A Divergent, Solid-Phase Approach to Dendritic Ligands on Beads. Heterogeneous Catalysis for Hydroformylation Reactions[1a]

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Received October 18, 1999

Introduction

Over the years, the interest in supporting homogeneous catalysts has grown significantly for several reasons.[2−4] Highly complex ligands and metal catalysts have become very expensive and must be recycled. Separation of high-boiling products from nonvolatile catalysts has also limited the commercialization of many excellent homogeneous catalysts. We began this work to develop new approaches for the heterogenization of metal catalysts. Most of the research in this area utilizes polymer-supported catalysts. In general, such systems are found to be more stable, but significantly less reactive. For industrial catalytic processes, there is a need for developing systems that function like homogeneous catalysis (i.e., high reactivity) and are easy to separate from the reaction mixture.

With this goal, we decided to explore the scope of dendritic, multivalent ligands anchored onto beads for heterogeneous catalysis. Dendrimers are relatively well-defined macromolecules with emerging applications in the area of material and biological sciences.[5−8] Several groups have utilized the hyper-branched nature of dendritic materials to obtain multivalent ligands and have tested them for homogeneous catalysis.[9,10] Due to the large size of such molecules, they could be separated from the reaction mixture using various size exclusion techniques. In addition, the dendritic ligands could also exhibit high reactivities as a result of the cooperative behavior.[11,13]

Results and Discussion

Recently, we reported the application of polyamino-amido diphosphonated dendrimers anchored onto silica gel for hydroformylation reactions.[12] In contrast to what is commonly known for heterogeneous catalysts, these systems, when complexed to Rh, were excellent catalysts. It was interesting to note that the hydroformylation of styrenes and vinyl esters gave a high selectivity for the branched products. Branched phenyl propionaldehydes are important because they could lead to several useful intermediates for the pharmaceutical industry (e.g., oxidation to nonsteroidal antiinflammatory agents). Herein, we report a solid-phase synthetic approach to obtain dendritic ligands anchored onto beads and their application for the hydroformylation of several olefins. There are several advantages with the use of polystyrene-based beads as a solid support: (i) the ease of solid-phase synthesis using a building block approach, (ii) characterization of products anchored onto beads after cleavage, (iii) better swelling properties in most solvents, and (iv) flexible polymeric backbones (Figure 1).[14−17] This could further be extended to develop a library approach to catalysis by high-throughput synthesis. Parallel to this approach in pharmaceutical research, combinatorial chemistry toward material sciences is relatively a new field and could reduce the time required to find lead catalysts.[18−20] As observed with the silica gel supported systems,[12] dendritic phosphine ligands anchored onto beads are excellent catalysts (i.e., highly reactive after several cycles, highly regioselective for the branched aldehyde of styrene and vinyl ester sytems) for the hydroformylation reaction of several olefins. *To our knowledge, this is the first study that utilizes a solid-phase*

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10.1021/jo991621h CCC: $19.00
Published on Web 03/01/2000

