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Pd Catalysis on Dendronized Solid Support: Generation Effects and the Influence of the Backbone Structure

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Abstract: Recent studies revealed that catalysts, prepared on dendronized support, frequently exhibit enhanced activity and selectivity as compared to their non-dendronized analogues. Regretfully, in early studies of the supported dendritic catalysis, no particular attention was paid to the coordinative nature of the dendritic backbone. In this study, we functionalized Wang polystyrene support with three types of dendritic templates: poly(aril benzyl ether), poly(aryl benzyl thioether), and poly(aryl benzyl amine). These dendronized resins were further decorated with phosphine ligands on the periphery and complexed with a Pd(0) catalytic precursor. The catalysis of the Heck and Suzuki reactions of bromobenzene with the first to third generation supported dendritic catalysts was examined and compared to that of the non-dendritic analogues. All of the examined reactions revealed a positive dendritic effect, reflected in up to 5-fold increase in yield, in the most prominent case. The reasons for the observed effect are the proximity of the ligating sites translated into reduced cross-linking and, probably, the increased distance of the catalyst from the polymer matrix. We proved, however, that the latter could not be achieved with a linear spacer. Although the Suzuki reaction was rather insensitive to the backbone structure, the Heck reaction catalysis at 80 °C exhibited substantial sensitivity to the nature of the dendritic backbone, with the polyether structure demonstrating the best outcome. This is the first demonstration of the influence of the coordinative ability of the backbone on the activity of a supported dendritic catalyst.

Introduction

The quest for easily separable catalysts is driven by economic considerations as well as by increasing environmental concerns. Along with relatively new approaches to catalyst separation (e.g., fluorous-phase soluble catalysts, dendrimer-, or other soluble polymer-supported catalysts),[1] the traditional immobilization of analogues of homogeneous catalysts on insoluble polymers has received special attention.[2] In recent years, research on polymer-bound catalysts was assisted by the enormously expanded volume of reliable procedures for solid-phase synthesis.[3] Additional motivation to develop such catalysts was provided by the emerging technique of solution-phase combinatorial chemistry, based on insoluble reagents, catalysts, and scavengers.[4] Unfortunately, in most cases, the immobilization of catalytic species on a polymer support is accompanied by a significant loss in catalytic activity and/or selectivity. Polymer-based catalysts are often ineffective, due to leaching of the catalytic metals, the unavailability and nonuniformity of the catalytic sites, and indefinable incorporation of catalysts within the polymer bulk.

Repeatedly, it was demonstrated that the supporting matrix crucially influences the performance of the catalyst. Recent studies revealed that catalysts, prepared on dendronized supports, can exhibit enhanced activity, selectivity, and recyclability (not necessarily together), relative to their analogues, attached to a nondendronized matrix.[5] In some cases, the improvement was generation-dependent and defined as the positive dendritic effect.

Dendrimers are branched, highly ordered oligomers, assembled in a modular fashion from polyfunctional building blocks and utilized for a surprisingly wide spectrum of applications, including catalysis.[6] While the majority of dendritic structures are prepared using orthodox solution chemistry, increasing attention has recently been diverted to dendron preparation on solid support.[7] Solid-phase synthesis provides solutions to a number of problems associated with dendrimer preparation, particularly the time-consuming purifications, and can also markedly improve the yield and homogeneity of the formed dendrons.

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10.1021/ja065265d CCC: $37.00

Most of the dendrons prepared on solid support are based on carbonyl- and amine-containing moieties (e.g., polylysine prepared by Tam, poly(amidoamine)(PAMAM) and poly(amidourea) prepared by Bradley).[8] Although it is likely that carbonyls and amines can coordinate to catalytic metal centers, all early studies of supported dendritic catalysts were based on polyamido backbones, particularly PAMAM dendrons.[5c−g,9,10] Some of these works demonstrated the influence of the dendritic backbone structure on the catalysis results,[5c−e] but no particular attention was paid to the coordinating nature of the dendritic backbone.

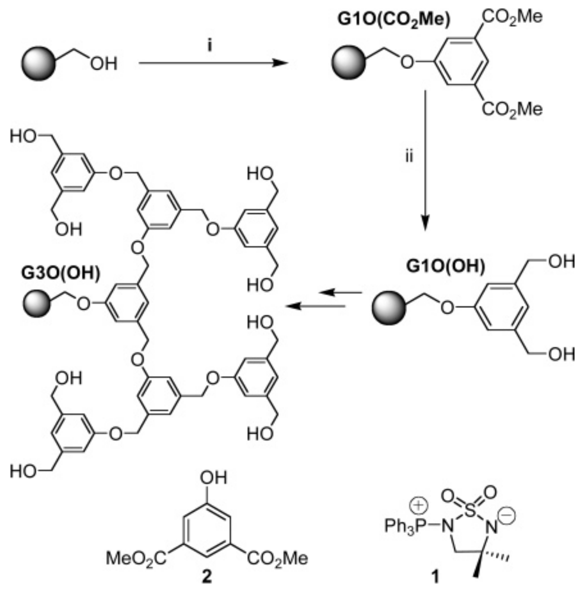
In our work, we decided to focus on polyether dendrons, because ethers are sufficiently stable and demonstrate poor ligating ability to transition metals and, particularly, late transition metals, which are the focus of our catalytic studies. We also decided to examine whether the coordinative nature of the dendritic backbone influences the behavior of the dendritic catalysts, and to generate dendrons that are based on thioether and amine linkage between the modules, in addition to those based on ether linkage. Herein, we report the study of the supported complexes based on these three types of dendrons, including the differences in their catalytic performance. Description of the synthesis and properties of the poly(aryl benzyl)ether dendrons has been published, as well as preliminary reports on polythioether dendron synthesis and the Heck reaction with polyether dendron-based catalysts.[5b,11]

Results and Discussion

The Poly(aryl benzyl)ether Dendron. The first synthetic route to this dendron on polystyrene was reported by Bradley.[12] However, it was based on a monomer that is not commercially available and must be prepared in four steps. On the other hand, as we communicated earlier, we were able to grow first to third generation dendrons of this type (**GnO**) through a repetitive Mitsunobu coupling−ester reduction sequence, while using the commercially available dimethyl 5-hydroxyphthalate (**2**, Scheme 1).[11a,13] Remarkably, use of the triphenylphosphine-sulfonamide betain **1** and $LiBH_4/B(OMe)_3$ reducing agent in the two sequence steps, respectively, leads to outstanding yields and purity.

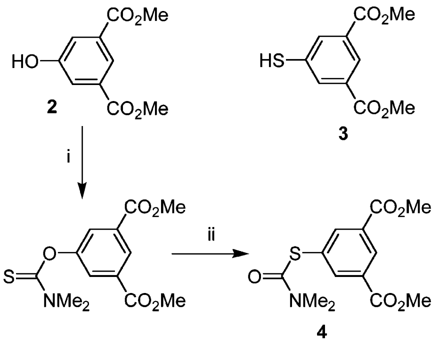
The structure and purity of the dendrons were determined via TFA-induced cleavage, followed by ^1H NMR, ^{13}C NMR, and MS analysis. According to the cleavage analysis and quantification, the overall yield of the third generation is 82%.

Scheme 1 [a]



[a] Reagents and conditions: (i) **1**, **2**, DCM, room temperature, 24 h; (ii) $LiBH_4$, $B(OMe)_3$, THF, 67 °C, 12 h.

Scheme 2 [a]



[a] Reagents and conditions: (i) dimethylthiocarbamoyl chloride, DABCO, DMA, 75 °C, 85%; (ii) 280 °C, 10 min, 95%.

