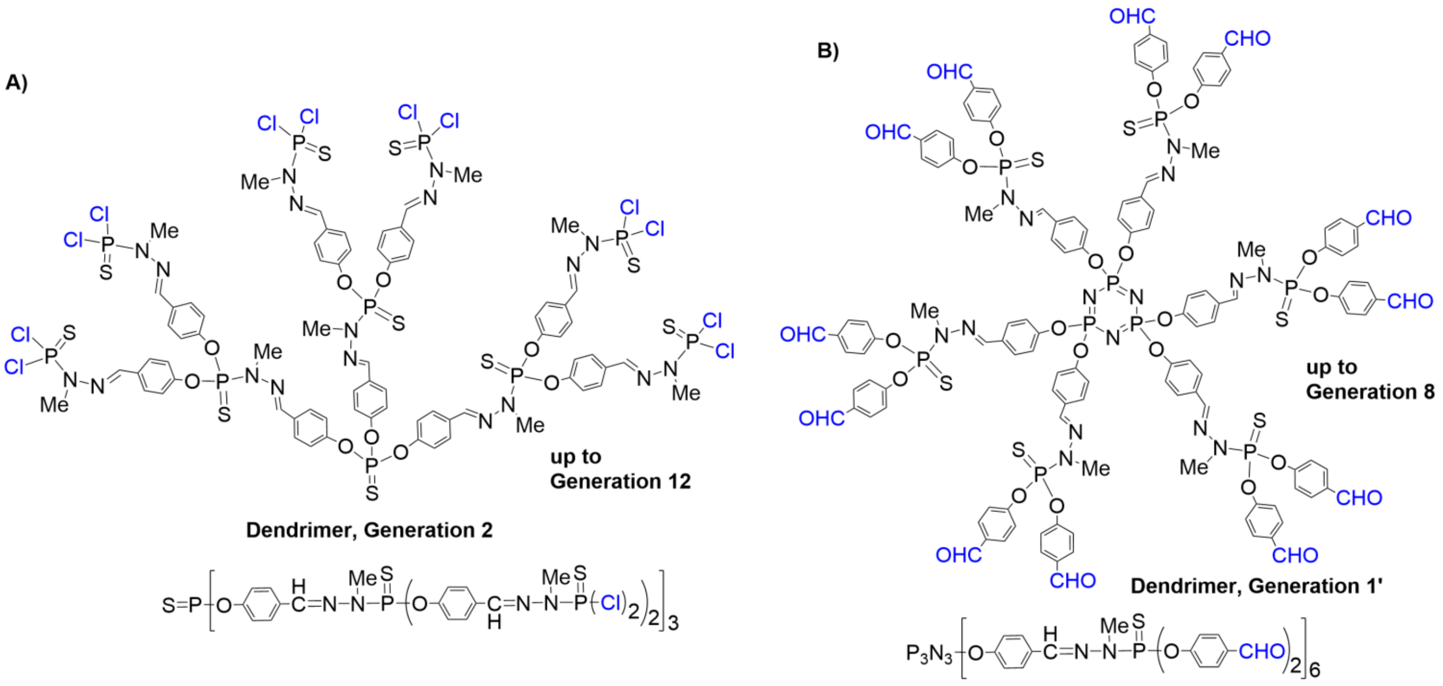

Figure 1. Full structure and linear representation of low-generations phosphorus-containing dendrimers.

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Figure 2A displays another type of dendritic structure, a dendron (dendritic wedge[10]), built from a trifunctional core,[11] whereas Figure 2B displays a dendron built from a hexa-functional core.[12] Dendrons can be drawn also both fully or in a linear form, as for dendrimers. The nature of the R group can be of different types, depending on the targeted properties.

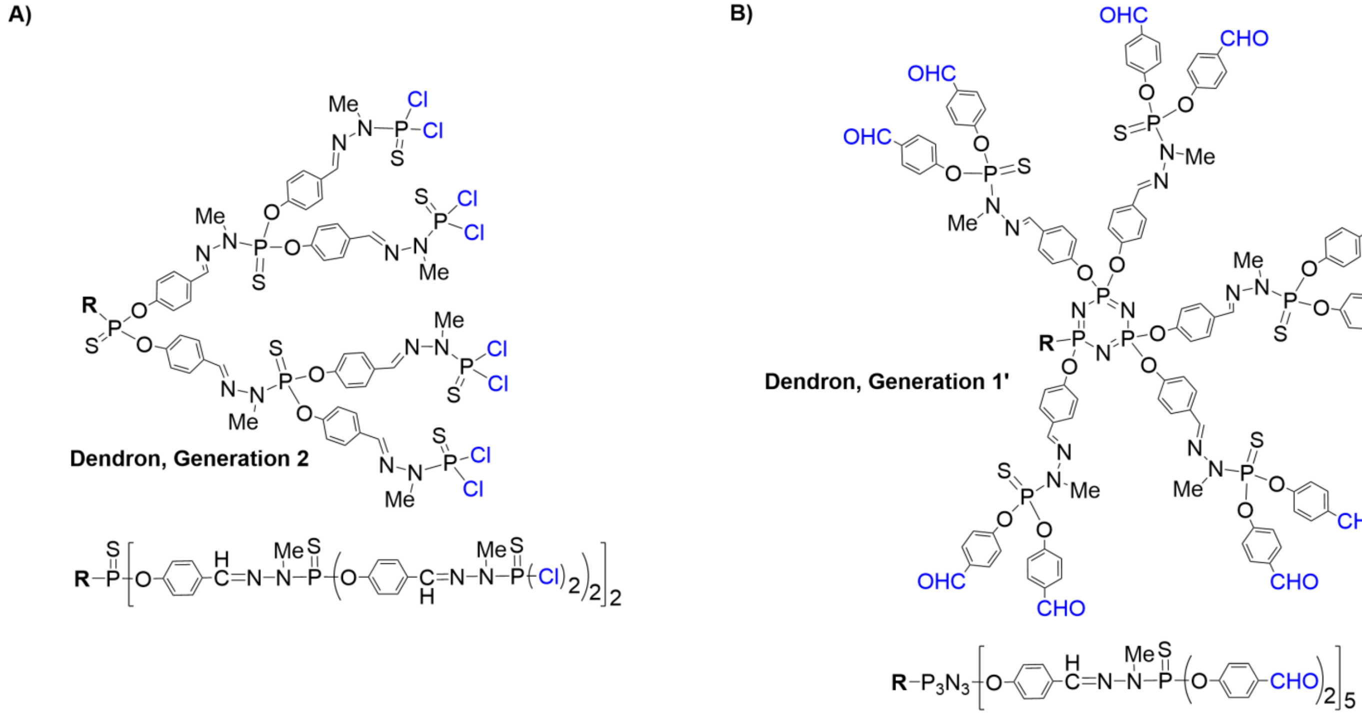


Figure 2. Full structure and linear representation of low-generations phosphorus-containing dendrons.

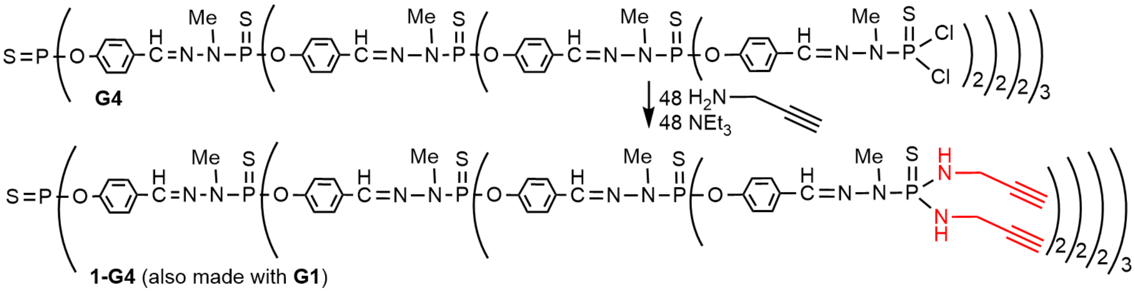
The introduction of alkyne groups —either at the periphery, within the dendritic scaffold, or at the core— expands the utility of phosphorus dendrimers and dendrons, enabling post-synthesis modifications, in particular via click chemistry[13] between the alkynes and diverse azides. Beyond the importance of alkynes for click chemistry, alkyne-containing natural and bio-inspired compounds display a wide range of biological properties.[14] For example, lipidic alkynylcarbinol derivatives, bio-inspired from either marine or terrestrial organisms, have been extensively studied for their remarkable anti-cancer[15] and anti-mycobacterial properties.[16]

This review will be organized depending on the location of the alkyne groups in the dendrimer structure. It will describe the synthesis and the properties which have been associated in some cases to these specifically-functionalized macromolecules, in particular in the fields of fluorescence, imaging, nanomaterials, and biology.

