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Letter

Diverse Approaches for the Difunctionalization of PPH Dendrimers, Precise Versus Stochastic: How Does this Influence Catalytic Performance?

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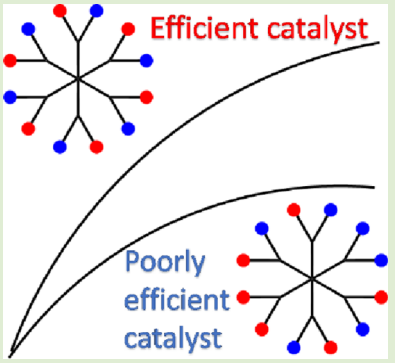
ABSTRACT: Random difunctionalization of dendrimer surfaces, frequently employed in biological applications, provides the advantage of dual functional groups through a synthetic pathway that is simpler compared to precise difunctionalization. However, is the random difunctionalization as efficient as the precise difunctionalization on the surface of dendrimers? This question is unanswered to date because most dendrimer families face challenges in achieving precise functionalization. Polyphosphorhydrazone (PPH) dendrimers present a unique opportunity to obtain precise difunctionalization at each terminal branching point. The work concerning catalysis we report with PPH dendrimers, whether precisely or randomly functionalized, addresses this question. Across PPH dendrimers, from generations 1 to 3, precise functionalization consistently outperforms random functionalization in terms of efficiency. This finding introduces a novel concept in dendrimer science, emphasizing the superiority of precise over random functionalization methodologies. Introducing a groundbreaking concept in the field of dendrimers.



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Dendrimers are macromolecules synthesized step-by-step (generation after generation), to ensure a supposed perfect structure.[1] Paradoxically, a random difunctionalization of the surface of dendrimers is frequently applied, thus affording "imperfect" nano-objects from "perfect" ones. The random difunctionalization is generally applied with the aim of affording two different properties to the dendrimers, for instance, one function for increasing the solubility in a given solvent such as water, the second affording the desired properties. The random difunctionalization is in particular used when studying biological properties of dendrimers.[2] However, inconsistencies between batches have been already pointed out, leading to batches with varying biological activities.[3] Meanwhile, to the best of our knowledge, no study up to now has compared the influence of random versus precise difunctionalization on all of the surfaces of dendrimers on a given property. In fact, such a comparison is not easy to carry out, as the precise difunctionalization of most types of dendrimers is not possible, except when using difunctionalized reagents, such as those based on triazine,[4] or Janus-type dendrimers,[5] or eventually after tedious purification by HPLC of one, two, or three functions on the surface of dendrimers.[6] Interestingly, polyphosphorhydrazone (PPH) dendrimers[7] possess the rare property of an easy sequential difunctionalization on one Cl, then on a second Cl, at each $P(S)Cl_2$ terminal function.[8]

In this Letter we describe both the precise and random difunctionalization of PPH dendrimers, from generation 1 to generation 3, with a perfluoroalkyl chain and an iminophosphine, suitable for the complexation of palladium. Both families were then used in catalytic experiments for detecting their different or similar properties.

The PPH dendrimers were synthesized as described previously,[6] to have $P(S)Cl_2$ terminal functions at each generation, from generation 1 (6 $P(S)Cl_2$) to generation 3 (24 $P(S)Cl_2$). The ligand chosen for the catalytic experiments of type iminophosphine was previously used by us for complexing palladium on a monomer and a first generation dendrimer[9] and was found efficient and usable in several catalytic experiments.[9,10] The other function that we chose was a perfluoroalkyl chain, which could potentially modify the solubility of the PPH dendrimers.

The $P(S)Cl_2$ functions of the PPH dendrimers react easily with phenols and amines. The easy and precise difunctionalization was previously observed essentially with amines.[8] It was carried out only one time with two phenol derivatives,[11] affording a difunctional dendrimer with a purity of ca. 95%. As in our experience, it is generally easier to functionalize the PPH dendrimers with phenols than with primary amines; we choose to use a phenol for both types of substituents. The perfluoroalkyl derivative **1** ($HOAr_1$) was synthesized by a