The Poly(aryl benzyl)thioether Dendron. As we recently communicated, we prepared the poly(aryl benzyl)thioether dendrons **GnS**, the sulfur analogue of the polyether dendrons **GnO**.[11b] The relevant monomer **3** is not commercially available, and its synthesis has never been reported. Luckily, we were able to convert the commercially available 5-hydroxy isophthalate diester **2** into **4**, the dimethylcarbamoyl derivative of **3**, via the Newman−Kwart rearrangement (Scheme 2).[14] The procedure is high-yielding, and a multigram scale preparation of **4** is possible. Because of the strong propensity of **3** (formed upon deprotective methanolysis of **4**) to undergo oxidative dimerization, we used **4** in the relevant dendron building procedures, forming **3** in situ.

The dendrimer-forming synthetic sequence included three repetitive steps: substitution of benzyl halide by the thiophenolate, reduction, and chlorodehydroxylation (Scheme 3). The last step reforms the benzyl halide terminal function, enabling the construction of the next generation of the dendrimer, and was cleanly accomplished with a PPh_3/C_2Cl_6 mixture.

The synthesis was monitored, and the products characterized, using gel-phase ^{13}C NMR as well as acidolytic cleavage, followed by ^1H and ^{13}C NMR, and mass spectrometry. Contrary to the case of polyether dendrons, in all experiments, the cleavage occurred between the resin and the Wang linker and not between the linker and the dendron (Scheme 4a). Thus, a 4-hydroxybenzyl-protected version of the dendron was always

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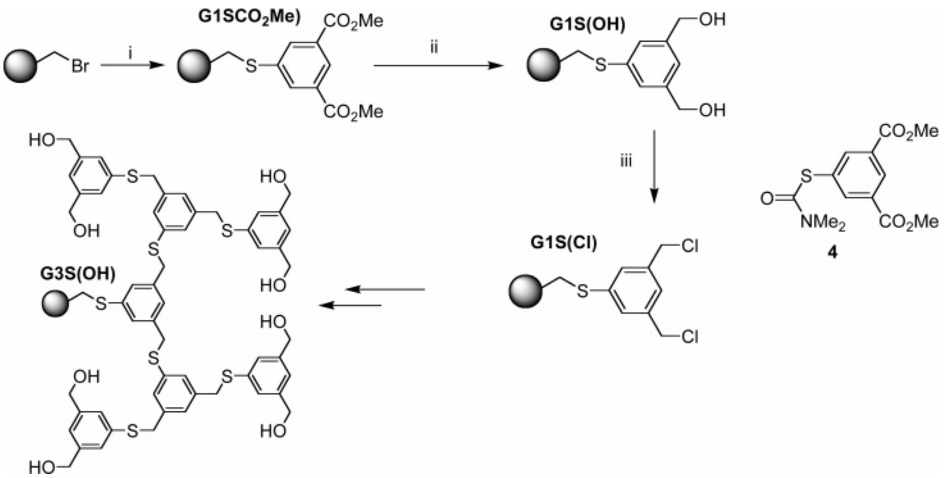
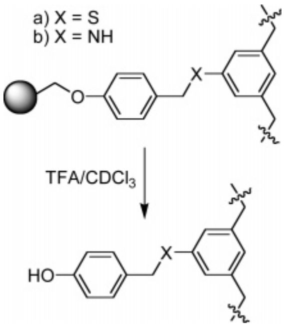
Scheme 3[a]



[a] Reagents and conditions: (i) **4**, NaOMe 0.5 M in methanol, DMF, 70 °C, 12 h; (ii) $LiBH_4$, $B(OMe)_3$, THF, 67 °C, 12 h; (iii) C_2Cl_6, PPh_3, THF, room temperature, 6 h.

Scheme 4



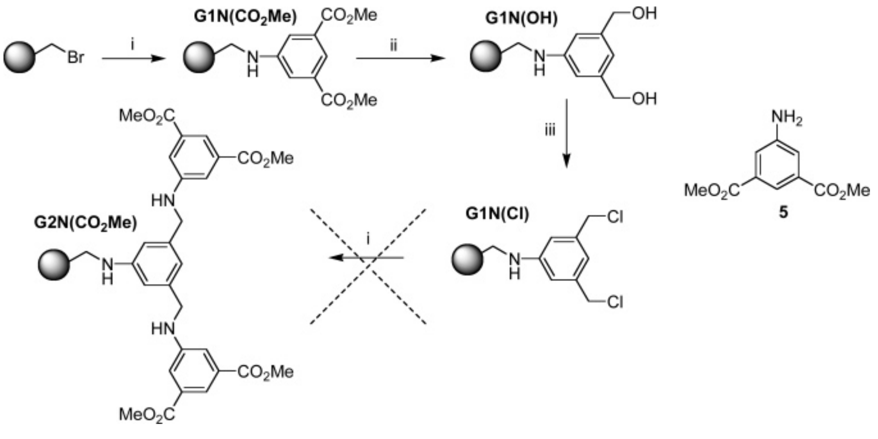
released from the resin. While the linker is clearly visible in the ^1H and ^{13}C NMR spectra of the cleavage solution, it is removed under the CI−MS conditions, and disulfide-bridged dendron dimers are observed in the MS spectra.

The aforementioned ^1H NMR measurements demonstrated excellent conversion and purity of each of the three repetitive steps as per the following characteristic changes. Immobilization of **3** is accompanied by the complete disappearance of the $-CH_2Cl$ signals (4.5 ppm) and appearance of the low-field aromatic signals of the peripheral isophthalate units (8.5 and 8.2 ppm). Reduction results in complete disappearance of the signals of the isophthalate diester along with the appearance of $-CH_2OH$/$-CH_2OCOCF_3$ peaks (4.8 and 5.4 ppm, respectively). The latter disappear completely upon chlorodehydroxylation and are replaced by the $-CH_2Cl$ signals (4.5 ppm).

The Poly(aryl benzyl)amine Dendron. Following the synthesis of the thioether analogue, we proceeded to prepare the poly(aryl benzyl amine) dendrons. The synthetic procedure was based on the substitution of the halide of the Wang Bromo resin by the commercial dimethyl 5-aminoisophthalate (**5**) and reduction of the ester groups with $LiBH_4$ as the first two steps (Scheme 5). Initially, we attempted to construct the dendron by chlorodehydroxylation of the alcohols of **G1N(OH)**, followed by another nucleophilic substitution to yield the next generation dendron. While the first of these two reactions gave a very clean product, **G1N(Cl)**, we found that the formed benzylic halides cannot be effectively substituted by **5**. Mild conditions left **G1N(Cl)** unchanged, while harsher conditions led to a mixture of products. The poor nucleophilicity of the aniline unit is likely to be responsible for the failure of this reaction.

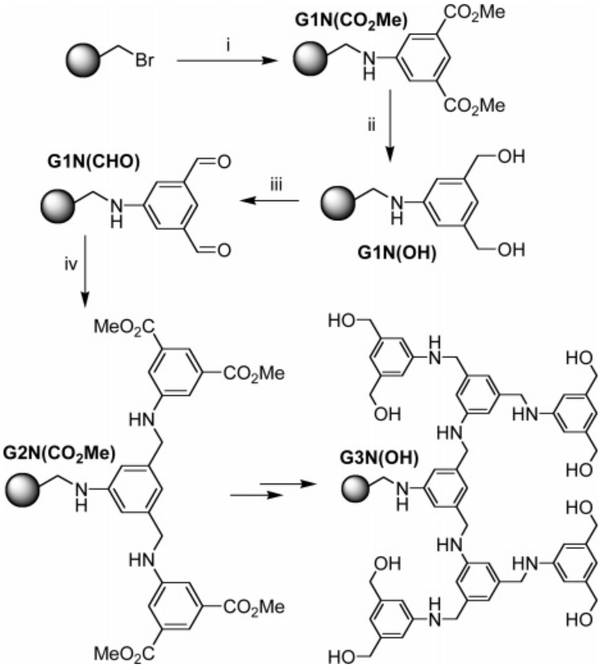
According to the alternative strategy, the synthesis starts with the halide substitution and reduction, as previously mentioned, but the alcohols are then oxidized to aldehydes using sulfur trioxide pyridine complex (Scheme 6). The next generation of

Scheme 5[a]



[a] Reagents and conditions: (i) **5**, 2,6-lutidine, TBAI, DMF, 80 °C, 3 days; (ii) $LiBH_4$, $B(OMe)_3$, THF, 67 °C, 12 h; (iii) C_2Cl_6, PPh_3, THF, room temperature, 6 h.