2. Alkynes on the Surface of Phosphorus Dendrimers

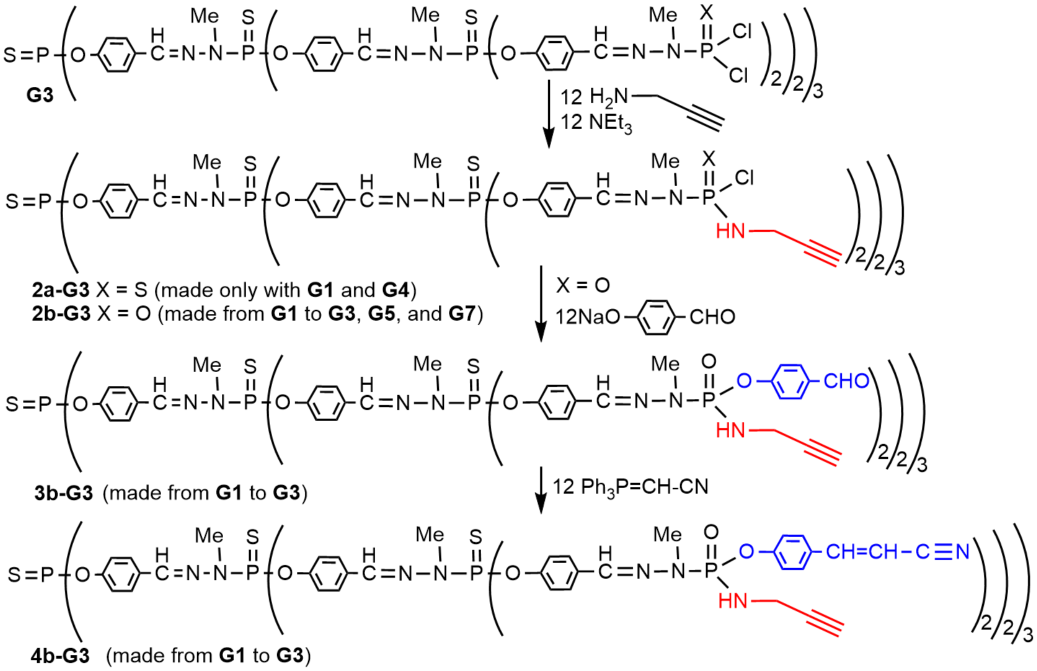
The very first examples of alkynes on the surface of phosphorus dendrimers of type poly(phosphorhydrazone) (PPH), concerned the reaction of propargyl amine on the $P(X)Cl_2$ (X = mainly S, rarely O) terminal functions of these dendrimers. The nucleophilic substitution of each Cl with propargylamine was carried out in the presence of triethylamine as a base on generations 1 and 4 of PPH dendrimers (Scheme 1). The reaction was monitored by ^{31}P NMR,[17] which displayed the disappearance of the signal at δ = 60.4 ppm for the $P(S)Cl_2$

peripheral functions and the appearance of a signal at δ = 67.5 ppm, corresponding to the fully disubstituted compound, as observed for dendrimer **1-G4** (Scheme 1).[18]



Scheme 1. First example of phosphorus dendrimers functionalized with alkynes.

During the course of this reaction, the presence of an intermediate signal could be observed by ^{31}P NMR at δ = ca 72 ppm, corresponding to the mono-substitution on the P(S)Cl$_2$ functions. Thus, it was attempted to prepare the dendrimers having both an amino propargyl group and a Cl on each peripheral phosphorus atom, dividing by two both the quantity of propargyl amine and of triethylamine. Such reactions were carried out with generations 1 and 4 of the dendrimers ended by P(S)Cl$_2$ groups, affording compounds **2a-G1** and **2a-G4** (Scheme 2). The same reaction was carried out with the dendrimers having P(O)Cl$_2$ groups on the upper layer, instead of the P(S)Cl$_2$ groups. The reactions occurred analogously, affording dendrimers **2b-G1** to **2b-G3**, **2b-G5** and even **2b-G7**. It was possible to substitute the remaining chlorine atoms by reaction with the sodium salt of hydroxy benzaldehyde to afford dendrimers from **3b-G1** to **3b-G3**. Furthermore, the aldehydes could be engaged in Wittig reactions, to afford dendrimers **4b-G1** to **4b-G3**.



Scheme 2. First examples of specific mono-substitution on the surface of phosphorus dendrimers, and reactivity.

Figure 3 displays the full structure of compound **4b-G3**.[19]

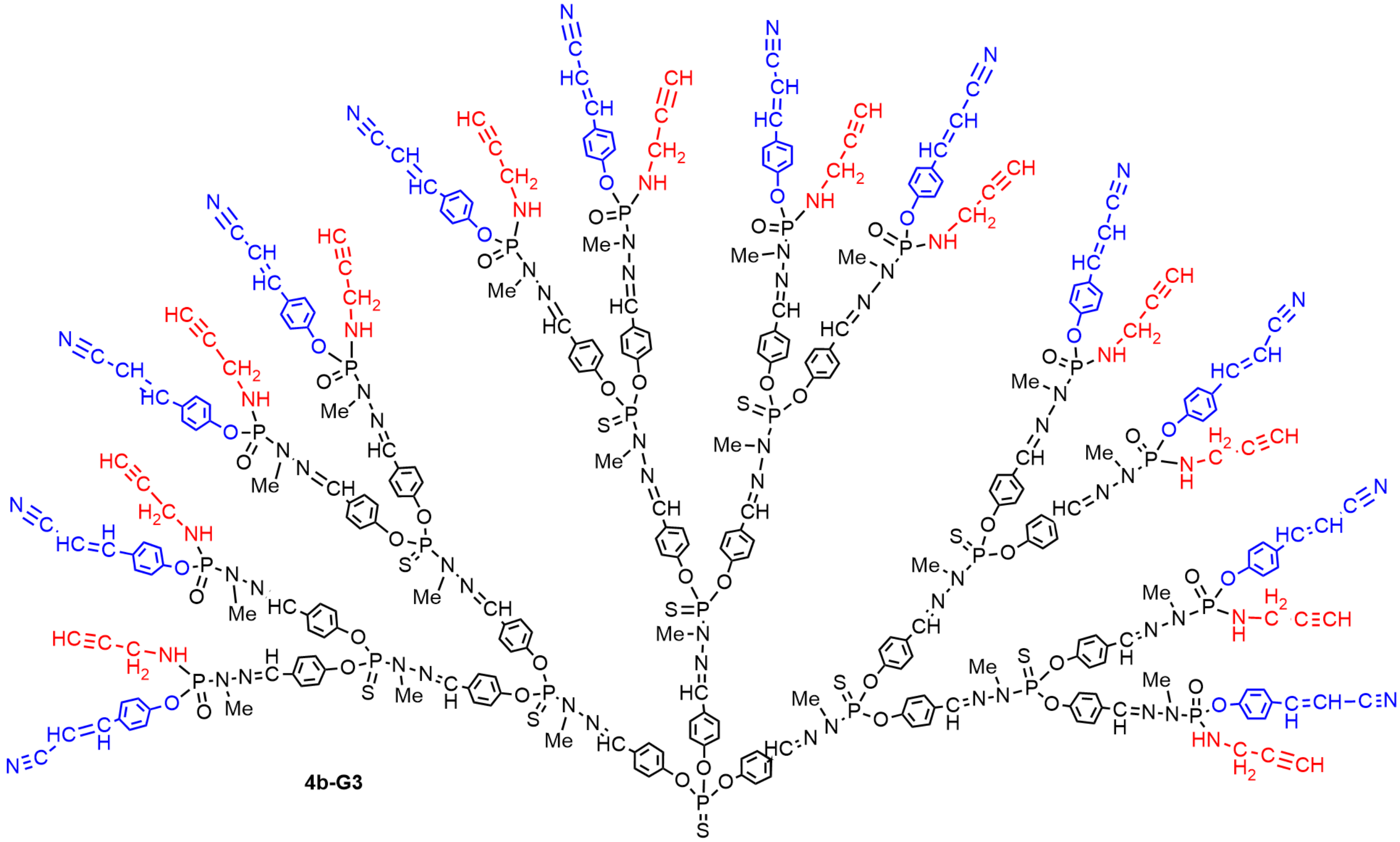
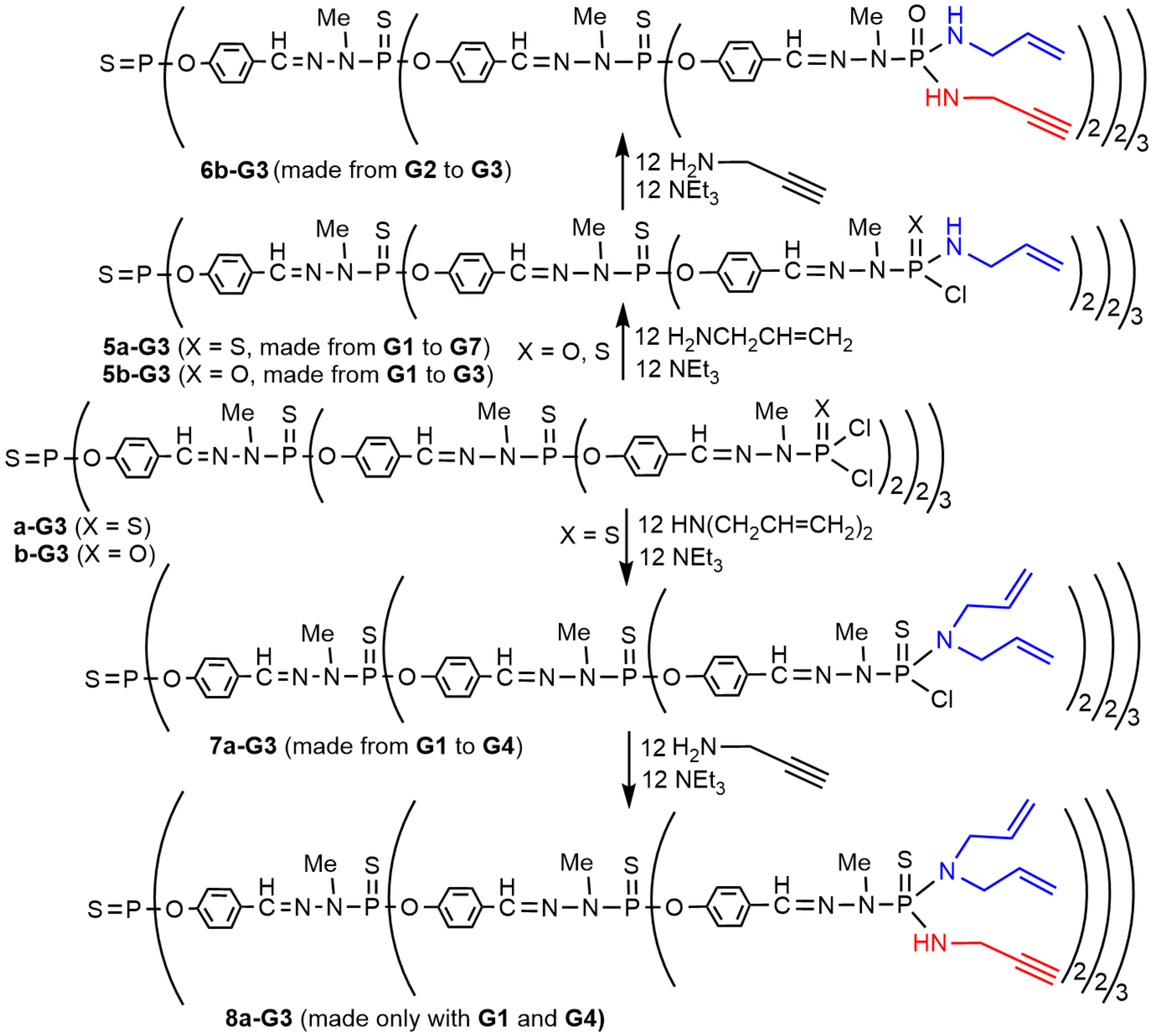