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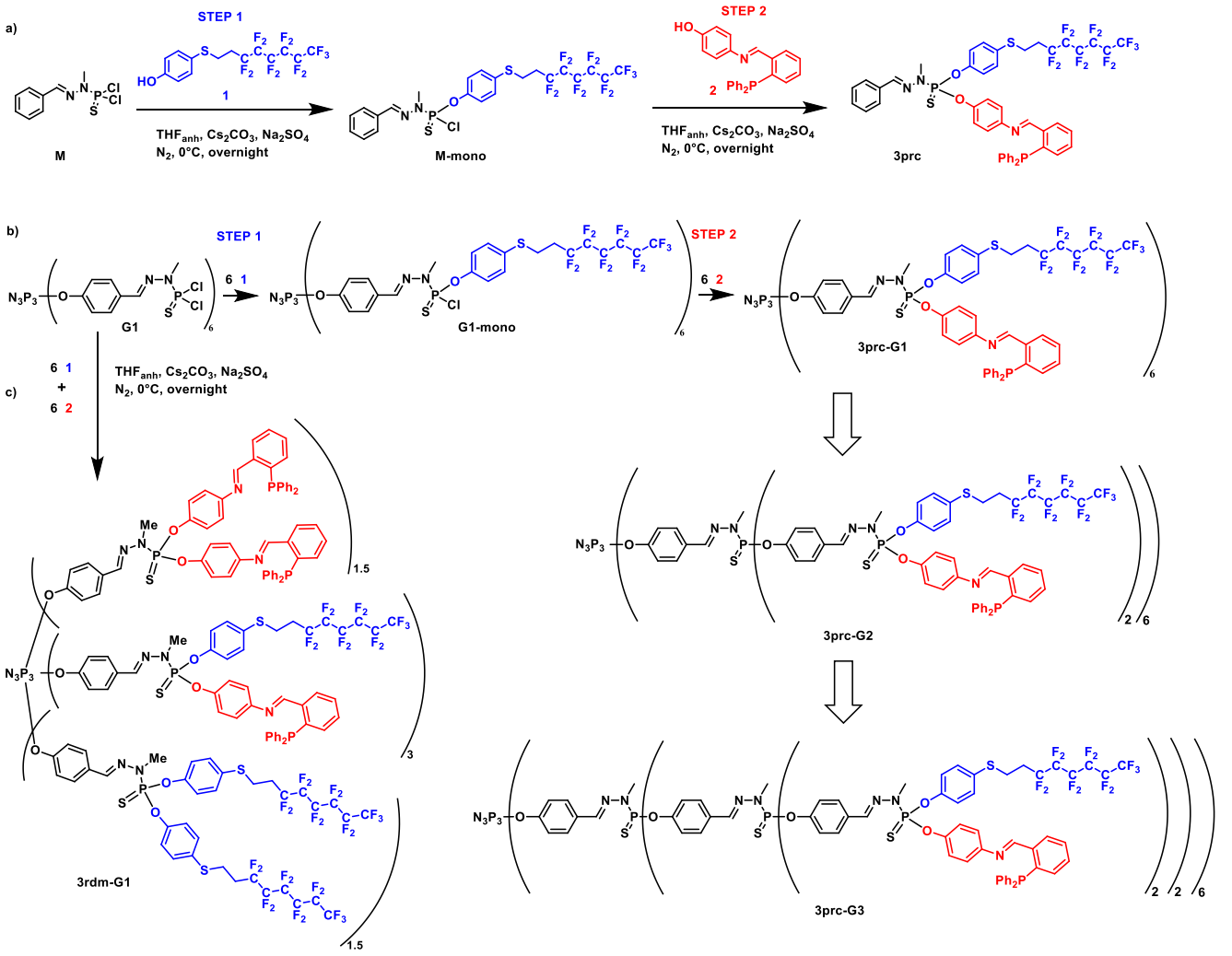
Scheme 1. Synthesis of the (a) Precisely Difunctionalized Monomer (3prc) (b) of the First-Generation Dendrimer (3prc-G1 Reaction Also Carried out to Synthesize 3prc-G2 and 3prc-G3) (c) and of 3rdm-G1 (Reaction Also Carried out to Synthesize 3rdm-G2 and 3rdm-G3); Structure of 3prc-G2 and 3prc-G3



substitution reaction between 4-mercaptophenol and 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane in the presence of triethylamine in refluxing THF overnight, instead of K_2CO_3 in refluxing acetone for 1 day.[12] The ligand **2** ($HOAr_2$) was synthesized as previously described[9] by a condensation reaction between 2-(diphenylphosphino) benzaldehyde and 4-aminophenol.

Having both phenols in hand, the first step was to study their grafting on a model compound (**M**) bearing a single $P(S)Cl_2$ function. It was decided to graft first phenol **1**, as it is a very stable compound, contrarily to phenol **2**, in which the phosphine can be easily oxidized. The monofunctionalized monomer **M-mono** was isolated and characterized, then phenol **2** bearing a phosphine was reacted to afford the difunctionalized monomer **3prc**. Both reactions were carried out under basic conditions, using cesium carbonate, whereas sodium sulfate was used as a drying agent. The monofunctionalization with phenol **1** was then attempted with generations 1 (**G1**), 2 (**G2**), and 3 (**G3**) of the PPH dendrimers in basic conditions. A very small proportion of unreacted $P(S)Cl_2$ and of doubly reacted $P(S)(OAr_1)_2$ was observed in all cases by $^{31}P\{^1H\}$ NMR (less than 5%) (Scheme 1).