Scheme 6[a]



[a] Reagents and conditions: (i) 2,6-lutidine, TBAI, **5**, DMF, 80 °C, 3 days; (ii) $LiBH_4$, $B(OMe)_3$, THF, 67 °C, 12 h; (iii) SO_3·Py, NEt_3, DMSO, 4 h, room temperature; (iv) $NaBH(OAc)_3$, $HC(OMe)_3$, **5**, DMF, 60 °C, 48 h.

the dendron is assembled via the reductive amination of the aldehydes with **5** in the presence of trimethylorthoformate, using sodium triacetoxyborohydride as a reducing agent. Apparently, the nucleophilicity of the aniline monomer is sufficient for formation of the transient imine conjugate during the reductive amination step. Repetitive ester reduction, oxidation, and reductive amination sequence led to the formation of the higher generations. We found that this synthetic scheme can be cleanly and effectively accomplished, yielding in eight steps, starting from Wang Bromo resin, 85% of the third generation dendron.

The synthesis was monitored, and the products characterized, using gel-phase ^{13}C NMR as well as acidolytic cleavage, followed by ^{1}H and ^{13}C NMR and mass spectrometry. Similar to the polythioether dendron, the cleavage always occurred between the resin and the Wang linker, thus forming the 4-hydroxybenzyl-protected version of the dendron (Scheme 4b). Again, similar to the polythioether case, the linker is clearly visible in the ^{1}H and ^{13}C NMR spectra upon cleavage, but is removed under CI−MS conditions.

Use of the amine linkage to the support required a slight change in the procedure for cleavage of the dendrons. We found that, as expected, only a low percentage of the dendrons were cleaved by a TFA/$CDCl_3$ (1:1 v/v) solution after 1 h of stirring. However, the dendrons were quantitatively released from the resin following 24 h cleavage.

Although characterization of the products of the first generation was easily accomplished using gel-phase ^{13}C NMR and/or acidolytic cleavage, followed by ^{1}H and ^{13}C NMR and mass spectrometry, it was much more difficult to characterize the products of the second and the third generations. Partial protonation of the amines in the cleavage solution caused severe difficulties in assignment of the peaks in the ^{1}H and ^{13}C NMR. In addition, line broadening by neighboring nitrogens interfered in the assignment of the gel-phase NMR spectra.

The hydroxy-terminated resin could not be analyzed using gel-phase ^{13}C NMR even for the first generation and even in polar solvents, such as dioxane-d_8. The density of the OH and NH groups seems to generate a hydrogen-bonded hydrophilic “film” that prevents the proper swelling of the polystyrene core polymer. Significantly improved gel-phase spectra were observed only after acylation of the OH and NH groups with acetyl chloride.

For quantitative determination of the dendron loading, we used two main strategies. First, we functionalized the hydroxy-terminated resins with Fmoc-Gly-OH and photometrically determined the Fmoc loading.[15] According to the second strategy, we esterified the hydroxy-terminated dendrons with 4-(diphenylphosphino)benzoic acid. Because we optimized this reaction’s conditions for the poly(aryl benzyl ether) and poly(aryl benzyl thioether) dendrons,[5a,11b] we assume that a complete conversion of the hydroxyl terminal groups into (diphenylphosphino)benzoxy moieties was achieved for all generations of the polyamine dendron. Quantification of the phosphine loading was achieved using the ^{31}P NMR. Each resin was mixed with commercial polystyrene-immobilized triphenylphosphine reference resin with a known loading. After the ^{31}P gel-phase NMR spectra were recorded, the yields were determined using the mixing ratio, the integral ratio, and the known reference loading.[16] More accurate results were obtained after the resins were allowed to swell in benzene-d_6 for 24 h. Both strategies usually showed an excellent agreement.

The Heck Reaction. To examine the dependence of the performance of polymer-bound catalytic systems on the dendritic architecture of the spacer, tethering the catalytic units to the matrix, the Heck reaction was chosen. Heck olefin arylation, one of the most widely used metal-catalyzed processes in synthetic organic chemistry, was successfully accomplished in solution with aryl iodides, bromides, and even chlorides, using a variety of catalytic systems, particularly phosphine−palladium complexes.[17] Heterogeneous catalysis, however, was performed almost entirely with iodides or electron-deficient bromides, mainly using metal palladium adsorbed on an inorganic support.[18−20] Only a few phosphine-based heterogeneous systems have been reported, and the reactivities of these systems were almost always limited to iodides.[21] The fundamental study by Hallberg and co-workers exposed the need for multiple phosphine ligation to Pd as a tool for effective bromoarene

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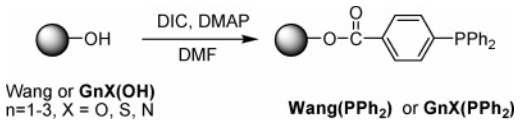
Scheme 7



olefination with a supported catalyst.[22] Unfortunately, such coordination modes result in severe cross-linking of the polymer, which frequently has a negative effect on the catalytic activity. Another work, performed in our group, demonstrated the clear advantage of the bidentate over monodentate phosphine ligands in the case of the heterogeneously catalyzed Heck reaction.[23] With this notion in mind, we decided to investigate catalytic systems that are based on phosphine−palladium complexes derived from dendronized polymeric supports.

The dendronized resins were decorated with phosphine groups via the attachment of 4-(diphenylphosphino)benzoic acid to the periphery of the dendrons, as explained for the polyamine dendrons characterization (Scheme 7). The resins were characterized using gel-phase ^{31}P NMR (signal at −4.2 ppm) and ^{13}C NMR as well as TFA-induced cleavage followed by ^{1}H NMR of the cleaved solution. Quantitative determination of the resin loading based on both ^{31}P and ^{1}H NMR usually showed excellent agreement. Complete conversion of the hydroxyl terminal groups into (diphenylphosphino)benzoxy moieties was achieved for all resins.

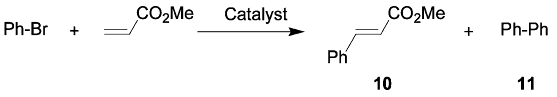
Study of the properties of the **Wang(PPh$_2$)** and **GnX(PPh$_2$)** resins revealed that THF is the best solvent for their swelling, and, accordingly, it was chosen for their complexation with metal precursors. Thus, incubation of the phosphine-terminated resins with Pd(dba)$_2$ in deoxygenated THF at ambient temperature for 4 h yielded reddish brown resins **6**−**9** (Scheme 8). Gel-phase ^{31}P NMR demonstrated quantitative complexation of the phosphines with Pd (signals at 25−30 ppm). ^{1}H NMR spectra of the TFA-cleaved solutions of resins **6**−**9** revealed that, for every two phosphine groups, one molecule of dibenzylidenacetone is present. Thus, the most probable structure of the Pd complexes on the supports is (phosphine)$_2$Pd(dba), and the loading of the active catalyst on support was calculated accordingly.[24] As to these calculations, the loading of Pd for resins **6**−**9** ranges between 0.3 and 0.5 mmol/g resin. Although upon increase of the dendron generation, there is an increase in the amount of the complexation sites per single attachment point on the matrix, this is counterbalanced by the increase in the mass of the spacer and some decrease in the overall synthetic yield.