Figure 3. Full structure of dendrimer **4b-G3**.

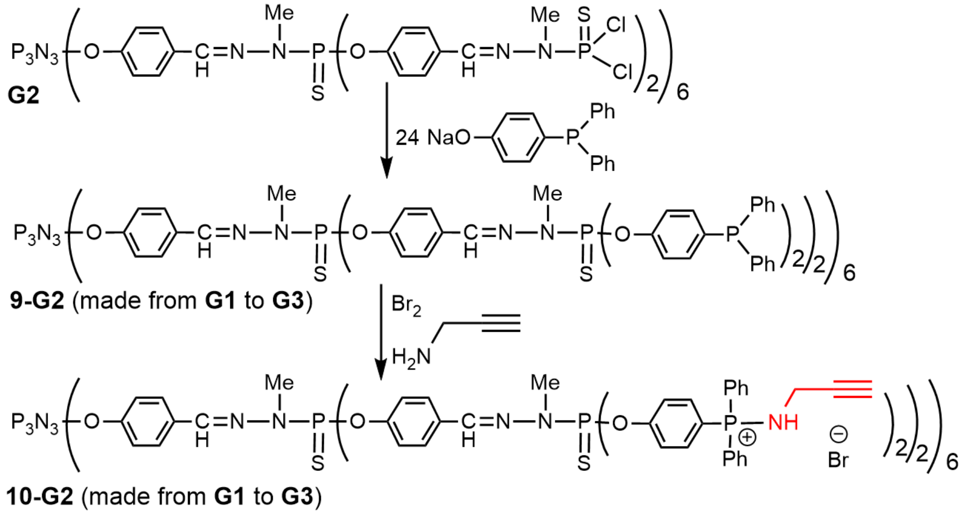
The same successive substitution process was applied to other amines. Allyl amine or diallyl amine were used in the first step, and then propargyl amine in the second step, as illustrated in Scheme 3. The reaction with allyl amine, leading to compounds **5a-Gn**, was carried out up to the seventh generation, and to the third generation for the **5b-Gn** series. Further reaction with propargyl amine was only carried out with the **b** series (P=O terminal groups), to afford compounds **6b-G2** and **6b-G3**. The first reaction with diallyl amine was carried out only with the **a** series (P=S terminal groups), affording compounds **7a-G1** to **7a-G4**. Reaction with propargyl amine was carried out with generations 1 and 4, affording compounds **8a-G1** and **8a-G4**, respectively.[19]



Scheme 3. Successive grafting of two different amines at the periphery of dendrimers.

It should be emphasized that such specific reactivity, i.e., allowing grafting of two different functions successively, is a unique property of phosphorus dendrimers.[20] It was shown recently, for the first time, that the precise grafting of two functions affords better results than random difunctionalization, at least concerning catalysis.[21]

Another method for grafting propargyl amine consisted first in the functionalization with phosphines to afford dendrimers **9-Gn** (**n** = 1, 2, and 3) (Scheme 4). Reaction with diverse amines, including propargyl amine, in the presence of Br_2, afforded the phosphoniums derivatives **10-Gn** (**n** = 1, 2, and 3). The reaction was monitored by ^{31}P NMR in particular, which displayed the disappearance of the signal corresponding to the phosphines at δ = ca –6 ppm, and the appearance of the signal corresponding to the phosphoniums at δ = ca 39 ppm.[22]

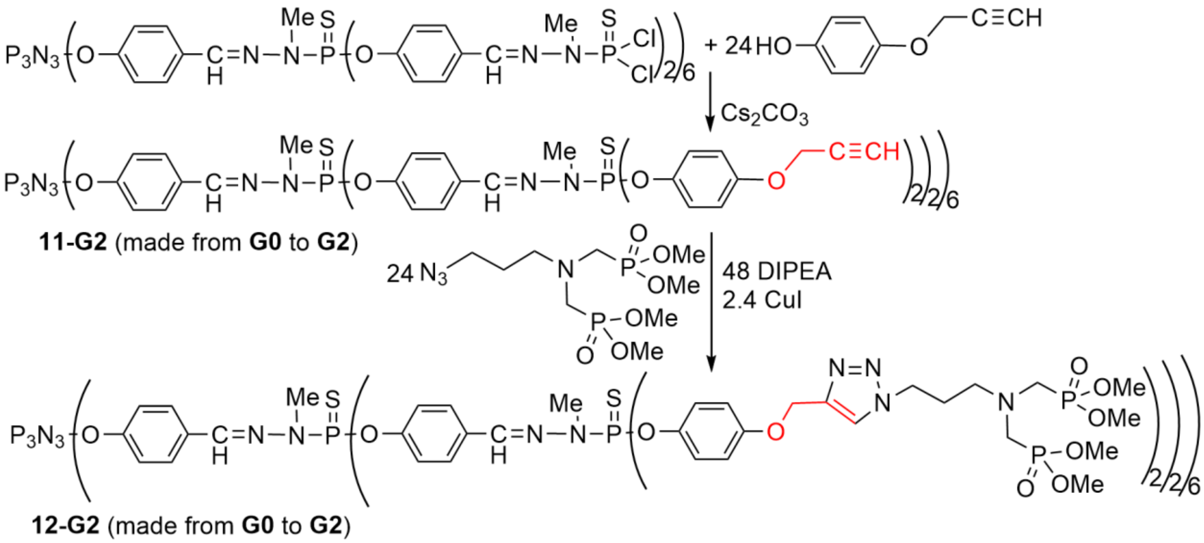

G2

9-G2 (made from **G1** to **G3**)

10-G2 (made from **G1** to **G3**)

Scheme 4. Two-step method for the grafting of propargyl amine on the surface of PPH dendrimers.

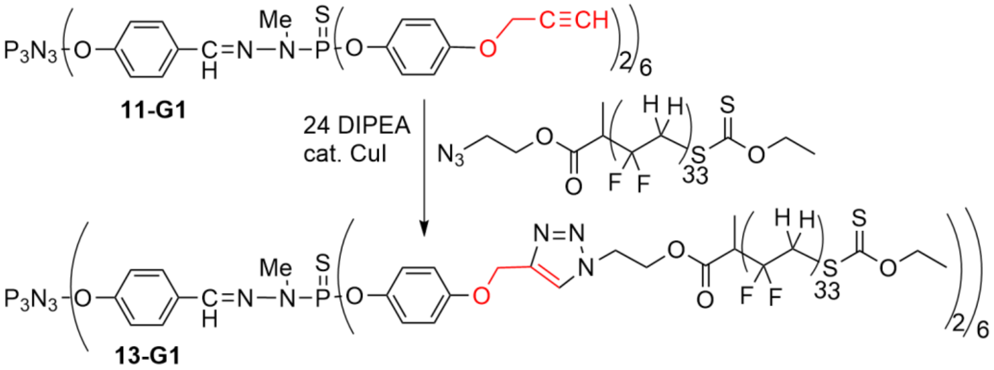
Substitution of the chlorine atoms of generations 0 to 2 dendrimers, by the 4-(prop-2-yn-1-yloxy) phenol, in the presence of Cs$_2$CO$_3$, also afforded alkyne terminal functions (compounds **11-Gn**, n = 0, 1, 2), as shown in Scheme 4. These dendrimers were then used for click reactions with azides, in the presence of DIPEA (diisopropylethylamine) and a catalytic amount of CuI, for copper-catalyzed azide-alkyne cycloaddition (CuAAC).[13] Such reactions produce triazole rings regioselectively, contrary to the original Huisgen reaction.[23] It was first carried out to graft azabisphosphonate terminal functions to afford the **12-Gn** family.[24] These azabisphosphonate functions were shown to display anti-inflammatory properties when grafted to the surface of generation 1 PPH dendrimers,[25] however, these properties were not tested with the family **12-Gn** (**n** = 0 to 2).


