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"Lego" Chemistry for the Straightforward Synthesis of Dendrimers

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Abstract: A new straightforward method of synthesis of dendrimers, using two branched monomers (CA_2 and DB_2), is described. Each generation is obtained in a single quantitative step, with only N_2 or H_2O as byproducts; generation 4 is obtained in only four steps. The end groups are alternatively phosphines and hydrazines; their versatile reactivity is illustrated by the reaction of generation 4 with a branched CD_5 monomer, which increases the number of end groups in a single step from 48 to 250.

Despite the enormous success met by dendrimers,[1] with around 6000 references already indexed, one should not forget the main drawback of these compounds, that is their multistep synthesis, which is always boring and time-consuming. Several improvements have been proposed to shorten the time dedicated to synthesis, such as the use of hypermonomers[2] (dendrons), "double-stage",[3] "double-exponential growth",[4] "orthogonal coupling"[5] strategies, or multiple additions "one-pot"[6] processes. However, several of these methods still have numerous drawbacks; often the number of steps is not significantly decreased, and the use of activating agents is frequently necessary, thus improvements are still needed. Having also in mind the necessity of a "green" chemistry, it is desirable that the byproducts are environmentally friendly, that only a very slight excess of reagents is used for quantitative reactions, and that no protection/deprotection process is applied.

Our first method of synthesis, which concerned phosphorus dendrimers,[7] was proposed as early as 1994;[8] it already fulfilled all three requirements, using two monomers, one of type $\mathbf{AX_2}$ ($H_2NNMeP(S)Cl_2$) and one of type **YD** ($NaOC_6H_4CHO$), whose quantitative reactions without any activating reagent generated only NaCl and H_2O as byproducts. Furthermore, the presence of aldehyde or $P(S)Cl_2$ end groups allowed a rich variety of functionalizations to be carried out,[9] which led to numerous properties and applications.[10] The only drawback of this synthesis is that two reactions are needed for synthesizing one generation, thus we proposed later an improvement based on the use of two branched monomers, $\mathbf{AB_2}$ and $\mathbf{CD_2}$ monomers, whose quantitative reactions generated only H_2O and N_2 as byproducts (Chart 1).[11] Besides the generation after generation growing, we also dem-

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(1) (a) Newkome, G. R.; Vögtle, F.; Moorefield, C. N. *Dendrimers and dendrons*; John Wiley and Sons: New York, 2001. (b) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and other dendritic polymers*; John Wiley and Sons: New York, 2001.

(2) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 82. (b) Twyman, L. J.; Beezer, A. E.; Mitchell, J. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 407. (c) L'abbé, G.; Forier, B.; Dehaen, W. *Chem. Commun.* **1996**, 2143. (d) Ohta, M.; Fréchet, J. M. J. *J. Macromol. Sci. Pure Appl. Chem.* **1997**, *A34*, 2025. (e) Bo, Z. S.; Zhang, X.; Zhang, C. M.; Wang, Z. Q.; Yang, M. L.; Shen, J. C.; Ji, Y. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2931. (f) Morgenroth, F.; Berresheim, A. J.; Wagner, M.; Müllen, K. *Chem. Commun.* **1998**, 1139. (g) Wiesler, U. M.; Müllen, K. *Chem. Commun.* **1999**, 2293. (h) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *J. Org. Chem.* **1999**, *64*, 7474. (i) Scott, D. A.; Krülle, T. M.; Finn, M.; Fleet, G. W. J. *Tetrahedron Lett.* **2000**, 3959. (j) Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 2499. (k) Abramov, A. M.; Shukla, R.; Amabilino, D. B.; Dehaen, W. *J. Org. Chem.* **2002**, *67*, 1004.

(3) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252. (b) Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. *J. Am. Chem. Soc.* **1992**, *114*, 1018. (c) Xu, Z. F.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537. (d) Ihre, H.; Hult, A.; Fréchet, J. M. J.; Gitsov, I. *Macromolecules* **1998**, *31*, 4061. (e) Forier, B.; Dehaen, W. *Tetrahedron* **1999**, *55*, 9829.