Table 1. Heck Reaction with Methyl Acrylate at 80 °C for 72 h[a]

entry	catalyst	conversion (%)	yield of **10** (%)	selectivity (**10**:**11**)
1	**6**	20	18	9.0
2	**7G1**	11	11	22
3	**7G2**	66	66	>130
4	**7G3**	100	100	>200
5	**8G1**	15	10	2
6	**8G2**	19	13	2.2
7	**8G3**	67	61	10.2
8	**9G1**	18	13	2.6
9	**9G2**	25	18	2.6
10	**9G3**	91	89	44.5
11	**12**	84	82	41

[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of methyl acrylate, 0.65 mmol of triethylamine, and the catalyst (0.0125 mmol of Pd) in 1 mL of *N*-methylpyrrolidone (NMP), 80 °C, 72 h.

The reaction of bromobenzene with methyl acrylate, chosen as a model for the Heck reaction with catalysts **6**−**9**, was performed under two different temperature regimes: at 80 °C for 72 h and at 120 °C for 14 h (eq 1). While the main product is *trans*-methyl cinnamate (**10**), in some experiments the bromobenzene homocoupling byproduct, biphenyl (**11**), was obtained.



(1)

The results of the model reaction, of the three types of dendrons at 80 °C for 72 h, summarized in Table 1 and Chart 1, demonstrate a remarkable improvement in the catalytic performance upon dendronization of the support for all types of dendrons, and the importance of the character of the dendron backbone on the performance.

The difference in the reactivity within the **7** series of catalysts is very dramatic under these conditions (Table 1, entries 1−4). While there is a notable decrease in the activity of **7G1**, as compared to that of **6**, the activity increases significantly for **7G2**, improves further for **7G3**, surpassing by far that of **6**, and rendering for **7G3** quantitative conversion and yield. It is noteworthy that, similar to **6** and **7G1**, most of the known catalytic systems for the Heck reaction of bomoarenes are not

Scheme 8

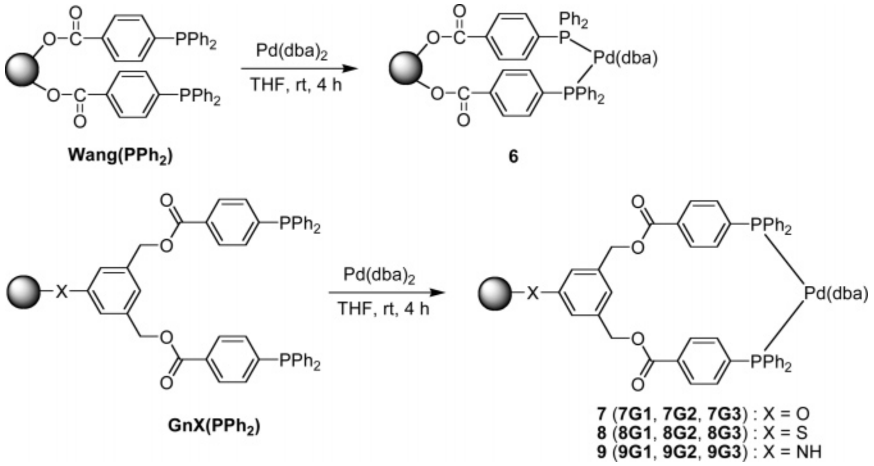
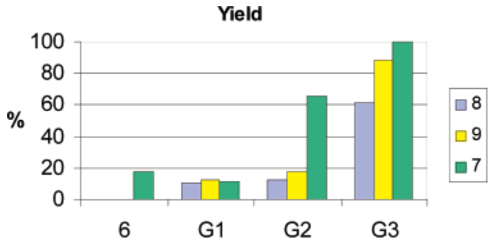
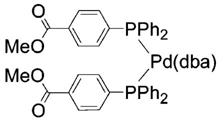


Chart 1. Catalytic Results of the Heck Reaction at 80 °C: Comparison of the Three Types of Dendrons



active enough at 80 °C and require higher temperatures (110−130 °C). The selectivity of the catalysis also improves significantly upon the increase of the dendron generation, and no biphenyl is observed for **7G2** and **7G3**. We also synthesized the non-dendritic homogeneous analogue **12** of complexes **7**, prepared in situ from Pd(dba)$_2$ and the methyl ester of the 4-(diphenylphosphino)benzoic acid. Remarkably, the conversion and selectivity achieved with **7G3** (Table 1, entry 4) are significantly higher than those obtained with **12** (Table 1, entry 11). One may argue that **12** incorporates monodentate phosphines, while those forming **7** are chelating in nature. However, the minimal chelate size on the dendronized resins is 20 atoms, the tether between every two phosphine groups is fairly flexible, and, thus, two resin-bound phosphines coordinated to Pd in **7** are very similar in nature to the monodentate ligands. Therefore, chelate effects are unlikely to be responsible for the superiority of **7G3** over **12**.



12

Similar results were obtained for the **8** and **9** series. The catalysts derived from the third generation are superior to the non-dendronized catalysts in all parameters.

Although there are no significant differences between the catalysts derived from the three types of the first generation dendron (**7G1**, **8G1**, **9G1**), a dramatic difference is observed for those based on the second generation (**7G2**, **8G2**, **9G2**), where **7G2** is a much more active and selective catalyst than the other two (Chart 1). This pattern is preserved for the third generation-derived catalysts (**7G3**, **8G3**, **9G3**).

The results of the model reaction with the three types of dendritic catalysts at 120 °C are summarized in Table 2 and Chart 2. In the case of the Heck reaction at 120 °C, the pattern for the **7** series follows the trends observed in the former case. Although, under these conditions, the conversions obtained with the dendritic catalysts are only marginally better than that of the catalyst derived from the Wang resin (**6**), the selectivity for the formation of the Heck product consistently improves from **6** to **7G3** (an 8-fold increase is achieved, Table 2, entries 1 and 4). This increase in selectivity is reflected in the substantially higher yield reached using the third generation-derived **7G3**, as compared to its nondendronized analogue.

Table 2. Heck Reaction with Methyl Acrylate at 120 °C for 14 h[a]

entry	catalyst	conversion (%)	yield of **10** (%)	selectivity (**10**:**11**)
1	**6**	95	75	3.8
2	**7G1**	100	81	4.3
3	**7G2**	100	86	6.1
4	**7G3**	100	97	32
5	**8G1**	56	51	10.2
6	**8G2**	45	37	4.6
7	**8G3**	93	89	22.2
8	**9G1**	100	90	9
9	**9G2**	100	93	13.3
10	**9G3**	100	93	13.3

[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of methyl acrylate, 0.65 mmol of triethylamine, and the catalyst (0.0125 mmol of Pd) in 1 mL of NMP, 120 °C, 14 h.