11-G2 (made from **G0** to **G2**)

12-G2 (made from **G0** to **G2**)

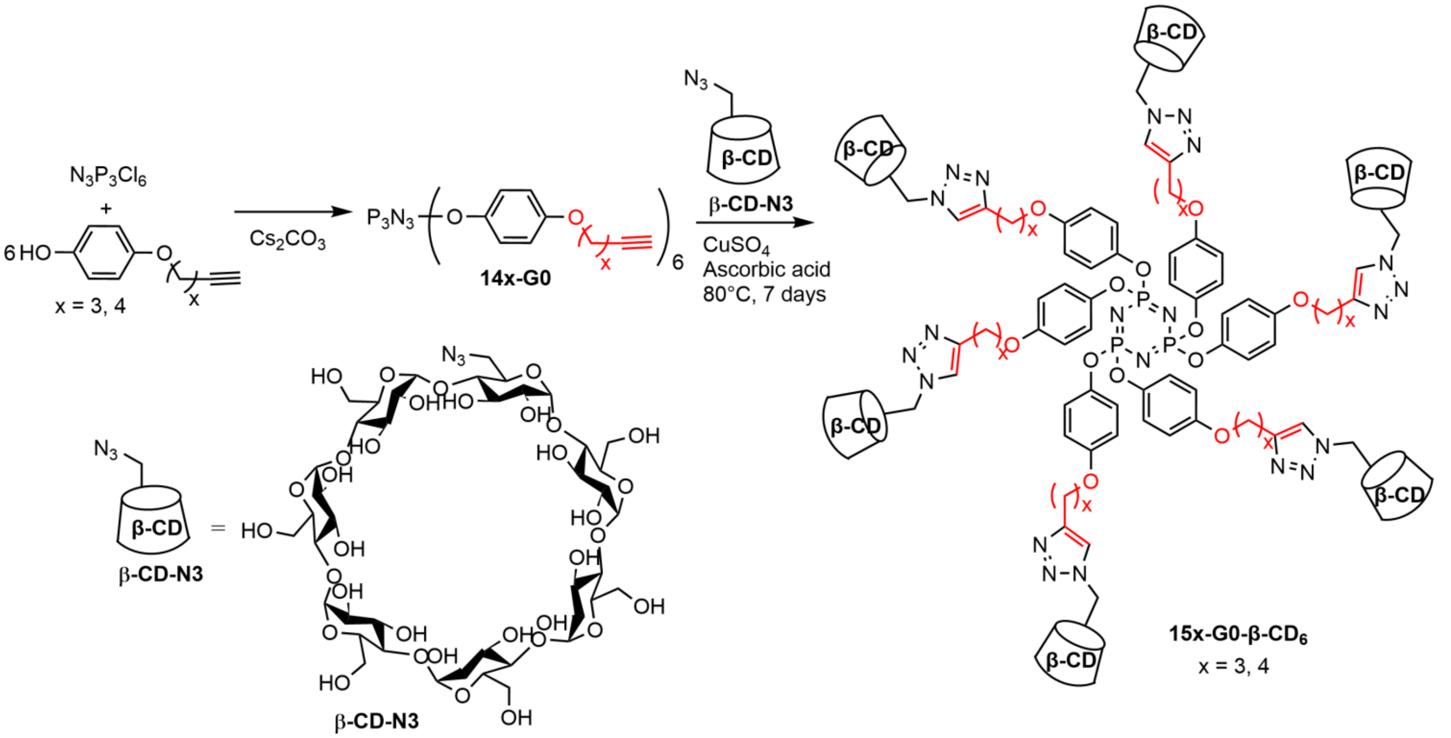
Scheme 5. Dendrimers functionalized with 4-(prop-2-yn-1-yloxy) phenol and used in click reactions.

An analogous process was carried out with the first generation **11-G1** and a polymer, poly(vinylidene fluoride) (PVDF),[26] synthesized by RAFT (Reversible Addition–Fragmentation Chain Transfer) polymerization, and functionalized with an azide at one end. Interestingly, the resulting polymeric dendrimer **13-G1** displayed crystallinity, as highlighted by high-resolution transmission-electron microscopy (HRTEM), with crystalline disc-like zones of ca. 5 nm. Furthermore, the dendritic polymer **13-G1** had a much higher hydrophobicity than its precursors, as shown by a water contact angle (WCA) reaching 108°.[27]



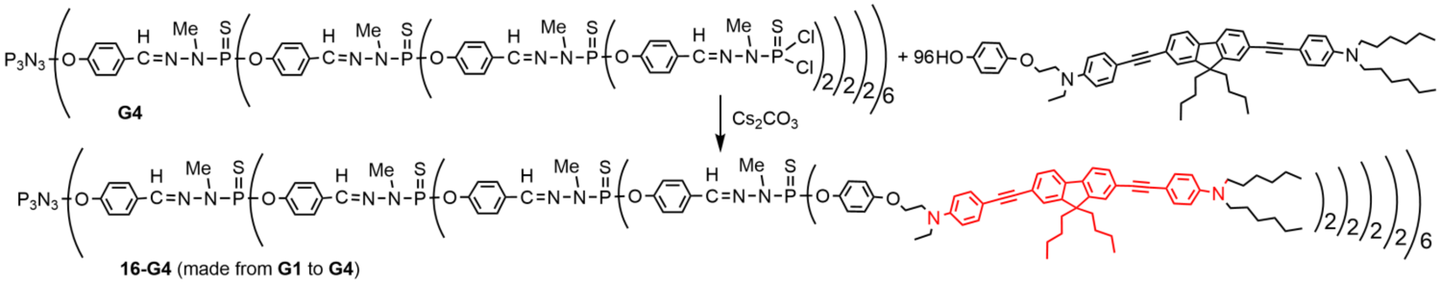
Scheme 6. Dendrimer functionalized with PVDF and linked by click reaction on its alkyne peripheral groups.

Longer linkers between the alkyne and the phenol (three or four CH_2 instead of one) were used to get small dendrimers functionalized with alkynes, compounds **14x-G0**. These longer linkers were necessary to decrease the crowding around the hexa-functional core when using very bulky azides such as the beta-cyclodextrin azide (β-CD-N3). The dendrimers functionalized with six β-CD, compound **15x-G0-β-CD₆**, were obtained by click reaction after heating for 7 days (Scheme 7). Interestingly, these compounds displayed a very high solubility in water, i.e., > 1 g/mL.[28]



Scheme 7. Highly water-soluble dendrimers functionalized with 6 β-cyclodextrins.

Other examples of alkyne derivatives on the surface of phosphorus dendrimers concerned fluorescent derivatives, specifically engineered to have two-photon absorption (TPA) properties.[29] Generations 1 to 4 of PPH dendrimers were functionalized with TPA fluorophores, synthesized in a three-step sequence starting from commercially available compounds. This fluorophore has two alkynes linked to a central fluorenyl core, and is functionalized on one side with a phenol, suitable to react with the $P(S)Cl_2$ terminal functions of dendrimers to afford compounds **16-Gn** (**n** = 1 to 4) (Scheme 8). The fluorescence quantum yield (Φ) decreased from 0.75 for **16-G1** to 0.48 for **16-G4**. On the contrary, the two-photon absorption cross-sections increased from 8880 GM for the first generation, to the very large value of 55,900 GM for the fourth generation **16-G4**,[30] comparable to that of metal quantum dots.[31]



Scheme 8. Alkyne-containing TPA fluorophores linked on the surface of dendrimers.