The main $^{31}P\{^1H\}$ NMR signal corresponding to the monosubstitution is observed at 68 ppm for all generations. The second phenol (**2**) was then reacted, also in the presence of cesium carbonate and sodium sulfate. After completion of this second reaction, dendrimers **3prc-Gn** (n = 1, 2, 3) (Scheme 1) were isolated, having less than 5% of symmetrical $P(S)(OAr_1)_2$ and $P(S)(OAr_2)_2$ terminal functions.

In the next experiment, generations 1, 2, and 3 of the PPH dendrimers were reacted simultaneously with both phenols **1** and **2** under basic conditions. As expected, this reaction provided randomly functionalized dendrimers **3rdm-Gn** (n = 1, 2, 3), in which ca. 50% of the terminal functions are of type $P(S)(OAr_1)(OAr_2)$, ca. 25% of type $P(S)(OAr_1)_2$, and ca. 25% of type $P(S)(OAr_2)_2$. Scheme 1 illustrates the reaction for the first generation and the structure of **3rdm-G1**.

Figure 1 displays the $^{31}P\{^1H\}$ NMR spectra (only the part corresponding to the P═S groups) of both the **3prc-G1** and **3rdm-G1** dendrimers (only one of the numerous possible structures is shown for the latter), pointing to the large difference between both families of dendrimers. It should be emphasized that ^{31}P NMR is a unique and very precious tool for the accurate characterization of dendrimers,[13] in particular, of highly sophisticated dendritic structures.[14] Indeed, neither

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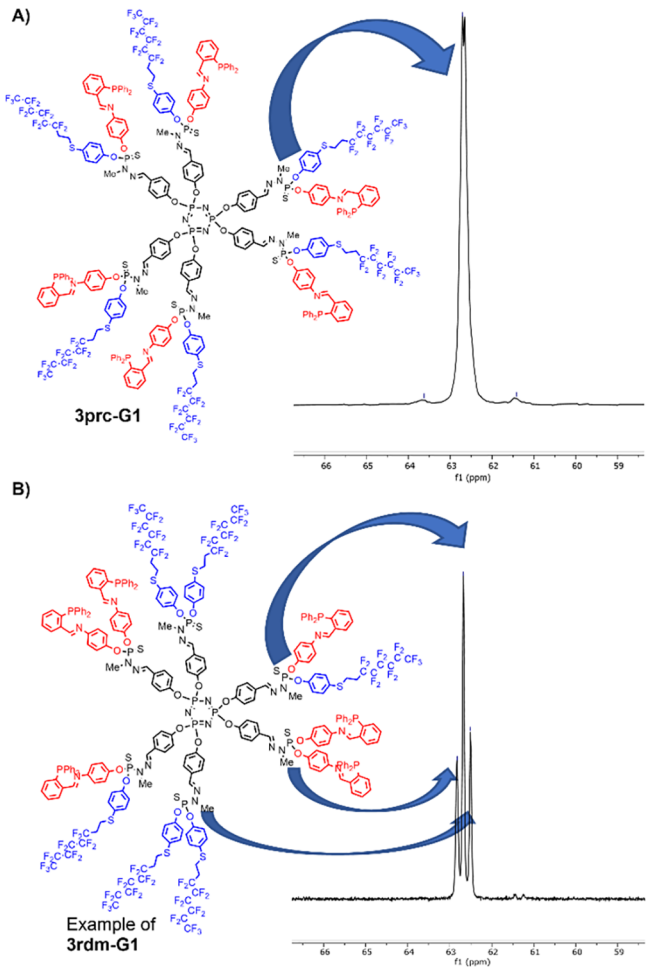


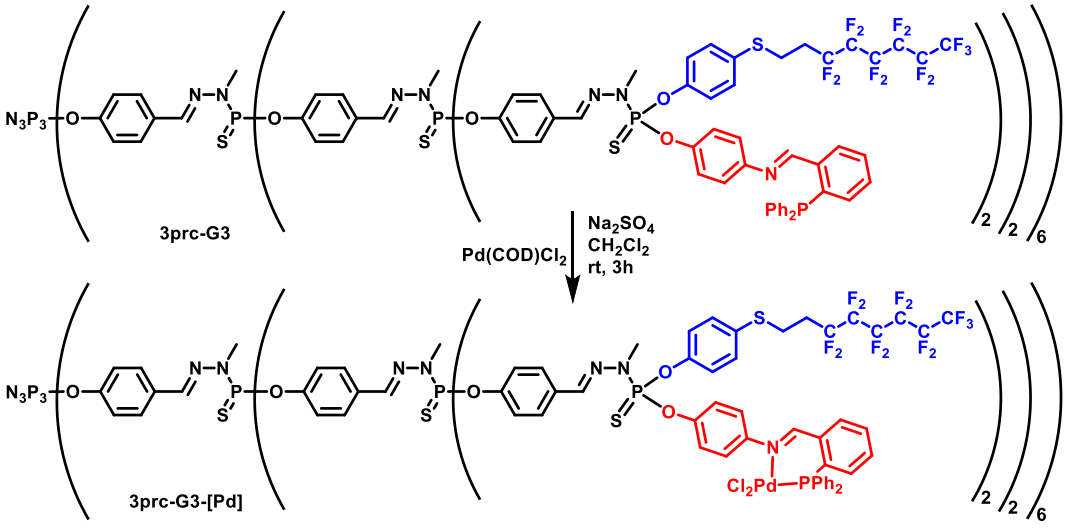
Figure 1. $^{31}P\{^{1}H\}$ NMR spectra of the P(S) groups in **3prc-G1** (A) and **3rdm-G1** (B) dendrimers.