Chart 2. Catalytic Results of the Heck Reaction at 120 °C: Comparison of the Three Types of Dendrons

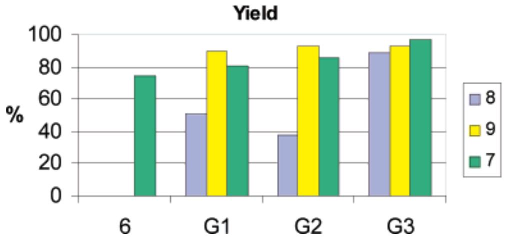


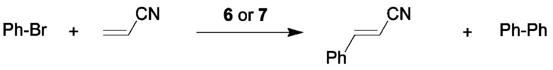
Table 3. Heck Reaction with Acrylonitrile[a]

entry	catalyst	conversion (%)	yield of cinnamnitrile **13** (%)	selectivity (**13**:**11**)
1	**6**	53	49	12
2	**7G1**	49	46	15
3	**7G2**	73	68	14
4	**7G3**	76	72	18

[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of acrylonitrile, 0.65 mmol of triethylamine, and the catalyst **7** (0.0125 mmol of Pd) in 1 mL of NMP, 120 °C, 14 h.

The performance of the polythioether-derived catalysts is inferior to those based on the other two dendron types, also at 120 °C (Chart 2). These results show that the backbone of the polythioether dendron (**8**) is, to some extent, a catalytic poison, as we assumed at the beginning of our work. The differences between the polyether and polyamine dendron-based catalysts **7** and **9** are very significant at low temperatures, but at high temperatures the differences were hardly observable, and it seems that, in some cases, the polyamine dendron is even slightly more active (Chart 2). It can be concluded that, at low temperatures, the competition between the heteroatom (nitrogen or sulfur), located in the dendron backbone, and the reacting olefin dominates the reaction outcome, while less so at higher temperatures.

This explanation is further supported by another experiment we performed. In this experiment, we used **7**, as catalysts, in the Heck arylation of acrylonitrile with bromobenzene (eq 2, Table 3).



13 **11**

(2)

At 80 °C, only traces of the product are observed, and it is hard to tell whether there is any dendritic effect. However, at 120 °C, the conversions and yields are much higher, and a prominent dendritic effect is visible. The substrate and product

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(22) Andersson, C.-M.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* **1985**, *50*, 3891.

(23) Mansour, A.; Portnoy, M. *Tetrahedron Lett.* **2003**, *44*, 2195.

(24) For similar (phosphine)$_2$Pd(dba) complexes on dendronized silica, see: Zweni, P. P.; Alper, H. *Adv. Synth. Catal.* **2004**, *346*, 849.

Table 4. Heck Reaction with Styrene[a]

entry	catalyst	conversion (%)	yield of trans stilbene **14** (%)	selectivity (**14**:**11**)
1	**6**[b]	99	67	2.0
2	**7G1**[b]	73	56	3.3
3	**7G2**[b]	100	81	4.3
4	**7G3**[b]	100	89	8.1
5	**6**[c]	100	66	1.9
6	**7G1**[c]	100	67	2.0
7	**7G2**[c]	100	68	2.1
8	**7G3**[c]	100	91	10

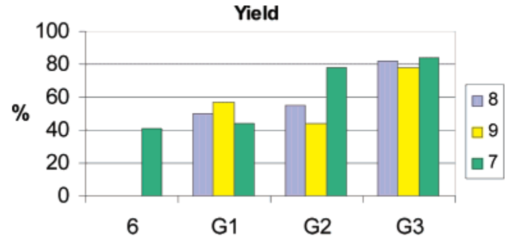
[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of styrene, 0.65 mmol of triethylamine, and the catalyst **7** (0.0125 mmol of Pd) in 1 mL of NMP. [b] 80 °C, 72 h. [c] 120 °C, 14 h.

Table 5. The Suzuki Reaction with 4-Methoxyphenylboronic Acid[a]

entry	catalyst	conversion/yield (%)
1	**6**	41
2	**7G1**	44
3	**7G2**	78
4	**7G3**	84
5	**8G1**	50
6	**8G2**	56
7	**8G3**	82
8	**9G1**	57
9	**9G2**	44
10	**9G3**	78

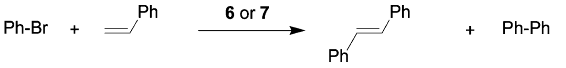
[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of 4-methoxyphenylboronic acid, 0.65 mmol of triethylamine, and the catalyst (0.0125 mmol of Pd) in 1 mL of NMP, 80 °C, 14 h.

Chart 3. Catalytic Results of the Suzuki Reaction at 80 °C: Comparison of the Three Types of Dendrons



can act as ligands, by themselves, coordinating to Pd through the nitrile group. Thus, the competition between the nitrile and the olefin coordination leads to a very low reactivity at 80 °C. At 120 °C, the kinetics is much faster, and the aforementioned competition is of lesser importance.

When styrene is examined as a substrate (eq 3), the trends in activity and selectivity of the catalysts **7** are very similar to those observed with methyl acrylate (Table 4), although the magnitude of the effect is somewhat smaller.

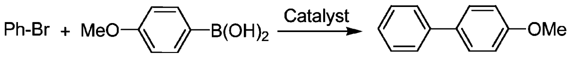


14 **11**

(3)

The Suzuki Reaction. The Suzuki reaction, the coupling of aryl halides with aryl boronic acids to form symmetrically or non-symmetrically substituted biaryls, is another popular method for C−C bond formation.[25] Like the Heck reaction, the Suzuki reaction is generally carried out using palladium phosphine complexes. Suzuki reaction, using Pd supported on active charcoal, silica, or micro- and mesoporous aluminosilicates as heterogeneous catalysts, has been reported.[26]

The Suzuki reaction was chosen as another process to be examined with supported dendronized palladium catalysts **7**−**9**. For this purpose, we used the reaction of bromobenzene and 4-methoxyphenylboronic acid as a model (eq 4). The conversion and yield, in the case of this reaction, are identical, because 4-methoxybiphenyl (**15**) is the only product.



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(4)

The results of the reaction with the three types of dendrons at 80 °C, summarized in Table 5 and Chart 3, demonstrate a significant improvement in the catalytic performance upon dendronization of the support for all types of dendrons. They also show that the character of the dendron is less significant, as for the third generation the three types of dendrons showed very similar reactivity (Table 5, entries 4, 7, and 10).

A possible explanation of this observation arises from examination of the mechanisms of the Heck and Suzuki reactions.[27] While both reactions start with the oxidative addition step, only in the case of the Heck reaction does the second step involve coordination of a weak ligand (olefin) to the metal prior to the formation of the C−C bond. In the case of the Suzuki reaction, the second step is the transmetallation, and there is no subsequent step in which a weak ligand (such as an olefin) has to compete for the coordination site on the metal. It is possible that, for this reason, the interference from the heteroatoms located in the dendron backbone is less significant in the Suzuki reaction.

The Nature of the Active Catalyst. Precipitation of metallic palladium occurs during the reaction, and, thus, the possibility of the catalysis being performed by Pd metal nanoparticles, stabilized inside the dendritic matrix, had to be considered.[28] It is well known that metal Pd adsorbed on an insoluble support or dendrimer-stabilized Pd nanoparticles catalyze the Heck reaction of aryl iodides or electron-withdrawing group-activated bromides.[18,29] However, these catalytic entities are usually incapable of functionalizing nonactivated aryl bromides (such as bromobenzene in this study).[19] Indeed, whereas at the end of the catalytic reaction the resin and the precipitated Pd are easily separated by simple filtration, this solid exhibited a substantially diminished catalytic activity in the recycling experiment. Additional data, ruling out the possibility of the metal palladium catalysis, were obtained in the experiment, in which the Heck reaction with the electron-rich butyl vinyl ether was tested with catalysts **6** and **7** (Scheme 9, Table 6).