A series of dendrimers built from a fluorescent core were decorated on the surface by the fluorophore shown in Scheme 8. The central fluorophore was functionalized with two phenols, each of them being suitable to react with hexachlorocyclotriphosphazene, from which the classical synthesis of phosphorus dendrimers was carried out. The last step was the grafting of the alkyne-containing fluorophore on the surface, producing dumbbell-like compounds **17-Gn** (**n** = 0 to 2) (Figure 4). As observed in the previous case, the fluorescence quantum yield (Φ) decreased from 0.44 for **17-G0** to 0.26 for **17-G2**. Interactions between the central fluorophore and those on the surface were observed, and were proposed to explain the lower Φ values of the **17-Gn** series compared to the **16-Gn** series. However, the two-photon absorption cross-sections increased from 7100 GM (**17-G0**) to 32,800 GM (**17-G2**).[32]

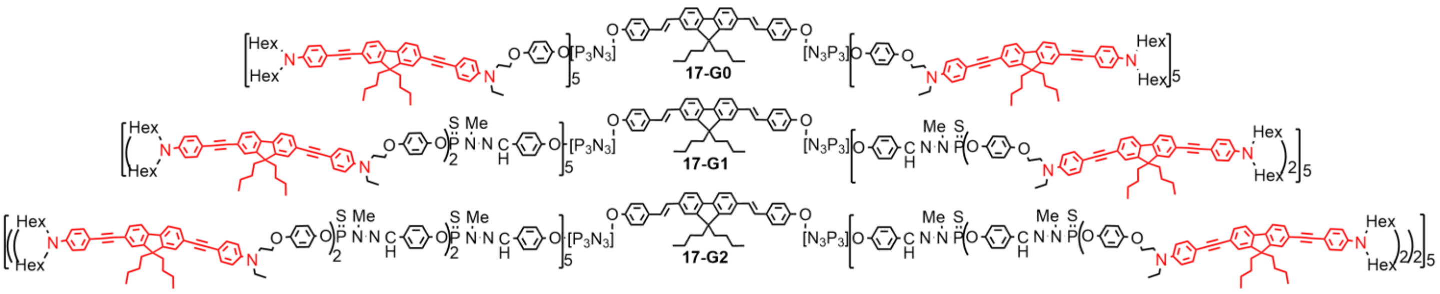
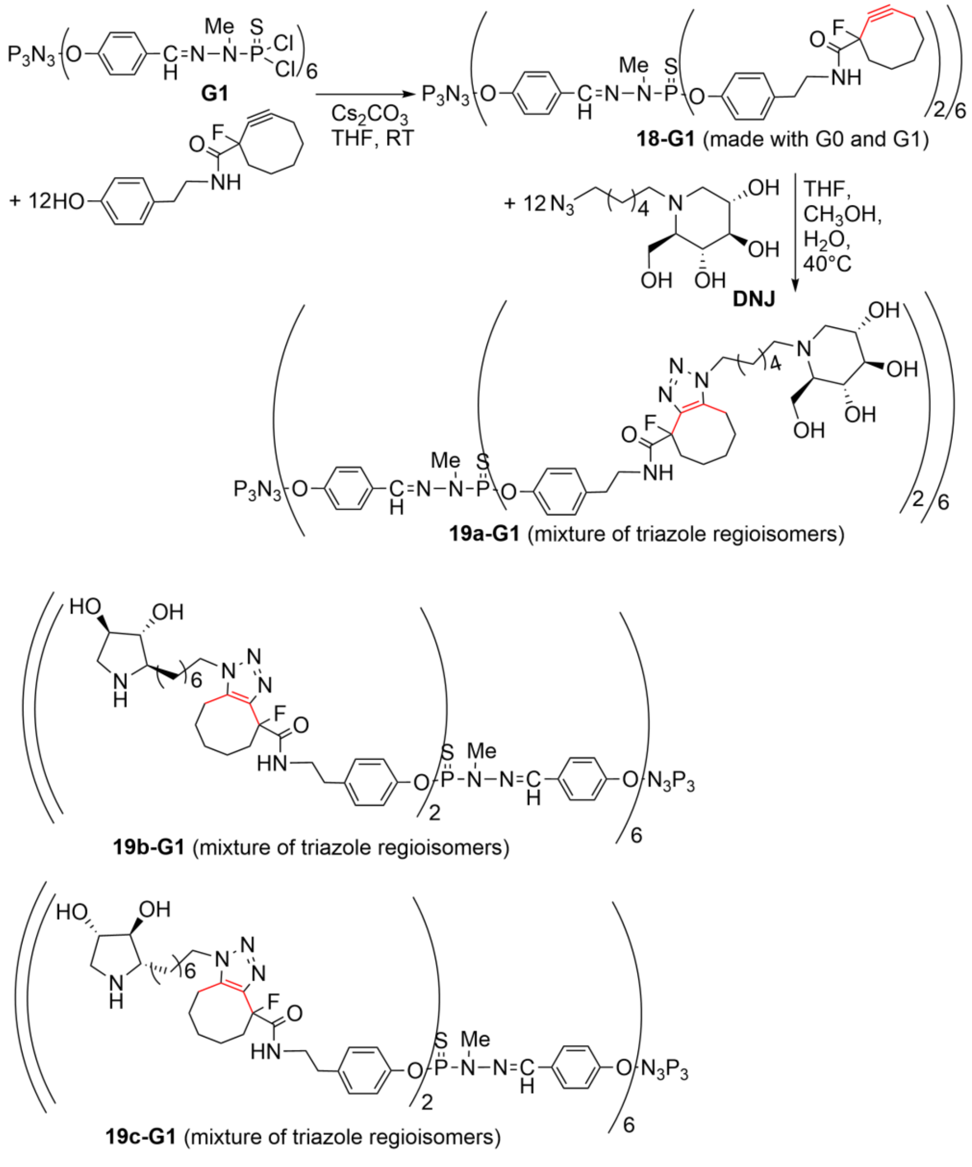


Figure 4. Dumbbell-like dendrimers built from a central fluorophore, and decorated with alkyne-containing fluorophores.

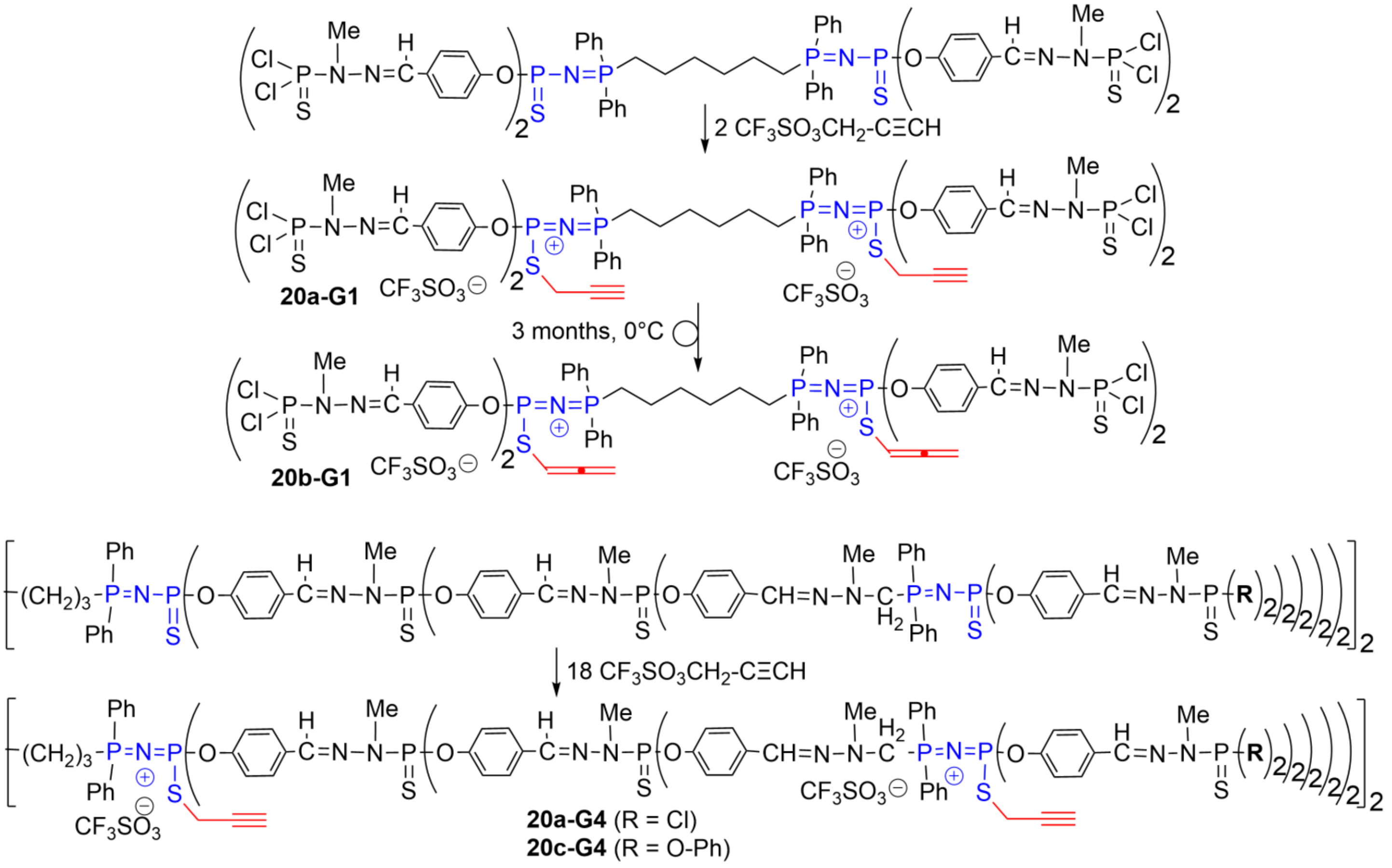
The most recent results regarding the grafting of alkynes on the surface of PPH dendrimers concerned a monofluorocyclooctyne derivative, usable for strain-promoted azide-alkyne cycloaddition (SPAAC),[33] that does not need copper to occur, contrary to classical click chemistry. This method avoids the cytotoxic effect of copper, which is a large drawback of the click chemistry for bio-related applications. Generations 0 and 1, functionalized, respectively, with 6 (**18-G0**) and 12 (**18-G1**) cyclooctyne derivatives, were then reacted with azido-functionalized peracetylated-*N*-hexyl-1-deoxynojirimycin (DNJ), affording dendrimers **19a-G0** and **19a-G1**, after deprotection, as a mixture of triazole regioisomers (Scheme 9). Both dendrimers were tested as multivalent inhibitors of β-glucocerebrosidase and acid α-glucosidase enzymes, involved in Gaucher (an orphan genetic disorder characterized by the accumulation of glucocerebroside in cells) and Pompe lysosomal-storage diseases, respectively, for which N-hexyl deoxynojirimycin is the reference treatment. Dendrimer **19a-G1** proved to be one of the best β-glucocerebrosidase inhibitors described. This dendrimer was able to cross the cell membrane, and to increase β-glucocerebrosidase activity in Gaucher cells.[34] A related synthesis was carried out starting also from **18-G1**, for SPAAC reaction with ω-azido C-alkyl pyrrolidines, leading to dendrimers **19b-G1** and **19c-G1**. The corresponding generations zero were also synthesized. The four compounds were evaluated as pharmacological chaperones in Gaucher patients' fibroblasts. An increase in β-glucocerebrosidase activity was measured at 1 µM and 0.1 µM for dendrimers of generations 0 and 1, respectively.[35]



Scheme 9. Monofluorocyclooctyne derivatives on the surface of dendrimers, and their use for SPAAC.