^{1}H nor ^{19}F NMR were found suitable to detect any difference between the families of random (**3rdm-Gn**) and precise (**3prc-Gn**) difunctionalization of the dendrimers surface. $^{13}C\{^{1}H\}$ NMR displays slight differences on some signals, but not as easily interpretable as $^{31}P\{^{1}H\}$ NMR spectra (see spectra in SI). Mass spectrometry is unusable, as cleavages and rearrangements are always observed with PPH dendrimers in MALDI-Tof experiments.[15]

The complexation ability of the iminophosphine was checked on the model compound **3prc** and then on dendrimers **3prc-Gn** and **3rdm-Gn** (n = 1−3), respectively, using Pd(1,5-cyclooctadiene)Cl_2 (Scheme 2). The complexation was, in particular, characterized by $^{31}P\{^{1}H\}$ NMR, which displayed the disappearance of the signal corresponding to the free phosphine at ca. δ = −13 ppm, on behalf of the appearance of the signal corresponding to the phosphine complex at ca. δ = 30.8 ppm. It can be noted that there is no control of the chirality on the P(S)(OAr_1)(OAr_2) surface groups, and thus, all catalytic tests were carried out with nonchiral ligands, reagents, and reactions.

Having in hand two families of dendrimer complexes, namely, precisely and randomly difunctionalized, from generations 1−3, they were then tested in the Stille coupling[16] of iodobenzene with tributylvinyltin in THF at 50 °C. In order to have an accurate comparison between the different generations, the same quantity of catalytic sites was used in all cases. For instance, the efficiency of 1 equiv of generation 3 having 24 ligands complexing Pd is compared with that of 4 equiv of generation 1 having 6 ligands complexing Pd, and with that of 24 equiv of the monomeric complex. Even if the distance between the catalytic sites and their accessibility changes with the generations, this is the only way to compare the efficiency between generations. Figure 2 displays the results of these catalytic experiments monitored by NMR for 7 h. All experiments were carried out in duplicate, and the uncertainty is given in Figure 2. The precisely functionalized dendrimers display a slightly positive dendritic effect on going from generation 1 to generation 3.[17] An analogous, slightly positive dendritic effect is observed with the randomly functionalized dendrimers. However, it is important to note that in all cases from generation 1 to generation 3 the precisely difunctionalized dendrimers **3prc-Gn-[Pd]** are more efficient catalysts than the randomly functionalized dendrimers **3rdm-Gn-[Pd]**. The difference is most accurate between the first generations **3prc-**

Scheme 2. Example of the Synthesis of the Palladium Complex of the Dendrimer 3prc-G3[a]



[a]Reaction was also carried out with the monomer **3prc** and dendrimers **3prc-Gn** (n = 1, 2) and **3rdm-Gn** (n = 1−3).

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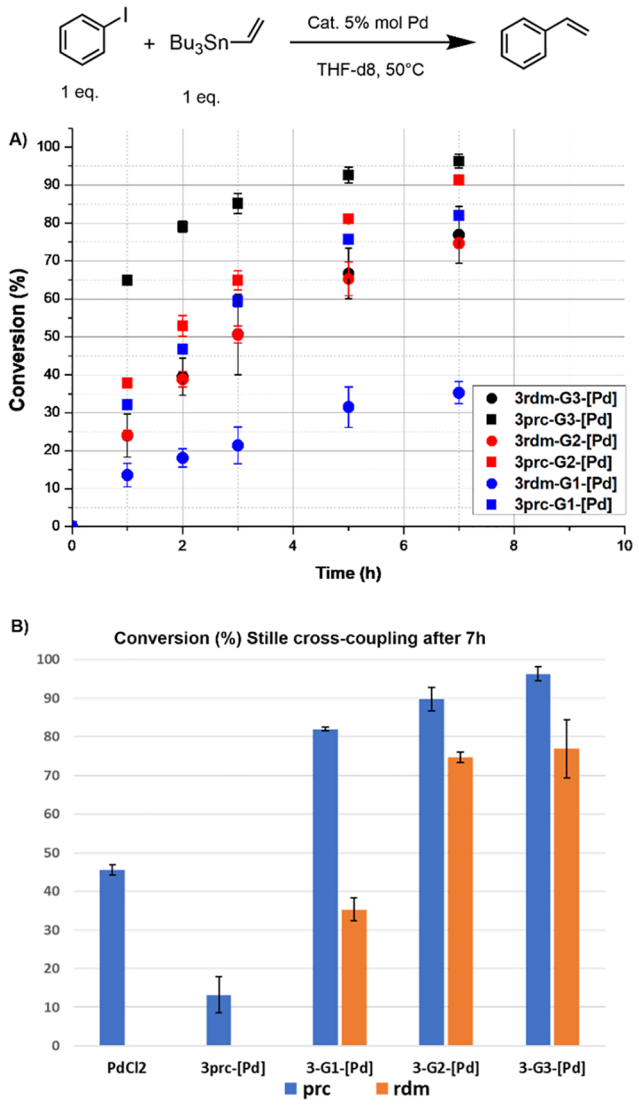