For this reactant, the regioselectivity and steroselectivity are important parameters, as three products, *cis*- and *trans*-1,2-disubstituted **17** and **18**, as well as 1,1-disubstituted **16** (undergoing hydrolysis to acetophenone **19** under the reaction/workup conditions), are formed. Moreover, the regio- and

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Scheme 9

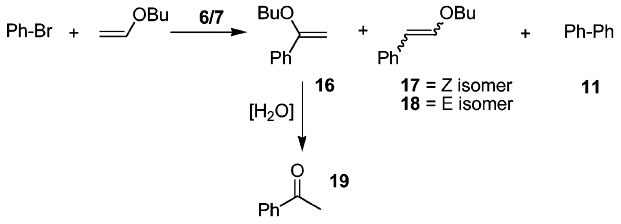

Table 6. Heck Reaction with Butyl Vinyl Ether[a]

entry	catalyst	conversion (%)	combined yield of **16** + **17** + **18** (%)	selectivity ([**16** + **17** + **18**]:**11**)
1	**6**[b]	55	46	5.1
2	**7G1**[b]	49	41	5.1
3	**7G2**[b]	54	46	5.8
4	**7G3**[b]	77	72	14
5	**6**[c]	100	58	1.4
6	**7G1**[c]	100	58	1.4
7	**7G2**[c]	100	75	3.0
8	**7G3**[c]	100	83	4.9

[a] Reagents and conditions: 0.5 mmol of bromobenzene, 0.6 mmol of butyl vinyl ether, 0.65 mmol of triethylamine, and the catalyst (0.0125 mmol of Pd) in 1 mL of NMP. [b] 80 °C, 72 h. [c] 120 °C, 14 h.

Table 7. Regio- and Stereoselectivity in the Heck Reaction of Butyl Vinyl Ether

catalyst	yield of β-arylation (**17** + **18**, %)	yield of α-arylation (**19**, %)	regioselectivity ([**17** + **18**]/[**19**])	stereoselectivity (**18**/**17**)
6[a]	37	9	4.1	2.6
7G1[a]	30	10	3.0	2.6
7G2[a]	29	17	1.7	2.8
7G3[a]	44	28	1.6	3.0
6[b]	33	25	1.3	2.4
7G1[b]	31	27	1.2	2.6
7G2[b]	40	35	1.1	3.0
7G3[b]	42	41	1.0	3.0

[a] 80 °C, 72 h. [b] 120 °C, 14 h. [c] Determined by ^{1}H NMR.

stereoselectivity in this reaction can provide important mechanistic input, as described below. The trends observed for the conversion to Heck products (**16**−**18**) and selectivity toward these products (versus **11**) are very similar to those obtained for methyl acrylate and styrene. At both temperatures, **7G3** is clearly superior to **6**.

According to the regio- and stereoselectivity data (summarized in Table 7), the proportion of the β-arylated products **17** + **18** decreases as the generation of the dendritic template increases. The decrease in the ratio β-arylation/α-arylation for butyl vinyl ether can be attributed to the higher portion of the olefin insertion occurring through cationic intermediates (enforcing α-arylation) versus neutral intermediates (yielding a mixture of α- and β-arylated enol ethers).[30] This change in the distribution between the two alternative catalytic pathways may result from the more polar environment of the catalytic units in higher generation catalysts. The reason for this change may also be associated with the increased local loading of free phosphines in higher generation dendrons. In recent work performed in our group, it was found that partial, rather than full, complexation of the tridentate phosphine ligand with a Pd(dba) fragment (complexation, leaving a free phosphine arm) led to a more active and selective Heck catalyst, which also induced a higher proportion of α- to β-arylation of butyl vinyl ether. We observed a similar phenomenon for partially complexed resin-bound phosphines in the carbonylation of bromobenzenes.[31] Thus, there is a possibility that, in our experiments with dendronized catalysts of higher generations, more active catalytic species are formed upon partial precipitation of palladium (because precipitation frees the phosphine sites), and these species are responsible for the decrease in the β-arylation/α-arylation ratio.

Even more significant is the ratio between products **18** (trans) and **17** (cis) (Table 7), which is known to be sensitive to the nature of the catalyst. According to the literature,[22] phosphine−Pd complexes as catalysts yield ca. a 2.5:1 ratio, while the “naked” Pd catalysts form a 1:1 product mixture. The ratio produced in our experiments (2.4−3.0 to 1) is much more characteristic of the phosphine−palladium catalysts.

Possible Sources of the Dendritic Effects. Positive dendritic effects, in general, and those in supported catalysis, in particular, seem to be complex phenomena, being an expression of various characteristic properties of the dendritic systems.[7] However, in the case at hand, we can point to two basic factors likely to play a role in inducing the positive effects. The first and, probably, dominant property indirectly responsible for the effects is the increased proximity of the ligating sites (higher local loading of the ligands). This property is translated into reduced cross-linking of polystyrene. The reduced cross-linking in our systems was observed with both the naked eye and NMR (a narrowing of signals in the gel-phase ^{31}P NMR) and may lead to improved swelling, a more solvent-like environment for catalytic sites, and improved reagent transport and product removal.

Another expression of the increased proximity of the ligating sites contributing to the positive effect is, most likely, the preorganization of the site to form a more effective catalytic unit through the release of free phosphine arms upon partial precipitation of Pd, as discussed above. The effect of partial complexation exists even in systems with random distribution of the ligating sites[22,31] and must be strengthened when the free ligands are preorganized in the complex proximity.

We previously demonstrated, for a different system, that increased proximity of the ligating sites can lead to differences in the population of the metal species on the resin.[5a] However, this is not the case for the current system because, as aforementioned, even for non-dendronized support, we found that two ligands coordinated to a single Pd(dba) fragment is the dominant species.

The second property that is substantially different for the dendronized, versus the non-dendronized support, is the length of the spacer between the anchoring site on the polymer core and the catalytic unit. Longer spacers may lead to the increased distance between the core and the catalytic moiety, placing the latter into the more solvent-like environment. To examine whether the longer spacer is the key to the improved performance of the higher generation-derived catalysts in our systems, we synthesized resin **20** starting from Wang trichloroacetimidate resin (Scheme 10). We assumed that the length of the spacer of the ligands in resin **20** is similar to that of **7G3**.

Resin **20** was complexed with Pd(dba)$_2$ under the conditions previously mentioned, yielding supported complex **21**. Gel-phase ^{31}P NMR demonstrated quantitative complexation of the phos-

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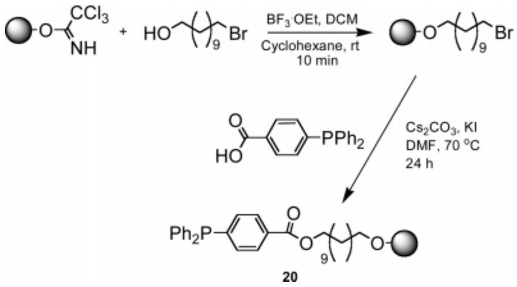
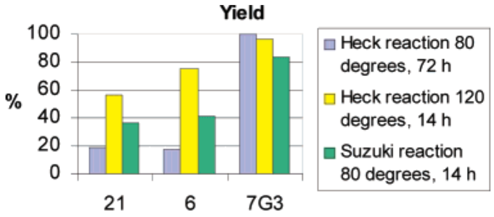
Scheme 10[a]



[a] Reagents and conditions: (i) BF$_3$·OEt, DCM, cyclohexane, room temperature, 10 min; (ii) Cs$_2$CO$_3$, KI, DMF, 70 °C, 24 h.

Chart 4. The Influence of the Length of the Catalyst Spacer on the Heck and Suzuki Reactions



phine ligands with Pd. The catalytic results of **21** were compared to those of **6** and **7G3** in the two test reactions as shown in Chart 4.