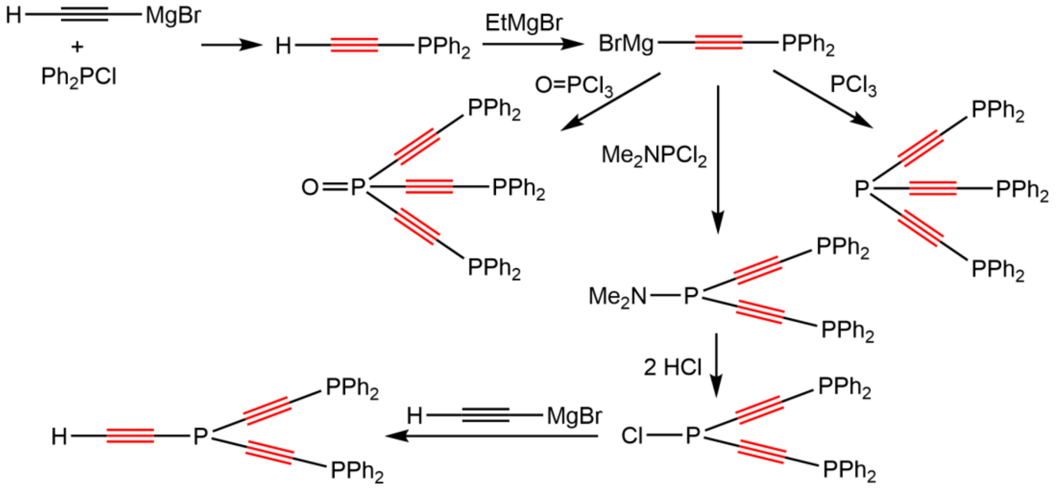
3. Alkynes in the Internal Structure of Phosphorus Dendrimers

The very first examples of alkynes inside phosphorus dendrimers were obtained by the post-synthesis alkylation of P=N-P=S linkages[36] inside the structure of some dendrimers. Indeed, such linkage can also be written as P^+-N=P-S^-, indicating an increased reactivity of the P=S groups included in such linkage, compared to the other type of P=S groups found in the dendrimer's structure. The first alkylation attempts were carried out with methyl triflate,[37] leading to highly sophisticated dendritic structures,[38] but the concept was later applied with propargyl triflate. Dendrimers built from a C_6 alkyl chain functionalized with a phosphine at each end were synthesized by Staudinger reaction[39] with a phosphorus azide, to create two Ph_2P=N-P=S linkages at the level of generation zero, then the dendrimer was grown, and an additional layer of Ph_2P=N-P=S linkages was created at the level of the second generation. Experiments were first carried out with the first generation. Reaction of two equivalents of propargyl triflate was monitored by ^{31}P NMR, which displayed the disappearance of two doublets at $\delta = 20.1$ ppm (PPh_2) and $\delta = 51.9$ ppm (P=S) with $^2J_{PP} = 35$ Hz, and the appearance of two new doublets at $\delta = 18.8$ ppm (P-S-R) and $\delta = 27.5$ ppm (PPh_2) with $^2J_{PP} = 13$ Hz for compound **20a-G1**. Remarkably, a very slow isomerization of the alkyne groups was observed within three months at 0°C in CH_2Cl_2, leading to two allenic systems inside the dendrimer (compound **20b-G1**, Scheme 10). Reaction of 18 equivalents of propargyl triflate was carried out with the fourth-generation dendrimer, leading to dendrimer **20a-G4** (R = Cl)[40] or **20c-G4** (R = O-Ph).[41] The post-synthesis reactivity inside phosphorus dendrimers was reviewed earlier.[42]



Scheme 10. Reaction of propargyl triflate inside dendrimers having P=N-P=S linkages in their structure.

It was attempted to synthesize phosphorus dendrimers having alkynes on all layers. Even if this attempt was not fully successful, a few branched architectures containing three alkynes were synthesized, as shown in Scheme 11. Both polymerization reactions, and oxidation of phosphines were observed, preventing the synthesis of larger compounds.[43]



Scheme 11. Small-branched molecules fully constituted of alkynes and phosphines.

As in the case of the functionalization of the surface of dendrimers, several examples of functionalization of the internal structure with alkynes concerned the insertion of fluorescent entities having TPA properties. The grafting of such fluorophores to the surface necessitated only a single phenol on one side of the fluorophore. The introduction of fluorophores in the internal structure of the branches necessitates both a phenol on one side for the grafting to $P(S)Cl_2$, and an aldehyde on the other side for continuing the growing of the dendritic structure. Such process was applied to a dendrimer having 6 fluorophores at the level of generation 0, on which 12 fluorophores were added at the level of generation 1 (dendrimer **21-G1** in Figure 5). Despite having a greater number of fluorophores than dendrimer **16-G1**, dendrimer **21-G1** had a lower fluorescence quantum yield (Φ) (0.43) and a slightly lower two-photon absorption cross-section (8500 GM).[44] The same type of internal fluorophore was also used at the level of generation 1 (instead of generation 0) and the terminal functions were either polyethylene glycol (PEG, compounds **22-G2**) or ammoniums (compound **23-G3**). Both compounds were soluble in DMSO and in water.[45] Finally, another type of fluorophore, having two additional thiophene groups, was created to be able to generate singlet oxygen ($^1O_2$) only under two-photon irradiation. Dendrimer **24-G2** was able to penetrate inside cancerous cells (MCF-7 human breast cancer cells), but was not toxic to these cells under one-photon irradiation or under day light. On the contrary, this dendrimer became highly toxic when irradiated in TPA conditions. Taken all together, these properties made this dendrimer promising for better photodynamic-therapy (PDT) medical treatments.[46]

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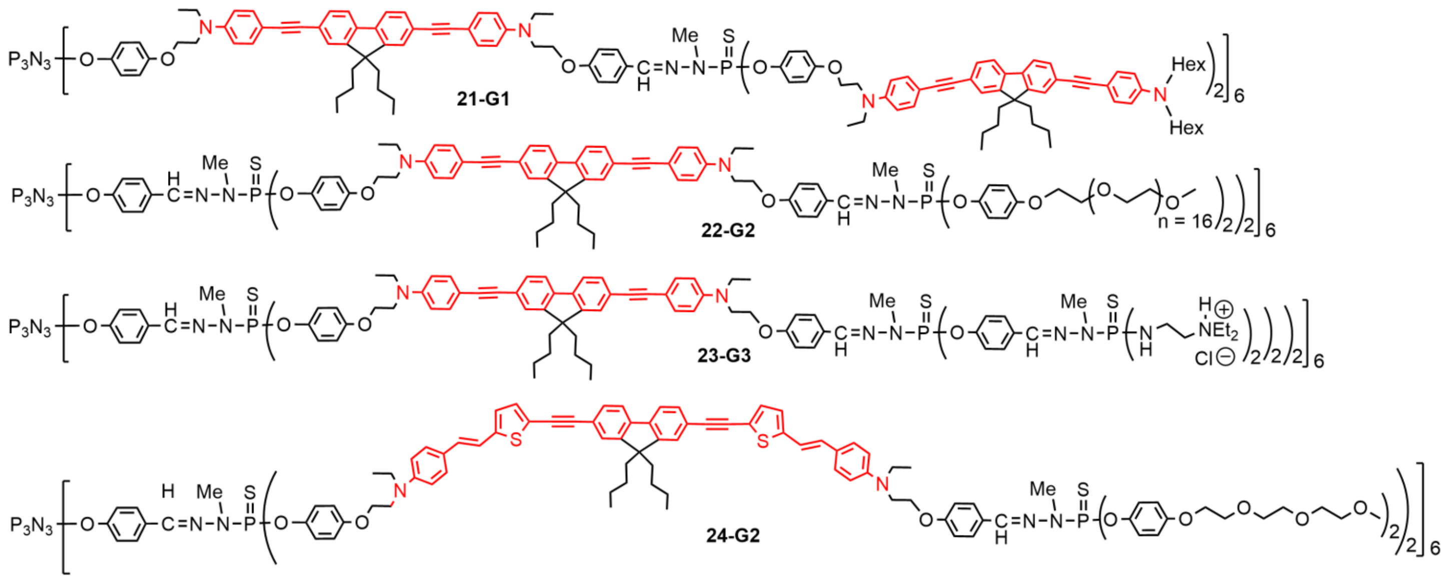


21-G1

22-G2

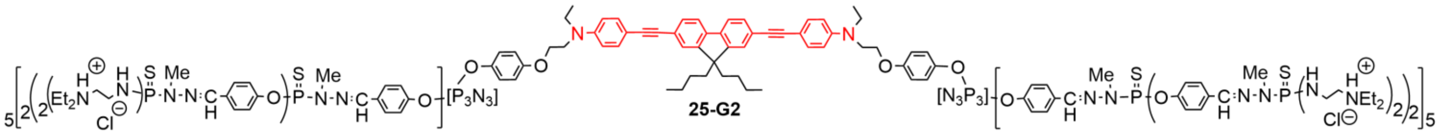
23-G3

24-G2

Figure 5. Different examples of dendrimers incorporating alkyne-containing fluorophores in the branches.