(4) (a) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159. (b) Chang, H. T.; Chen, C. T.; Kondo, T.; Siuzdak, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 182. (c) Klopsch, R.; Franke, P.; Schlüter, A. D. *Chem. Eur. J.* **1996**, *2*, 1330. (d) Ashton, P. R.; Anderson, D. W.; Brown, C. L.; Shipway, A. N.; Stoddart, J. F.; Tolley, M. S. *Chem. Eur. J.* **1998**, *4*, 781. (e) Chi, C.; Wu, J.; Wang, X.; Zhao, X.; Li, J.; Wang, F. *Tetrahedron Lett.* **2001**, *42*, 2181. (f) Chi, C.; Wu, J.; Wang, X.; Zhao, X.; Li, J.; Wang, F. *Macromolecules* **2001**, *34*, 3812.

(5) (a) Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 913. (b) Xu, Z.; Moore, J. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1354. (c) Zeng, F. W.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326 (d) Deb, S. K.; Maddux, T. M.; Yu, L. P. *J. Am. Chem. Soc.* **1997**, *119*, 9079. (e) Deb, S. K.; Maddux, T. M.; Yu, L. P. *Polym. Mater. Sci. Eng.* **1997**, *77*, 163. (f) Klopsch, R.; Koch, S.; Schlüter, A. D. *Eur. J. Org. Chem.* **1998**, 1275. (g) Ingerl, A.; Neubert, I.; Klopsch, R.; Schlüter, A. D. *Eur. J. Org. Chem.* **1998**, 2551. (h) Freeman, A. W.; Fréchet, J. M. J. *Org. Lett.* **1999**, *1*, 685. (i) Ishida, Y.; Jikei, M.; Kakimoto, M. *Macromolecules* **2000**, *33*, 3202.

(6) (a) Rannard, S. P.; Davis, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 11729. (b) Hayakawa, T.; Yamakawa, Y.; Nomura, M.; Okazaki, M.; Takeuchi, K.; Asai, M.; Ueda, M. *Polym. J.* **2000**, *32*, 784.

(7) (a) Majoral, J. P.; Caminade, A. M. *Chem. Rev.* **1999**, *99*, 845. (b) Majoral, J. P.; Caminade, A. M.; Maraval, V. *Chem. Commun.* **2002**, 2929. (c) Majoral, J. P.; Caminade, A. M. *Top. Curr. Chem.* **2003**, *223*, 111.

(8) (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. *Angew. Chem., Int. Ed.* **1994**, *33*, 1589. (b) Launay, N.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3282. (c) Lartigue, M. L.; Donnadieu, B.; Galliot, C.; Caminade, A. M.; Majoral, J. P.; Fayet J. P. *Macromolecules* **1997**, *30*, 7335.

(9) See for example: (a) Slany, M.; Bardají, M.; Casanove, M. J.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764. (b) Launay, N.; Slany, M.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **1996**, *61*, 3799. (c) Bardají, M.; Kustos, M.; Caminade, A. M.; Majoral, J. P.; Chaudret, B. *Organometallics* **1997**, *16*, 403. (d) Prévôté, D.; Caminade, A. M.; Majoral, J. P. *J. Org. Chem.* **1997**, *62*, 4834. (e) Majoral, J. P.; Caminade, A. M. *Top. Curr. Chem.* **1998**, *197*, 79. (f) Caminade, A. M.; Laurent, R.; Chaudret, B.; Majoral, J. P. *Coord. Chem. Rev.* **1998**, *178*−*180*, 793.

(10) See for example: (a) Loup, C.; Zanta, M. A.; Caminade, A. M.; Majoral, J. P.; Meunier, B. *Chem. Eur. J.* **1999**, *5*, 3644. (b) Boggiano, M. K.; Soler-Illia, G. J. A. A.; Rozes, L.; Sanchez, C.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4249. (c) Maraval, V.; Laurent, R.; Caminade, A. M.; Majoral, J. P. *Organometallics* **2000**, *19*, 4025. (d) Le Derf, F.; Levillain, E.; Gorgues, A.; Sallé, M.; Sebastian, R. M.; Caminade, A. M.; Majoral, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 224. (e) Marmillon, C.; Gauffre, F.; Gulik-Krzywicki, T.; Loup, C.; Caminade, A. M.; Majoral, J. P.; Vors, J. P.; Rump, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2626. (f) Caminade, A. M.; Maraval, V.; Laurent, R.; Majoral, J. P. *Curr. Org. Chem.* **2002**, *6*, 739. (g) Koprowski, M.; Sebastian, R. M.; Maraval, V.; Zablocka, M.; Cadierno-Menendez, V.; Donnadieu, B.; Igau, A.; Caminade, A. M.; Majoral, J. P. *Organometallics* **2002**, *21*, 4680.