The catalytic results obtained with complex **21** and those obtained with complex **6** are very similar, while the reactivity of catalyst **7G3** is much higher. From these results, we can conclude that the length of the spacer between the core and the catalytic unit is, by itself, not the cause of the increased reactivity, although it is possible that, when combined with a dendritic architecture, the longer spacer indeed increases the average distance of the catalytic units from the core.

A very recent series of experiments, where **GnO** resins were functionalized with bidentate chelating phosphine ligands, demonstrated a negative effect in the Heck reaction.[32] These data strongly support the preorganization of the ligating sites and reduced cross-linking, rather than increased average distance of the units from the core, as the main reasons for the positive effects reported here.

Conclusions

This study established effective and clean routes to the construction of poly(aryl benzyl ether), poly(aryl benzyl thioether), and poly(aryl benzyl amine) dendrons on polystyrene beads from readily available starting materials. These synthetic routes led to dendronized supports with up to third generation dendrons grafted on the polymer core. These supports, once functionalized with phosphine−palladium complexes, exhibited remarkable dendritic effects in the Heck and Suzuki reactions of bromobenzene. The generation dependence is most notable for the Heck reaction at 80 °C, unusually mild conditions for this reaction, and results in a fivefold increase in yield for the reaction with methyl acrylate, when the best dendritic catalyst (third generation **7G3**) is compared to the non-dendritic analogue. Experimental and literature data point to the phosphine−palladium complexes as the active catalysts, while the Pd precipitated during the processes is, most probably, not involved in the catalysis.

Analysis of the possible sources of the dendritic effect pointed to the increased proximity of the ligands, translated into reduced cross-linking of the polymer and preorganization of the ligating site, as the main property leading to the increased activity and selectivity of the higher generation catalysts. It was demonstrated that the length of the spacer, on its own, is not the source of the effect.

Catalysis dependence on the nature of the dendritic backbone was exposed. This backbone influence is stronger for the Heck reaction at lower temperatures, with the polyether backbone being the optimal one. The backbone influence is smaller for the Heck reaction at higher temperatures and for the Suzuki coupling. Competition of the backbone coordinating elements with the substrate is suggested as the reason for the observed behavior.

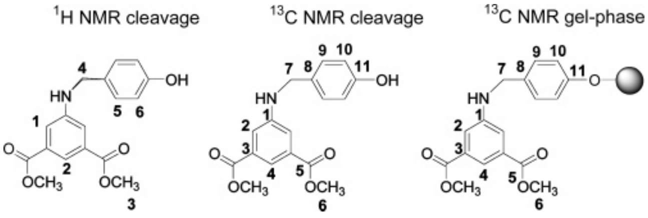
Experimental Section

General Information. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE-200 and AVANCE-400 spectrometers. MS and MALDI-TOF MS were recorded on Micromass VG-Autospec M250 and Bruker Reflex-3 mass spectrometers or a Voyager DE-STR, respectively.

Yields were determined using the ^{1}H NMR of TFA:CDCl$_3$ (1:1) cleavage solutions with C$_6$H$_6$ (7.36 ppm) as an internal standard. Alcohols were partially converted to TFA esters under these conditions.

The syntheses of poly(aryl benzyl ether) and poly(aryl benzyl thioether), functionalization of Wang and **GnO(OH)** resins with diphenylphosphinobenzoic acid, and a general procedure for the Heck reaction with bromobenzene were previously communicated.[5a,b,11]

Synthesis of G1N(CO$_2$Me) (Attachment of Dimethyl 5-Aminoisophthalate to Wang Resin). Dimethyl 5-aminoisophthalate (0.45 g, 2.2 mmol, 3 equiv), 2,6-lutidine (0.25 mL, 2.2 mmol, 3 equiv), and tetrabutylammonium iodide (0.8 g, 2.2 mmol, 3 equiv) were added to a suspension of Bromo Wang resin (1.0 g, 0.72 mmol/g, 0.72 mmol, 1 equiv) in DMF (10 mL). The suspension was mixed at 80 °C for 3 days. The resin was washed with DMF (3 × 20 mL), DMF/water (1:1, 3 × 20 mL), THF/water (1:1, 3 × 20 mL), THF (3 × 20 mL), and dichloromethane (3 × 20 mL), and then dried under vacuum. Yield >99%, purity >99%, loading 0.66 mmol/g. Partial gel-phase ^{13}C NMR (100.8 MHz, C$_6$D$_6$): δ 165.9 **C5**, 153.2 **C11**, 148.4 **C1**, 131.0 **C3**, 117.2 **C2** + **C4**, 114.6 **C10**, 69.1 **C$_{\text{Merrifield}}$**, 51.2 **C6**, 40.1 **C7**. Following TFA-induced cleavage: ^{1}H NMR (200 MHz, CDCl$_3$/TFA 1:1) δ 8.86 (s, 1H, **H2**), 8.48 (s, 2H, **H1**), 7.23 (d, J = 7.0 Hz, 2H, **H5**), 6.93 (d, J = 7.0 Hz, 2H, **H6**), 4.73 (s, 2H, **H4**), 4.09 (s, 6H, **H3**). Partial ^{13}C NMR (100.8 MHz, CDCl$_3$/TFA 1:1): δ 166.9 **C5**, 132.8 **C9**, 132.6 **C4**, 130.2 **C3**, 129.4 **C2**, 115.9 **C10**, 54.1 **C6**. MS (EI) found (m/z), 209.1; calcd for C$_{10}$H$_{11}$NO$_4$, 209.2.



Typical Procedure for the Reduction Step. Synthesis of G1N(OH). LiBH$_4$ (6.6 mL, 13 mmol, 20 equiv, 2 M in THF) and B(OMe)$_3$ (0.074 mL, 0.66 mmol, 1 equiv) were added to a suspension of the resin **G1N(CO$_2$Me)** (1.0 g, 0.66 mmol/g, 0.66 mmol, 1.3 mmol groups of ester, 1 equiv) in THF (10 mL). The mixture was refluxed overnight.

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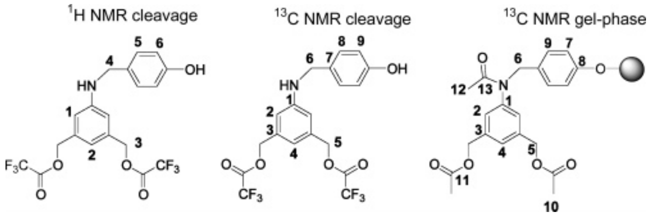
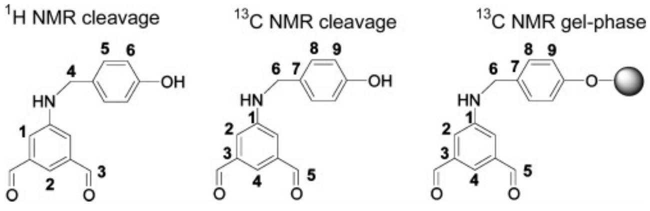
(32) Mansour, A. Supported Catalytic Systems Based on Aminoalcohol-Derived Phosphine Ligands. Ph.D. Thesis, Tel Aviv University, Tel Aviv, 2005.