4. Alkyne at the core of phosphorus dendrimers and dendrons

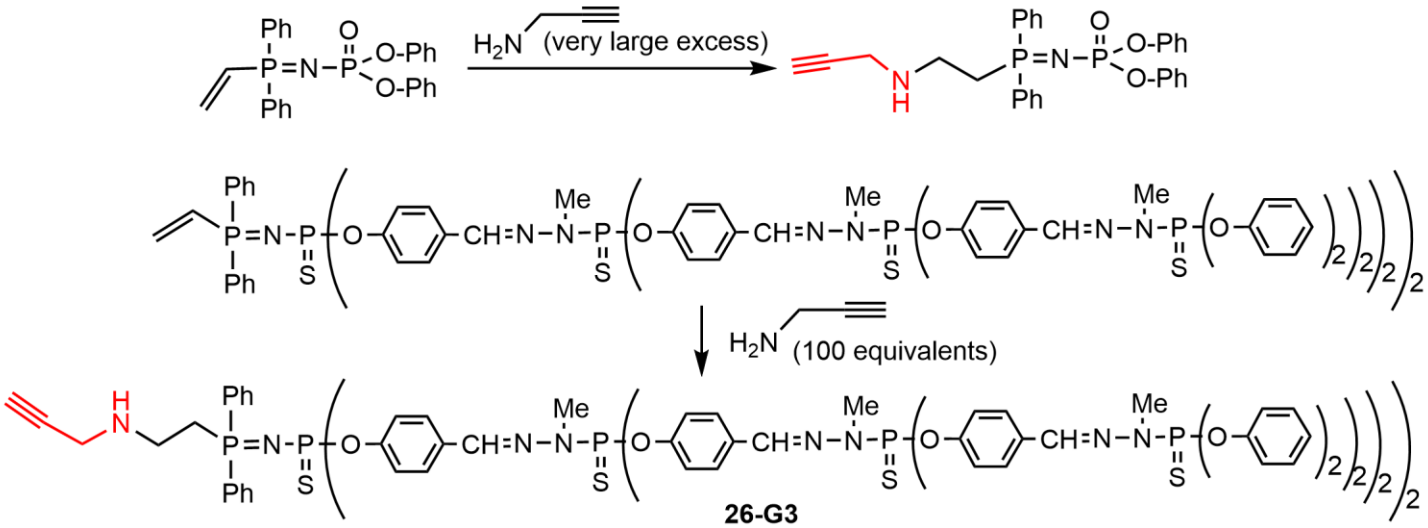
TPA fluorophores functionalized on both sides with a phenol can be used as cores to produce dumbbell-like dendrimers, as already shown in Figure 4. The same process was applied to a fluorophore incorporating two alkyne groups. The synthesis was carried out up to the second generation, and ammonium groups were added in the last step to get dendrimer **25-G2**, which was soluble in water. The fluorescence quantum yield (*Φ*) measured in DMSO was relatively good (0.42), but decreased dramatically when measured in water (0.075). Such a low value indicated that the fluorophore was not sufficiently isolated from the external environment by the dendritic branches,[47] contrary to what was observed in the case of a shorter fluorophore at the core.[48] Anyway, the TPA properties were sufficient to perform *in vivo* experiments, using dendrimer **25-G2** as a contrast agent. 3-Dimensional, *in vivo*, two-photon imaging of blood vessels of stage 53 of *Xenopus laevis* tadpole was obtained after intra-cardiac injection of dendrimer **25-G2**.[44]



25-G2

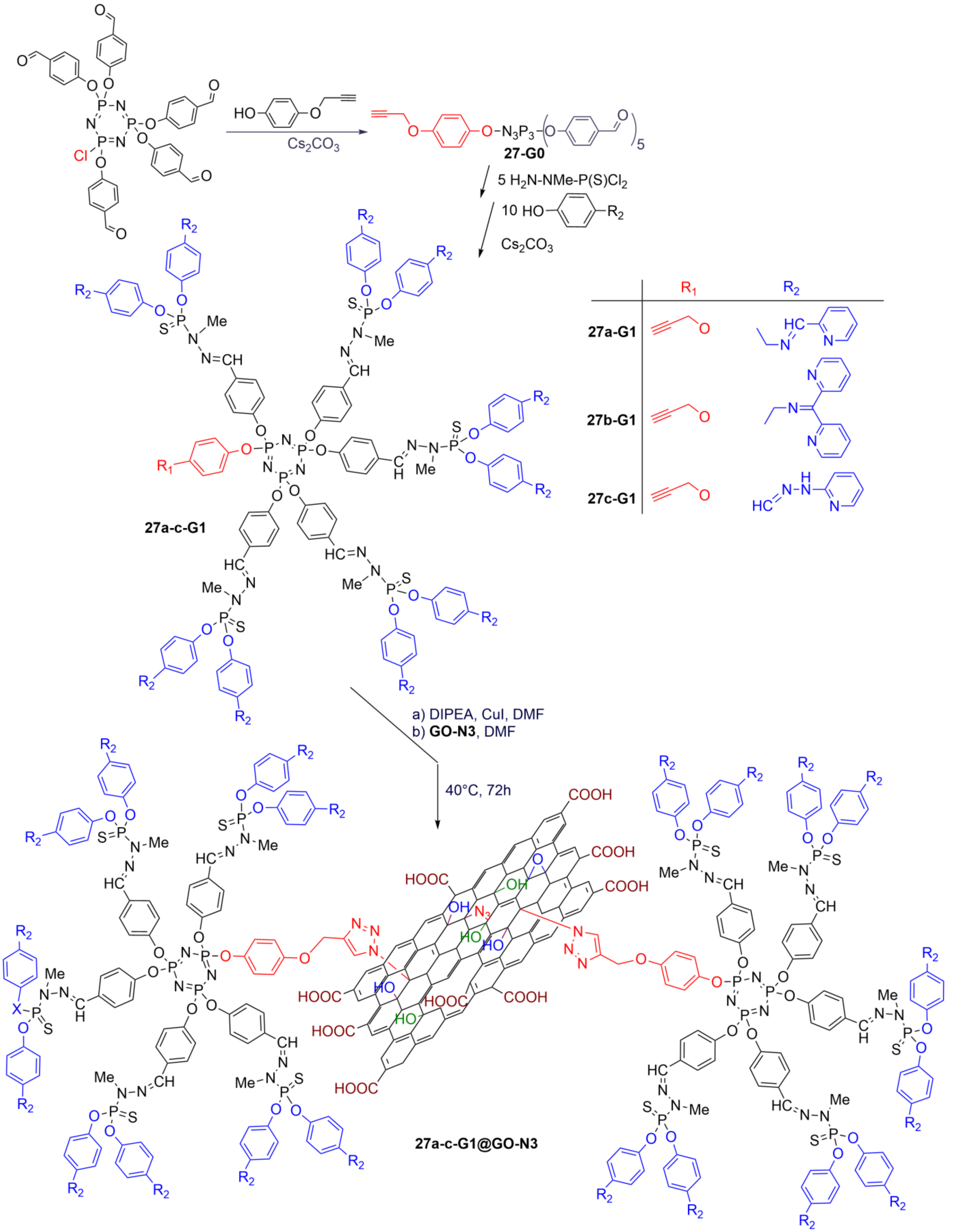
Figure 6. TPA fluorophore at the core of a water-soluble dumbbell-like dendrimer, used for *in vivo* TPA imaging.