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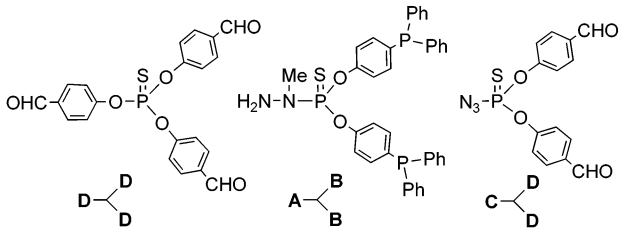
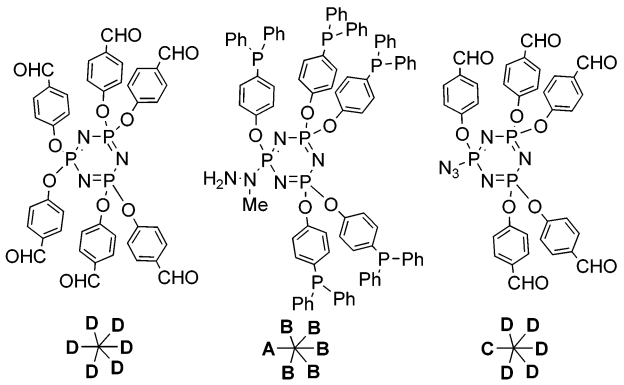
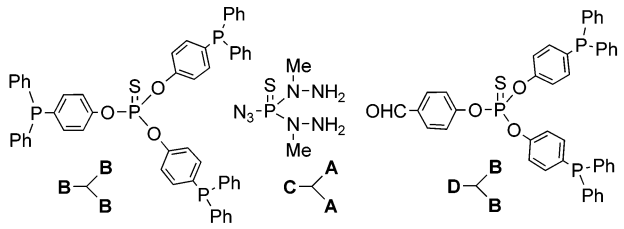
CHART 1. Various Types of Branched Monomers



D_3 + 3 AB_2 + 6 CD_2 + 12 AB_2 + 24 CD_2 (ref)



D_6 + 6 AB_2 + 12 CD_5 + 60 AB_2 + 120 CD_5 (ref)
D_6 + 6 AB_5 + 30 CD_2 + 60 AB_5 + 300 CD_2 (ref)
D_6 + 6 AB_5 + 30 CD_5 + 150 AB_5 (ref)

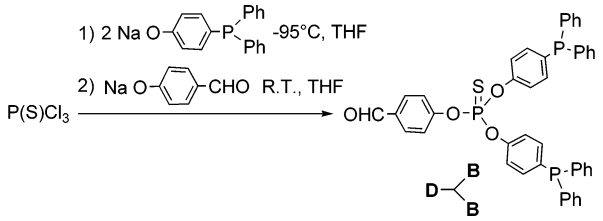


B_3 + 3 CA_2 + 6 DB_2 + 12 CA_2 + 24 DB_2 (this work)

onstrated that a one-pot multiple additions process afforded also the fourth generation with good purity.[11] We recently proposed a new improvement of the **AB_2** + **CD_2** process, using **AB_5** and **CD_5** monomers[12] for multiplying by five the number of end groups; these were used either alone or in combination with **AB_2** and **CD_2** monomers (Chart 1). We report here another straightforward synthesis of dendrimers derived from the same concept, but using **CA_2** and **DB_2** monomers, i.e., monomers whose reactive groups are inverted compared to the **AB_2** + **CD_2** method, demonstrating a real "lego"[13] chemistry for the tailored synthesis of dendrimers.