Figure 2. Stille cross-coupling catalytic experiments with precisely and randomly difunctionalized dendrimers from generation 1 to generation 3 and monomers: (A) evolution with time; (B) comparison of efficiency after 7 h.

G1-[Pd] and **3rdm-G1-[Pd]**, but it is still large with generations 2 and 3.

Part B of Figure 2 displays the results after 7 h, with additional information about the use of $PdCl_2$ alone and of the monomer. There is a large difference in the efficiency between monomer **3prc-[Pd]**, which is less efficient than $PdCl_2$ alone, and the different generations of the dendrimers, illustrating again a dendritic effect. As we had previously demonstrated a different efficiency of the Pd-iminophosphine catalysts, depending on the type of Stille couplings carried out,[9] we decided to test **3prc-G1-[Pd]** and **3rdm-G1-[Pd]** in another type of Stille couplings. The reagents used in this case were methyl-2-iodobenzoate and 2-(tributylstannyl) thiophene, and the catalysis was carried out for 22 h at 50 °C in THF. As shown in Figure 3, in this case also the precisely difunctionalized dendrimer **3prc-G1-[Pd]** was more efficient than the randomly difunctionalized dendrimer **3rdm-G1-[Pd]**.

In order to confirm more (or not) the large difference in efficiency between random and precisely difunctionalized dendrimers observed in the catalysis of Stille couplings, the

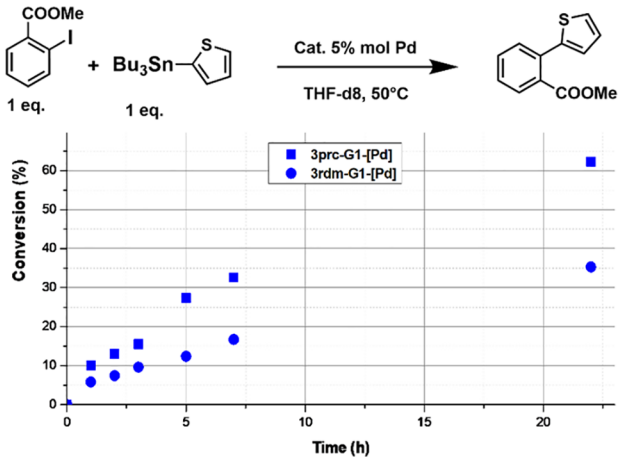

Figure 3. Another example of Stille coupling with precisely and randomly functionalized dendrimer **3-G1-[Pd]**.

model **3prc-[Pd]** and the first generations **3prc-G1-[Pd]** and **3rdm-G1-[Pd]** were tested in another type of cross-coupling reactions, the Heck reaction.[18] The reagents used were iodobenzene and methyl acrylate, in the presence of NEt_3.[18] It was shown previously that the presence of triethylamine increases the selectivity of the Heck coupling product.[19] In our case, we observed 100% selectivity in the *trans* product.

As the reaction occurs more slowly than the previous ones, experiments were carried out for a longer time, 30 h. A weak dendritic effect was observed on going from monomer **3prc-[Pd]** to **3prc-G1-[Pd]**. In this case as previously, the precisely difunctionalized dendrimer **3prc-G1-[Pd]** was found more efficient than the random difunctionalized dendrimer **3rdm-G1-[Pd]**, as illustrated in Figure 4.

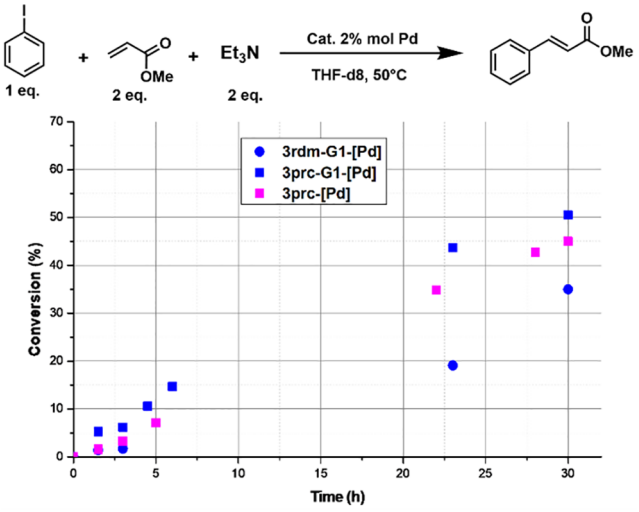

Figure 4. Heck cross-coupling reaction catalyzed by the monomer **3prc-[Pd]** and both dendrimers **3prc-G1-[Pd]** and **3rdm-G1-[Pd]**.