Besides dendrimers, alkynes were also grafted at the core of dendrons, first for those having a vinyl group activated by the presence of P=N-P=X linkages (X = essentially S, but also O). Different primary amines were added by Michael-type additions. One of the chosen amines was propargylamine, used in large excess (100 equivalents) and reacted either with small compounds,[49] or to a third generation dendron, affording compound **26-G3** (Scheme 12).[50]



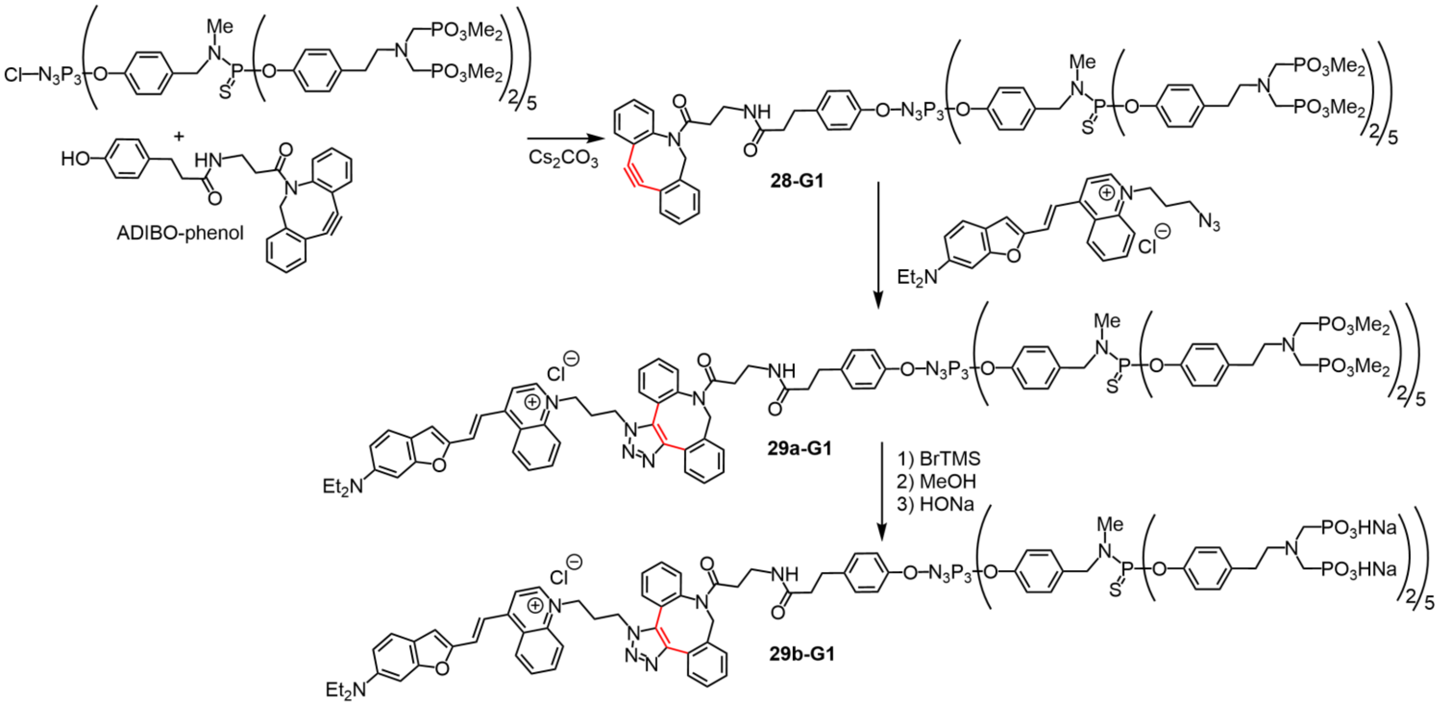
Scheme 12. Michael-type addition of propargyl amine at the core of dendrons.

A series of dendrons, built thanks to the selective reactivity of the cyclotriphosphazene core, was functionalized with five equivalents of hydroxybenzaldehyde, then with one equivalent of 4-(prop-2-yn-1-yloxy)-phenol. The aldehydes were used for growing the dendritic structure, which was then functionalized with different types of pyridyl imine groups, affording dendrons **27x-G1** (**x** = a, b, c) (Scheme 13). These pyridyl imines were previously grafted to the surface of dendrimers, and displayed anti-cancer properties either free[51] or by complexing metals such as copper[52] or gold.[53] These dendrons were then grafted via click reactions to graphene oxide (GO) pre-functionalized with azides, affording materials **27x-G1@GO-N3** (**x** = a, b, c) (Scheme 13). The anti-cancer properties of both the dendrons and the dendrons grafted to GO were tested against HCT116 cells (human colon cancer). The most active dendrons at the concentration of 10^{-5} M were **27a-G1** (0.6% of viability) and **27b-G1** (1.8% of viability). Both dendrons remained the most active when grafted to GO but with a much lower activity of 82.1% of viability for **27a-G1@GO-N3**, and 74.2% of viability for **27b-G1@GO-N3**, both tested at 10^{-5} M.[54]



Scheme 13. Dendrons functionalized with pyridyl imines on the surface and a single alkyne group at the core, and then grafted to graphene oxide (GO) pre-functionalized with azides.

The most recent example of an alkyne at the core of phosphorus dendrons concerned the grafting of an azadibenzocyclooctyne (ADIBO) moiety to the cyclotriphosphazene core, to afford dendron **28-G1** (Scheme 14). ADIBO is used for strain-promoted azide-alkyne cycloaddition (SPAAC). Dendron **28-G1** was reacted with a fluorescent azide to provide the near-infra-red (NIR) fluorescent dendron **29a-G1** (only one of the regio-isomer is shown in Scheme 13). Finaly the methyl phosphonate functions were deprotected to afford dendron **29b-G1**, which is soluble in water. Such type of azabisphosphonate terminal functions on the surface of a first-generation dendrimer displayed numerous anti-inflammatory properties,[55] and was found usable for instance against rheumatoid arthritis,[56] neuro-inflammation[57] or psoriasis,[58] and also to expand autologous NK cells that can be used in cell-based anticancer therapies,[59] in particular multiple myeloma.[60] Dendron **29b-G1** was used as a tool to decipher the mechanism of action in the case of psoriasis.[61]



Scheme 14. Synthesis of a dendron having a strained alkyne at the core, and its use in strain-promoted azide-alkyne cycloaddition (SPAAC), to produce the NIR-fluorescent and water-soluble dendron **29b-G1**.

5. Conclusions

Alkyne-functionalized phosphorus dendrimers and dendrons represent powerful platforms for precision macromolecular engineering. Their modular synthesis, functional versatility, and broad applicability make them valuable tools in both fundamental research and applied sciences. This review has shown the diverse methods applied for grafting alkyne derivatives either on the surface of phosphorus dendrimers, inside their internal structure, or at the core. The alkynes were reacted, in some cases, with differently functionalized azides in copper-catalyzed azide-alkyne cycloaddition (CuAAC), and, very recently, in strain-promoted azide-alkyne cycloaddition (SPAAC), to avoid the toxicity of residual copper. After fundamental research, recent advancements concern fluorescence, *in vivo* imaging, photodynamic therapy (PDT), anti-inflammatory properties, potential treatment of orphan diseases, and the functionalization of materials. Future research in the field should take advantage of the work described in this paper, in particular the SPAAC method for the clean functionalization of dendrimers, and the development of other types of fluorophores, including alkynes in their structure.

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Valérie Maraval is a Research Engineer at the CNRS and head of the *Dendrimers & Small Therapeutic Molecules* group at the Laboratoire de Chimie de Coordination in Toulouse, France. She obtained her PhD from Toulouse University in 2000, then carried out a postdoctoral fellowship with Bernard Meunier in collaboration with the company Aventis. She subsequently worked for two years as a CNRS Engineer in the group of Jean-Pierre Majoral in Toulouse. Recruited by the CNRS in 2005, she worked at the Laboratoire de Chimie de Coordination with Remi Chauvin until 2022. She then moved to the group of Anne-Marie Caminade, before becoming the leader of this group in 2025. Her research focuses on two main areas: (i) the development of dendrimers for biological and materials-related applications, and (ii) the development of bio-inspired lipidic alkynylcarbinol derivatives to investigate their anti-cancer and anti-infectious properties.

Cédric-Olivier Turrin is a Research Director at the CNRS (Centre National de la Recherche Scientifique) at the Laboratoire de Chimie de Coordination in Toulouse, France, and co-founder and CEO of IMD-Pharma. He was trained as a chemical engineer at CPE-Lyon (1997) and obtained a PhD from the University of Toulouse in 2000, focused on dendrimer science. After a postdoctoral stay at ETH Zurich, he joined the CNRS in 2001 as a permanent researcher. His work has mainly addressed phosphorus dendrimers, ranging from rational synthetic strategies to applications in materials science and nanomedicine. More recently, his research has focused on phosphonate-terminated dendrimers and their applications in immunology. He has co-authored more than 115 peer-reviewed publications, co-edited two books on dendrimers, and is inventor or co-inventor of nine patents. In parallel with his academic activities, he has also been involved in the translation of dendrimer-based technologies toward biomedical and therapeutic applications. He co-founded IMD-Pharma in 2016 and has served as its CEO since 2021.

Anne-Marie Caminade is Emeritus Director of Research Exceptional Class at the CNRS in the Laboratoire de Chimie de Coordination in Toulouse, France. She was the head of the Dendrimers and Heterochemistry group (2007-2024) and the Deputy Director of the Laboratoire de Chimie de Coordination (2021-2024). She graduated from the Toulouse University for two PhDs in 1984 and 1988. She was a Post-doc at the IFP close to Paris in 1984, and got an Alexander von Humboldt grant in 1988 for a second Post-doc in Saarbrucken University (Germany). She was appointed by the CNRS with a permanent position (1985-2025). She was the creator of the phosphorus dendrimers in 1993, and proposed several innovative concepts in the field, such as the first examples of reactivity inside dendrimers, dendritic catalyst recovery using a magnet, the demonstration of the importance of the internal structure, especially for biological properties, and the influence of the precise difunctionalization of dendrimers *versus* their random difunctionalization. She is the co-author of 580 publications and 18 patents, Editor of 5 books, and guest editor of numerous special issues of journals. Her h_{index} is 84. She received numerous Prizes and Awards, the most recent being from the French (2021 and 2022), German (2022), Spanish (2024), and Italian (2024) Chemical Societies. She also became Knight of the Legion of Honor (2021, the highest civilian grade in France). She is a member of the Academia Europaea and of the European Academy of Sciences. She is shareholder of IMD-Pharma.

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