The method of synthesis envisaged requires the use of three building blocks: two branched monomers (**CA_2** and **DB_2**) and a core, which can be of either type **B_3** or **A_3**, depending on which type of branched monomer will be used first. We decided to use the triphosphine **B_3** as the core, whose synthesis was already reported,[14] as well as

SCHEME 1. Synthesis of the Branched Monomer DB_2



that of the **CA_2** branched monomer.[15] The other branched monomer (**DB_2**) is synthesized by the reaction of 2 equiv of $NaOC_6H_4PPh_2$ with $P(S)Cl_3$ at low temperature, followed by the reaction of 1 equiv of $NaOC_6H_4CHO$ (Scheme 1). The **DB_2** monomer is obtained in good yield after purification by column chromatography (83%).

Having in hand the three building blocks, we begun to carry out the synthesis of the dendrimer by reacting 3 equiv of **CA_2** with 1 equiv of the **B_3** core. The expected Staudinger reactions occur upon heating for 6 days at 35 °C, with elimination of N_2 and formation of P═N linkages, to afford the first generation **G_1** in one step (Scheme 2). The completion of the reaction is monitored by ^{31}P NMR, with the disappearance of both singlets corresponding to the phosphines ($\delta = -6.1$ ppm) and to N_3-P (δ 82.7), and with the appearance of a set of two doublets, characteristic of P═N−P═S linkages at δ 12.6 (P═N) and 71.4 ppm (P═S), with $^2J_{PP} = 17$ Hz. The structure of **G_1** was also confirmed by ^1H and ^{13}C NMR, mass spectrometry (FAB), and elemental analysis.

Starting from **G_1**, the condensation reaction with 6 equiv of **DB_2** occurs readily overnight at room temperature, to afford the second generation **G_2**. The completion of the reaction is also monitored by ^{31}P NMR, which displays an important shielding of the signal corresponding to the P═S group of the P═N−P═S linkages, from δ 71.4 ppm for **G_1** to δ 57.3 ppm for **G_2**. Using again the **CA_2** derivative (12 equiv) to react with **G_2** affords **G_3** after heating for 6 days at 35 °C (the same conditions than used previously for **G_1**). Starting from **G_3**, the fourth generation **G_4** is obtained by the condensation reaction of 24 equiv of the **DB_2** monomer at room temperature. All these compounds are isolated in nearly quantitative yields, and they are all characterized by ^{31}P NMR, which is a remarkably efficient tool to monitor the completion of reactions. As an illustration, Figure 1 displays the ^{31}P NMR spectrum of **G_4** (48 phosphine end groups), in which all the signals corresponding to the eight types of phosphorus atoms are clearly distinguishable, including the signal corresponding to the single phosphorus of the core (P_0), and the two sets of two doublets corresponding to the P═N−P═S linkages of the first and the third generations. Beside the signal corresponding to the phosphine end groups (δ −6.0 ppm), the signals of the phosphorus atoms of the internal skeleton appear in three areas, depending on their environment: around +10 ppm for the iminophosphorane groups (Ar_3P═N), around +50 ppm for thiophosphate groups (S═P(O-)$_3$),

(11) Brauge, L.; Magro, G.; Caminade, A. M.; Majoral, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 6698. Correction: *J. Am. Chem. Soc.* **2001**, *123*, 8446.