In this paper, we have demonstrated for the first time that the precise difunctionalization on all of the surface of dendrimers affords different results than their random difunctionalization. We have shown that the precise functionalization of PPH dendrimers is more efficient in two types of cross-coupling catalytic reactions. The difference is clearly visible for all generations, from the first to the third. Thus, besides the problems of reproducibility between batches

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previously known,[3] the difference in efficiency between precisely and randomly difunctionalized dendrimers must be taken into account and should be checked in each case. Indeed, examples in which randomly functionalized dendrimers are more efficient than precisely functionalized dendrimers can probably also exist. We believe that this original finding is not limited to catalysis, but can be considered as a global warning when using randomly functionalized dendrimers in any field, such as in biology where it is widely used with only very few questions.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.4c00204.

Materials, characterization methods, and experimental section; $^{31}P\{^{1}H\}$ NMR, ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, and $^{19}F\{^{1}H\}$ NMR, IR(ATR), and MS spectra of new products; general procedures for catalysis (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Massimo Petriccone** data curation, formal analysis, investigation, methodology, writing-original draft; **Régis LAURENT** conceptualization, methodology, supervision, writing-original draft; **Anne-Marie Caminade** conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review & editing; **Rosa-María Sebastián** conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review & editing.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. A New Class of Polymers: Starburst-Dendritic Macromolecules. *Polym. J.* **1985**, *17*, 117−132. (b) Majoral, J. P.; Caminade, A. M. Dendrimers Containing Heteroatoms (Si, P, B, Ge, or Bi). *Chem. Rev.* **1999**, *99*, 845−880. (c) Astruc, D.; Boisselier, E.; Ornelas, C. Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, Photonics, and Nanomedicine. *Chem. Rev.* **2010**, *110*, 1857−1959. (d) Caminade, A.-M.; Turrin, C.-O.; Laurent, R.; Ouali, A.; Delavaux-Nicot, B. *Dendrimers: Towards Catalytic, Material and Biomedical Uses*; John Wiley & Sons Ltd.: Chichester, U.K., 2011. (e) Caminade, A. M. Inorganic Dendrimers: Recent Advances for Catalysis, Nanomaterials, and Nanomedicine. *Chem. Soc. Rev.* **2016**, *45*, 5174−5185. (f) Sun, H. J.; Zhang, S. D.; Percec, V. From Structure to Function via Complex Supramolecular Dendrimer Systems. *Chem. Soc. Rev.* **2015**, *44*, 3900−3923. (g) Mignani, S.; Rodrigues, J.; Tomas, H.; Zablocka, M.; Shi, X.; Caminade, A.-M.; Majoral, J.-P. Dendrimers in Combination with Natural Products and nalogues as Anti-Cancer Agents. *Chem. Soc. Rev.* **2018**, *47*, 514−532.

(2) (a) Wong, P. T.; Tang, K.; Coulter, A.; Tang, S.; Baker, J. R.; Choi, S. K. Multivalent Dendrimer Vectors with DNA Intercalation Motifs for Gene Delivery. *Biomacromolecules* **2014**, *15* (11), 4134−4145. (b) Wang, L. N.; Yang, L.; Pan, L.; Kadasala, N. R.; Xue, L.; Schuster, R. J.; Parker, L. L.; Wei, A.; Tao, W. A. Time-Resolved Proteomic Visualization of Dendrimer Cellular Entry and Trafficking. *J. Am. Chem. Soc.* **2015**, *137* (40), 12772−12775. (c) Guo, Z.; Cheng, H.; Li, Z.; Shao, S.; Sarkar, P.; Wang, S.; Chaudhuri, R.; Perkins, N. G.; Ji, F.; Wei, W.; Xue, M. Single-Cell Profiling of Fatty Acid Uptake Using Surface-Immobilized Dendrimers. *J. Am. Chem. Soc.* **2021**, *143* (29), 11191−11198. (d) Jin, Y.; Fan, J.; Wang, R.; Wang, X.; Li, N.; You, Q.; Jiang, Z. Ligation to Scavenging Strategy Enables On-Demand Termination of Targeted Protein Degradation. *J. Am. Chem. Soc.* **2023**, *145* (13), 7218−7229.

(3) Thomas, T. P.; Huang, B. H.; Choi, S. K.; Silpe, J. E.; Kotlyar, A.; Desai, A. M.; Zong, H.; Gam, J.; Joice, M.; Baker, J. R. Polyvalent Dendrimer-Methotrexate as a Folate Receptor-Targeted Cancer Therapeutic. *Mol. Pharmaceutics* **2012**, *9*, 2669−2676.