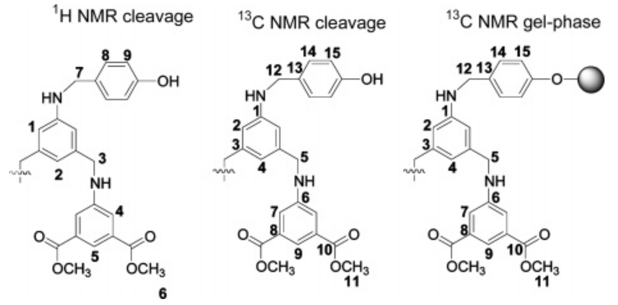
The resin was washed with water (3 × 20 mL), a solution of ammonium chloride/THF (1:1, 3 × 20 mL), a solution of 10% HCl/THF (1:1, 3 × 20 mL), water (3 × 20 mL), THF (3 × 20 mL), dichloromethane (3 × 20 mL), and then dried under vacuum. Yield >95%, purity >95%, loading 0.65 mmol/g. Partial gel-phase ^{13}C NMR after acylation of the OH and NH groups with acetyl chloride (100.8 MHz, C_6D_6): δ 175.9 **C13**, 169.1 **C11**, 143.2 **C1**, 137.8 **C3**, 130.0 **C9**, 114.3 **C7**, 69.4 **C$_{\mathbf{Merrifield}}$**, 64.5 **C5**, 51.6 **C6**, 22.1 **C12**, 19.8 **C10**. Following TFA-induced cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 7.60 (s, 1H, **H2**), 7.44 (s, 2H, **H1**), 7.16 (d, J = 8.2 Hz, 2H, **H5)**, 6.90 (d, J = 8.2 Hz, 2H, **H6**), 5.39 (s, 4H, **H3**), 4.63 (s, 2H, **H4**). Partial ^{13}C NMR (100.8 MHz, $CDCl_3$/TFA 1:1): δ 138.0 **C3**, 132.9 **C8**, 130.4 **C4**, 124.1 **C2**, 117.0 **C9**, 68.4 **C5**. HRMS (EI): found (m/z), 345.0439; calcd for $C_{12}H_9F_6NO_4$, 345.0436.



Typical Procedure for the Oxidation Step. Synthesis of G1N-(CHO). Sulfur trioxide pyridine complex (1.8 g, 11 mmol, 17 equiv) was added to a mixture of DMSO (7.5 mL) and triethylamine (7.5 mL). The mixture was mixed for 15 min at room temperature and then added to a suspension of **G1N(OH)** (1.0 g, 0.65 mmol/g, 0.65 mmol, 1 equiv) in DMSO (10 mL). The suspension was mixed at room temperature for 5 h. The resin was washed with DMSO (3 × 20 mL), DMSO/water (3 × 20 mL), THF/water (3 × 20 mL), THF (3 × 20 mL), and dichloromethane (3 × 20 mL) and then dried under vacuum. Yield >99%, purity >95%, loading 0.65 mmol/g. Partial gel-phase ^{13}C NMR (100.8 MHz, C_6D_6): δ 190.7 **C5**, 148.8 **C1**, 145.3 **C7**, 137.9 **C3**, 121.2 **C4**, 116.5 **C2**, 114.9 **C9**, 69.7 **C$_{\mathbf{Merrifield}}$**, 46.9 **C6**. Following TFA-induced cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 10.13 (s, 2H, **H3**), 8.72 (s, 1H, **H2**), 8.46 (s, 2H, **H1**), 7.23 (d, J = 7.0 Hz, 2H, **H5**), 6.93 (d, J = 7.0 Hz, 2H, **H6**), 4.73 (s, 2H, **H4**). Partial ^{13}C NMR (100 MHz, $CDCl_3$/TFA 1:1): δ 193.0 **C5**, 138.0 **C3**, 134.1 **C4**, 131.8 **C8**, 130.3 **C2**, 116.0 **C9**. HRMS (EI): found (m/z), 149.0474; calcd for $C_8H_7NO_2$, 149.0477.



Typical Procedure for the Reductive Amination Step. Synthesis of G2N(CO$_2$Me). Dimethyl 5-aminoisophtalate (1.3 g, 6.5 mmol, 10 equiv) and a catalytic amount of acetic acid were mixed in DMF until full dissolution. The solution was added to **G1N(CHO)** (1.0 g, 0.65 mmol/g, 0.65 mmol, 1.3 mmol groups of aldehyde, 1 equiv), in DMF (10 mL). Sodium triacetoxyborohydride (4.1 g, 19 mmol, 30 equiv) and trimethyl orthoformate (1 mL) were added to the suspension of the resin. The suspension was mixed at 60 °C for 48 h. The resin was washed with DMF (3 × 20 mL), DMF/water (1:1, 3 × 20 mL), THF/water (1:1, 3 × 20 mL), THF (3 × 20 mL), and dichloromethane (3 × 20 mL) and dried under vacuum. Yield >99%, purity >95%, loading 0.52 mmol/g. Partial gel-phase ^{13}C NMR (100.8 MHz, dioxane-d_8): δ 169.4 **C10**, 131.3 **C8**, 120.5 **C7** + **C9**, 55.3 **C11**, 44.2 **C5**. Following TFA-induced cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1) δ 8.86 (s, 2H, **H5**), 8.47 (s, 4H, **H4**), 8.15–8.75 (br, 3H, **H1** + **H2**), 6.70–7.25 (broad, 4H, **H8** + **H9**), 4.90–5.00 (broad, 6H, **H3** + **H7**), 4.09 (s, 12H, **H6**). Partial ^{13}C NMR (100.8 MHz, $CDCl_3$/TFA 1:1): δ 166.0 **C10**, 132.7 **C9**, 132.3 **C4**, 132.1 **C2**, 129.8 **C8**, 128.5 **C7**, 116.2 **C14**, 53.8 **C11**. HRMS (EI): found (m/z), 535.1943; calcd for $C_{28}H_{29}N_3O_8$, 535.1950.



General Procedure for Complexation of Resins Wang(PPh$_2$), GnX(PPh$_2$), and 20 with Pd(dba)$_2$. Syntheses of 6–9 and 21. In a glove box, a solution of Pd(dba)$_2$ in THF (0.7 equiv/phosphine group, 0.5 mmol/10 mL of THF) was added to the phosphine-bearing resin swollen in THF (10 mL/g resin). The suspension was gently stirred for 4 h. The product resin was filtered, washed with THF and ether, and dried under vacuum.

6. Loading of palladium: 0.38 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 24.9.

7G1. Loading of palladium: 0.36 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 25.9.

7G2. Loading of palladium: 0.47 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 25.9.

7G3. Loading of palladium: 0.31 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 27.0.

8G1. Loading of palladium: 0.37 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 25.2.

8G2. Loading of palladium: 0.51 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 25.9.

8G3. Loading of palladium: 0.52 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 26.0.

9G1. Loading of palladium: 0.40 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 26.1.

9G2. Loading of palladium: 0.50 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 27.0.

9G3. Loading of palladium: 0.44 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 30.0.

21. Loading of palladium: 0.23 mmol/g. ^{31}P NMR (162 MHz, C_6D_6): 25.9.

General Procedure for the Suzuki Catalysis. Bromobenzene (52 μL, 0.5 mmol, 1 equiv), 4-methoxyphenylboronic acid (91 mg, 0.6 mmol, 1.2 equiv), triethylamine (90 μL, 0.65 mmol, 1.3 equiv), and one of the resins **6**/**7**/**8**/**9**/**21** (0.0125 mmol of Pd, 0.025 equiv) in NMP (1 mL) in a pressure tube were sealed under nitrogen and heated to 80 °C for 14 h with stirring. After being cooled, the resin was filtered off and washed with acetonitrile. The combined organic solution was prepared for HPLC and NMR analysis.

Acknowledgment. This research was supported by the Israel Science Foundation. The fellowship of A.D. from the Ministry of Science, Israel, is gratefully acknowledged.

Supporting Information Available: General experimental conditions, procedures for the synthesis of **20**, **G2N**, **G3N**, **GnN-(PPh$_2$)**, and **GnS(PPh$_2$)**, and their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA065265D