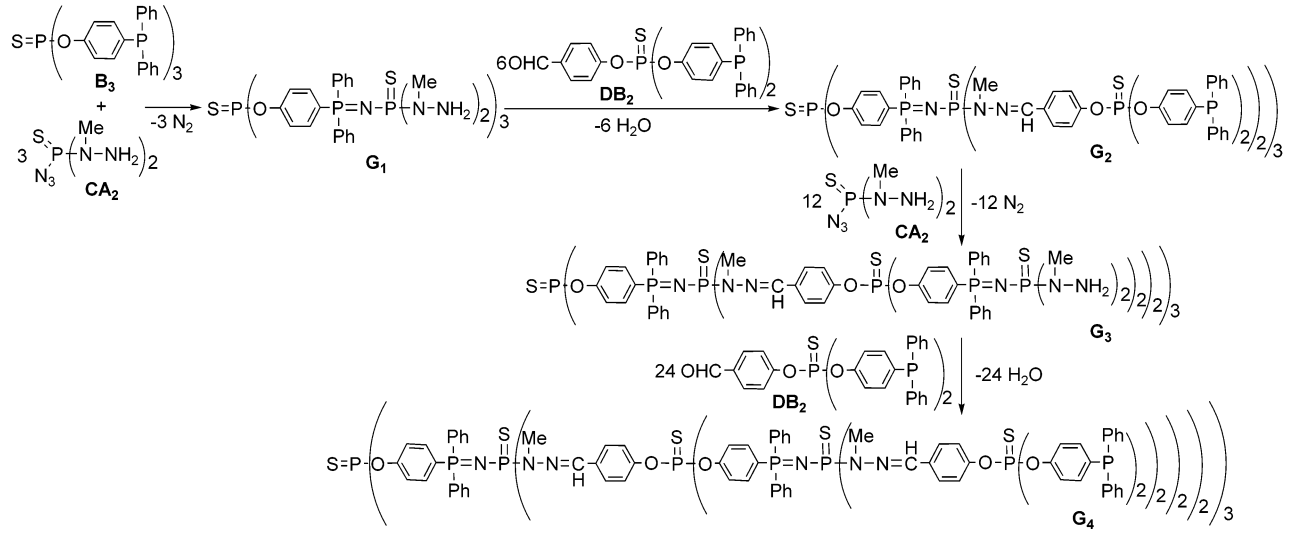
(12) Maraval, V.; Caminade, A. M.; Majoral, J. P.; Blais, J. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1822.

(13) The term "molecular lego" was first proposed by Stoddart: Stoddart, F. *Chem. Brit.* **1988**, *24*, 1023.

(14) Merino, S.; Brauge, L.; Caminade, A. M.; Majoral, J. P.; Taton, D.; Gnanou, Y. *Chem. Eur. J.* **2001**, *7*, 3095.

(15) Mitjaville, J.; Caminade, A. M.; Mathieu, R.; Majoral, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 5007.

SCHEME 2. Synthesis of the Dendrimer



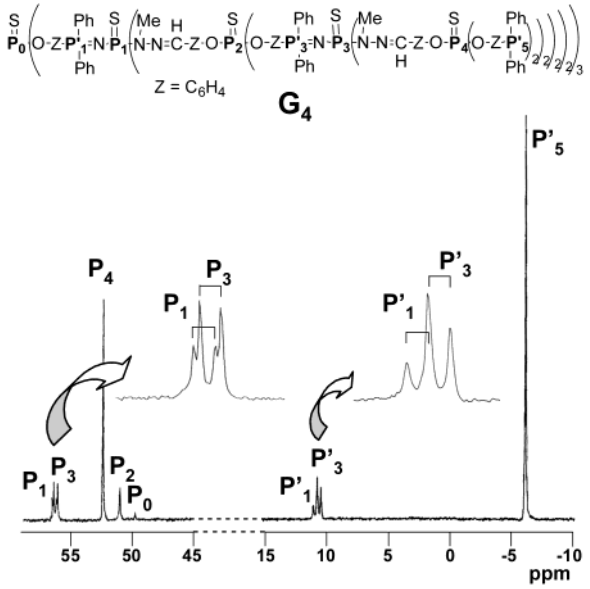


FIGURE 1. ^{31}P NMR spectrum of $\mathbf{G_4}$.

and around +57 ppm for the trisaminothiophosphine groups (S=P(N<)$_3$).

Obviously, all these compounds are also characterized by ^{1}H and ^{13}C NMR and elemental analyses. It is worth noting that the methyl groups are also useful probes for both ^{1}H and ^{13}C NMR, since their chemical shifts vary from 2.69 (^{1}H) and 39.8 ppm (^{13}C) for $NMeNH_2$ to approximately 3.20 (^{1}H) and 33 ppm (^{13}C) for NMeN=C.

The $\mathbf{CA_2}$ + $\mathbf{DB_2}$ method described here affords either hydrazides or phosphines as end groups, whereas the method we described previously ($\mathbf{AB_2}$ + $\mathbf{CD_2}$ or $\mathbf{AB_5}$ + $\mathbf{CD_5}$)[11,12] gave either phosphines or aldehydes as end groups, depending on the number of the generation. All these end groups are useful for further reactions, and both methods are compatible, illustrating the concept of "lego"[13] chemistry. For instance, the dendrimer $\mathbf{G_4}$ is reacted with 48 equiv of the $\mathbf{CD_5}$ monomer (Scheme 3). The completion of the reaction is observed after 3 days at 35 °C, as shown here again by ^{31}P NMR, with the disappearance of the signal corresponding to the phosphines end groups, and the appearance of a complex ABB′M type system corresponding to P=N−[PN]$_3$. This single step allows multiplying by five the number of end groups, from 48 PPh_2 for $\mathbf{G_4}$ to 250 CHO for $\mathbf{G_5}$.