(4) (a) Zhang, W.; Nowlan, D. T.; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. Orthogonal, Convergent Syntheses of Dendrimers Based on Melamine with One or Two Unique Surface Sites for Manipulation. *J. Am. Chem. Soc.* **2001**, *123* (37), 8914−8922. (b) Steffensen, M. B.; Simanek, E. E. Synthesis and Manipulation of Orthogonally Protected Dendrimers: Building Blocks for Library Synthesis. *Angew. Chem. Int. Ed.* **2004**, *43* (39), 5178−5180.

References in (c) Simanek, E. E. Two Decades of Triazine Dendrimers. *Molecules* **2021**, *26*, 4774.

(5) (a) Zhang, D.; Atochina-Vasserman, E. N.; Maurya, D. S.; Liu, M.; Xiao, Q.; Lu, J.; Lauri, G.; Ona, N.; Reagan, E. K.; Ni, H.; Weissman, D.; Percec, V. Targeted Delivery of mRNA with One-Component Ionizable Amphiphilic Janus Dendrimers. *J. Am. Chem. Soc.* **2021**, *143* (43), 17975−17982. (b) Zhang, D.; Atochina-Vasserman, E. N.; Lu, J.; Maurya, D. S.; Xiao, Q.; Liu, M.; Adamson, J.; Ona, N.; Reagan, E. K.; Ni, H.; Weissman, D.; Percec, V. The Unexpected Importance of the Primary Structure of the Hydrophobic Part of One-Component Ionizable Amphiphilic Janus Dendrimers in Targeted mRNA Delivery Activity. *J. Am. Chem. Soc.* **2022**, *144* (11), 4746−4753. (c) Zhang, D.; Xiao, Q.; Rahimzadeh, M.; Liu, M.; Rodriguez-Emmenegger, C.; Miyazaki, Y.; Shinoda, W.; Percec, V. Self-Assembly of Glycerol-Amphiphilic Janus Dendrimers Amplifies and Indicates Principles for the Selection of Stereochemistry by Biological Membranes. *J. Am. Chem. Soc.* **2023**, *145* (7), 4311−4323. (d) Lu, J.; Atochina-Vasserman, E. N.; Maurya, D. S.; Sahoo, D.; Ona, N.; Reagan, E. K.; Ni, H.; Weissman, D.; Percec, V. Targeted and Equally Distributed Delivery of mRNA to Organs with Pentaerythritol-Based One-Component Ionizable Amphiphilic Janus Dendrimers. *J. Am. Chem. Soc.* **2023**, *145*, 18760−18766.

(6) (a) Mullen, D. G.; Borgmeier, E. L.; Desai, A. M.; Van Dongen, M. A.; Barash, M.; Cheng, X.-M.; Baker Jr, J. R.; Banaszak Holl, M. M. Isolation and Characterization of Dendrimers with Precise Numbers of Functional Groups. *Chem.—Eur. J.* **2010**, *16*, 10675−10678. (b) Dougherty, C. A.; Vaidyanathan, S.; Orr, B. G.; Banaszak Holl, M. M. Fluorophore:Dendrimer Ratio Impacts Cellular Uptake and Intracellular Fluorescence Lifetime. *Bioconjugate Chem.* **2015**, *26*, 304−315.

(7) (a) Launay, N.; Caminade, A. M.; Lahana, R.; Majoral, J. P. A General Synthetic Strategy for Neutral Phosphorus-Containing Dendrimers. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1589−1592. (b) Launay, N.; Caminade, A. M.; Majoral, J. P. Synthesis and Reactivity of Unusual Phosphorus Dendrimers. A Useful Divergent Growth Approach Up to the Seventh Generation. *J. Am. Chem. Soc.* **1995**, *117*, 3282−3283. (c) Ouali, A.; Laurent, R.; Caminade, A. M.; Majoral, J. P.; Taillefer, M. Enhanced Catalytic Properties of Copper in O- and N-Arylation and Vinylation Reactions, Using Phosphorus Dendrimers as Ligands. *J. Am. Chem. Soc.* **2006**, *128* (50), 15990−15991. (d) Neumann, P.; Dib, H.; Caminade, A. M.; Hey-Hawkins, E. Redox Control of a Dendritic Ferrocenyl-Based Homogeneous Catalyst. *Angew. Chem. Int. Ed.* **2015**, *54* (1), 311−314.

(8) (a) Lartigue, M. L.; Slany, M.; Caminade, A. M.; Majoral, J. P. Phosphorus-Containing Dendrimers: Synthesis of Macromolecules with Multiple Tri- and Tetrafunctionalization. *Chem.—Eur. J.* **1996**, *2*, 1417−1426. References included in (b) Petriccone, M.; Laurent, R.; Turrin, C.-O.; Sebastián, R. M.; Caminade, A.-M. Specific Bifunctionalization on the Surface of Phosphorus Dendrimers Syntheses and Properties. *Organics* **2022**, *3*, 240.