In conclusion, we have described a new and straightforward method of synthesis of dendrimers, which exemplifies the rapid methods we discovered previously. Each generation is obtained in a nearly quantitative yield, using a quasistoichiometric amount of reagents (generally 1.02 equiv per function), and the only byproducts are N_2 and H_2O. This method of synthesis gives "layer-block" dendrimers, that is to say dendrimers constituted alternatively of two types of layers, P(S)-$OC_6H_4PPh_2$=NP(S) and P(S)NMeN=CHC_6H_4OP(S). Depending on the generation, the end groups are either phosphines or hydrazides, both being potentially useful for further reactions, as illustrated by the reactivity of $\mathbf{G_4}$ with a $\mathbf{CD_5}$ monomer. Indeed, this reaction allows the direct grafting of 250 aldehyde end groups in one step from the 48 phosphine end groups of the fourth generation. This compound is also a potentially useful precursor for a versatile reactivity on the surface of dendrimers.

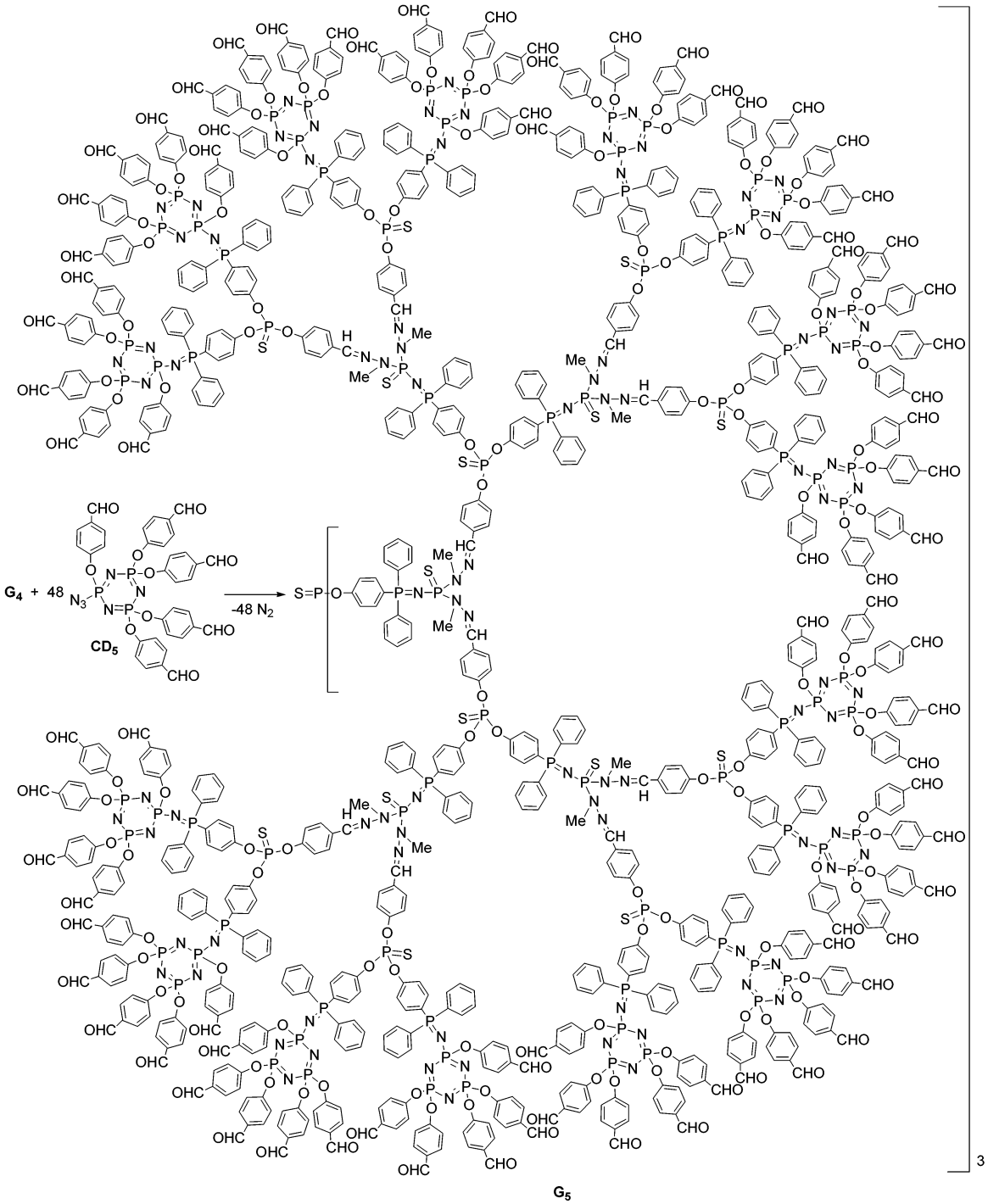
Experimental Section

Compounds $\mathbf{B_3}$,[14] $\mathbf{CA_2}$,[15] $\mathbf{CD_5}$,[10] and $HOC_6H_4PPh_2$[16] were synthesized as described previously.

$\mathbf{G_5}$ Dendrimer. To a solution of $\mathbf{G_4}$ dendrimer (50 mg, 0.002 mmol) in THF (2 mL) was added a solution of monomer $\mathbf{CD_5}$ (77 mg, 0.099 mmol) in THF (2 mL). The resulting solution was stirred at 35 °C for 3 days, then the solvent was removed under vacuum. The residue was washed 3 times with a mixture ethyl acetate/ether/pentane (1/1/2) to remove the small excess of monomer $\mathbf{CD_5}$. $\mathbf{G_5}$ dendrimer was obtained as a white powder in 95% yield (116 mg). ^{31}P {^{1}H} NMR ($CDCl_3$, δ, ppm, J_{PP}): 4.2 (ddd, ^2J = 31.8 Hz, ^2J = 63.3 Hz, ^2J = 91.3 Hz), 7.0 (br d, ^2J = 63.3 Hz), 7.1 (br d, ^2J = 91.3 Hz), 11.6 (d, ^2J = 31.8 Hz), 11.8 (d, ^2J = 27.1 Hz), 50.0, 50.9, 51.0, 56.6 (d, ^2J = 27.1 Hz). ^{1}H NMR ($CDCl_3$, δ, ppm, J_{HP}): 3.16 (br d, ^3J = 8 Hz, 90H), 6.91−7.58 (m, 1992H), 9.75 (s, 48H), 9.79 (s, 192H). ^{13}C {^{1}H} NMR ($CDCl_3$, δ, ppm, J_{CP}): 33.0 (br s), 121.2 (br s), 121.4, 127.0 (br d, ^1J =

(16) Herd, O.; Hessler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69.

SCHEME 3. Synthesis of G_5



108 Hz), 128.4, 128.6 (dd, ^1J = 108 Hz, ^3J = 3 Hz, C_5^i), 128.6, 128.7 (d, ^3J = 13 Hz), 130.9, 131.1, 132.0 (br s), 132.4 (d, ^2J = 11 Hz), 132.8, 132.9, 134.6 (d, ^2J = 12 Hz), 149.3 (d, ^2J = 8 Hz), 149.5 (d, ^2J = 8 Hz), 153.4 (br s), 155.4 (d, ^2J = 10 Hz), 156.9 (d, ^2J = 8 Hz), 190.7, 190.8. IR (KBr, $\bar{\nu}$, cm^{-1}): 1700. Anal. Calcd for $C_{3054}H_{2322}N_{267}O_{573}P_{253}S_{46}$ (61241): C, 59.90; H, 3.82; N, 6.11. Found: C, 60.11; H, 3.93; N, 6.02.

Supporting Information Available: Experimental procedures and ^{31}P, ^{1}H and ^{13}C NMR data for all compounds (**DB$_2$**, **G$_1$**, **G$_2$**, **G$_3$**, **G$_4$**, **G$_5$**), with the assignment of all signals. ^{31}P and ^{13}C NMR spectra of dendrimer **G$_5$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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