(9) Koprowski, M.; Sebastián, R. M.; Maraval, V.; Zablocka, M.; Cadierno, V.; Donnadieu, B.; Igau, A.; Caminade, A.-M.; Majoral, J.-P. Iminophosphine Palladium Complexes in Catalytic Stille Coupling Reactions: From Monomers to Dendrimers. *Organometallics* **2002**, *21*, 4680−4687.

(10) Cao, C. T.; Zhou, W.; Cao, C. Abnormal Effect of Hydroxyl on the Longest Wavelength Maximum in Ultraviolet Absorption Spectra for Bis-Aryl Schiff Bases. *J. Phys. Org. Chem.* **2017**, *30*, No. e3672.

(11) El Brahmi, N.; El Kazzouli, S.; Mignani, S.; Laurent, R.; Ladeira, S.; Caminade, A.-M.; Bousmina, M.; Majoral, J.-P. Symmetrical and Unsymmetrical Incorporation of Active Biological Monomers on the Surface of Phosphorus Dendrimers. *Tetrahedron* **2017**, *73*, 1331−1341.

(12) (a) Yoshida, T.; Hirakawa, T.; Nakamura, T.; Yamada, Y.; Tatsuno, H.; Hirai, M.; Morita, Y.; Okamoto, H. Gelation Properties of Aprotic Low-Molecular-Mass Organic Gelators Based on a Gemini 4-[2-(Perfluoroalkyl)ethylsulfanyl]phenoxy Derivative Unit. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1447−1452. (b) Yoshida, T.; Nakamura, T.; Morita, Y.; Okamoto, H. Gelation by Novel Aprotic Low-Molecular-Mass Organic Gelators Based on a Gemini 4-[2-(Perfluorobutyl)ethylthio]phenoxy Unit. *Chem. Lett.* **2015**, *44*, 512−514.

(13) Caminade, A.-M.; Laurent, R.; Turrin, C. O.; Rebout, C.; Delavaux-Nicot, B.; Ouali, A.; Zablocka, M.; Majoral, J. P. Phosphorus Dendrimers as Viewed by ^{31}P-NMR Spectroscopy; Synthesis and Characterization. *C. R. Chim.* **2010**, *13*, 1006−1027.

(14) Galliot, C.; Larre, C.; Caminade, A. M.; Majoral, J. P. Regioselective Stepwise Growth of Dendrimer Units in the Internal Voids of a Main Dendrimer. *Science* **1997**, *277*, 1981−1984.

(15) Blais, J.-C.; Turrin, C.-O.; Caminade, A. M.; Majoral, J. P. MALDI TOF Mass Spectrometry for the Characterization of Phosphorus-Containing Dendrimers. Scope and Limitations. *Anal. Chem.* **2000**, *72*, 5097−5105.

(16) Cordovilla, C.; Bartolome, C.; Martinez-Ilarduya, J. M.; Espinet, P. The Stille Reaction, 38 Years Later. *ACS Catal.* **2015**, *5*, 3040−3053.

(17) (a) Helms, B.; Frechet, J. M. J. The Dendrimer Effect in Homogeneous Catalysis. *Adv. Synth. Catal.* **2006**, *348*, 1125. (b) Caminade, A.-M.; Ouali, A.; Laurent, R.; Turrin, C.-O.; Majoral, J. P. The Dendritic Effect Illustrated with Phosphorus Dendrimers. *Chem. Soc. Rev.* **2015**, *44*, 3890−3899.

(18) (a) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009−3066. (b) Mc Cartney, D.; Guiry, P. J. The Asymmetric Heck and Related Reactions. *Chem. Soc. Rev.* **2011**, *40*, 5122−5150. (c) Yeung, L. K.; Lee, C. T.; Johnston, K. P.; Crooks, R. M. Catalysis in Supercritical CO_2 Using Dendrimer-Encapsulated Palladium Nanoparticles. *Chem. Commun.* **2001**, 2290−2291. (d) Liang, R.-X.; Jia, Y.-X. Aromatic π-Components for Enantioselective Heck Reactions and Heck/Anion-Capture Domino Sequences. *Acc. Chem. Res.* **2022**, *55* (5), 734−745.

(19) Zhao, F. Y.; Bhanage, B. M.; Shirai, M.; Arai, M. Heck Reactions of Iodobenzene and Methyl Acrylate with Conventional Supported Palladium Catalysts in the Presence of Organic and/and Inorganic Bases without Ligands. *Chem.—Eur. J.* **2000**, *6*, 843−848.

(20) Banaszak Holl, M. M.; Dougherty, C. A.; Vaidyanathan, S. Tailoring Dendrimer Conjugates for Biomedical Applications: the Impact of Altering Hydrophobicity. *J. Nanopart. Res.* **2018**, *20*, 284.

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