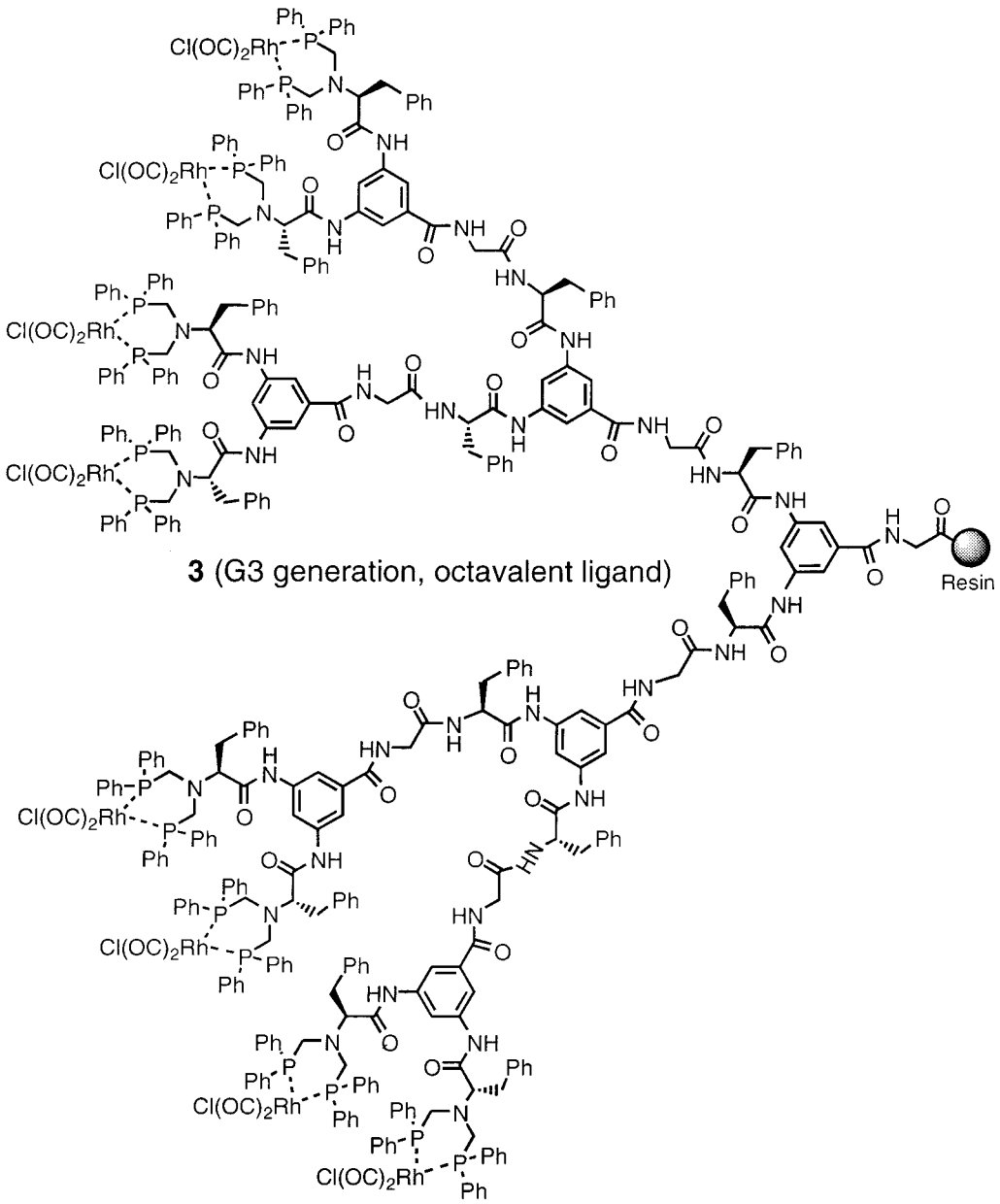


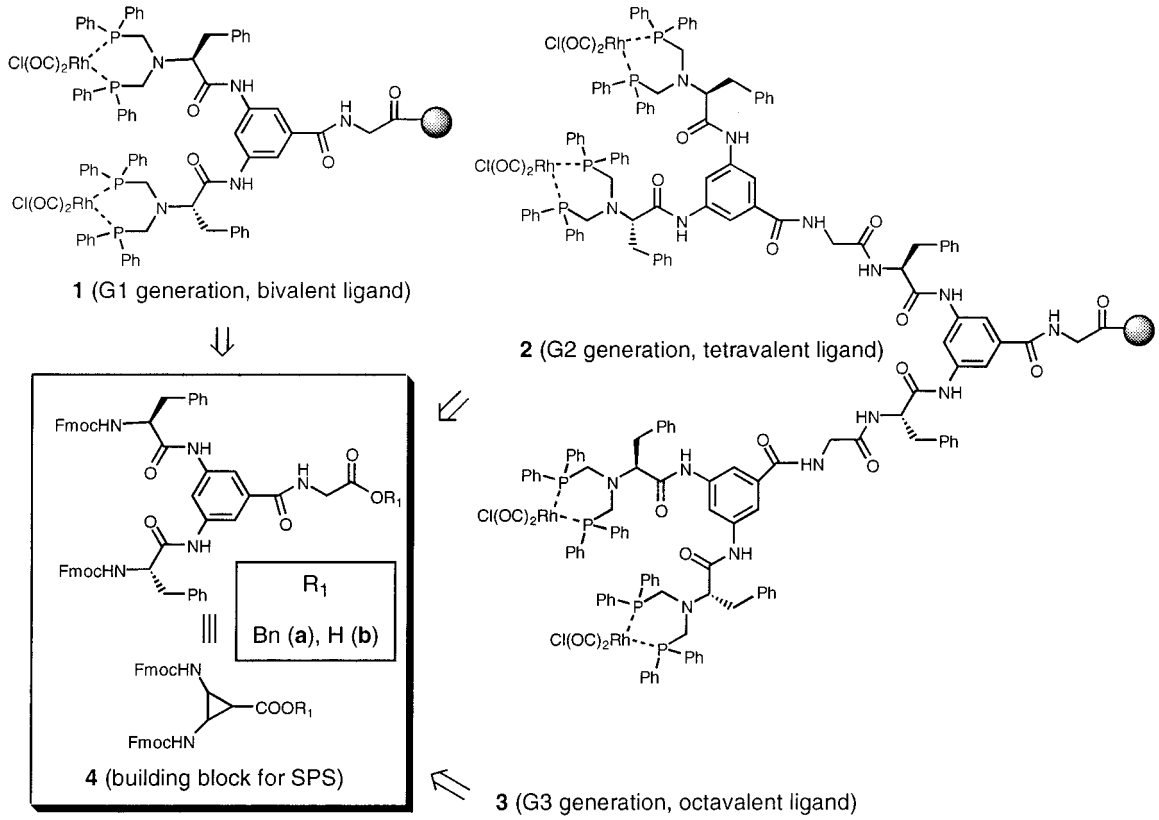
Figure 1. G3 Generation, octavalent dendritic ligands on beads.

synthesis of dendritic materials having phosphine ligands to explore for hydroformylation applications.

For dendritic molecules, multistep solution chemistry presents a synthetic challenge because of the need to purify products at every stage. With few exceptions, most of the efforts toward dendritic materials have been made using solution-phase approaches. No purification is required in solid-phase synthesis, a major advantage over the traditional solution chemistry. The reactions are driven to completion by addition of the excess reagents. The product is anchored onto the support, and after the reaction is complete, the excess reagents are removed by filtration. A pseudopeptide-based building block (Scheme 1, **4b**) was utilized for solid-phase synthesis. The building block, **4b**, has two Fmoc-protected amino groups and a carboxylic acid, and was synthesized on large scale using solution chemistry. Various generations **(1-G1, 2-G2**, and **3-G3)** of branched, dendritic molecules were then planned for assembly by solid-phase synthesis. Using this approach, it is possible to obtain two amino groups with compound **1-G1**, four with **2-G2**, and eight with **3-G3**. Amino groups at each generation were then modified to obtain mutlivalent phosphine ligands at the surface of beads.

3,5-Diaminobenzoic acid was coupled with glycine-benzyl ester using DIC/HOBt at room temperature to give the benzyl ester derivative in 72% yield. It was then coupled with Fmoc-phe-OH using similar reaction conditions. Di-Fmoc protected pseudopeptide benzyl ester was purified by silica gel chromatography (85% yield) and then subjected to hydrogenation using 10% Pd/C to obtain di-Fmoc-protected pseudopeptide carboxylic acid, **4b**, that was directly used for solid-phase synthesis. All the compounds were well characterized using NMR and MS-electrospray. Fmoc-Rink amide MBHA resin (Novabiochem, loading 0.45 mmol/gm) was treated with 20% piperidine in DMF to remove the Fmoc group. Di-Fmoc-protected pseudopeptide building block **4b** was coupled with the free amino group on the resin using a DIC/HOBt coupling method (4.0 equiv of **4b**, 4.0 equiv of DIC, 4.0

Scheme 1. Retrosynthetic analysis: solid-phase synthesis of dendritic ligands on beads

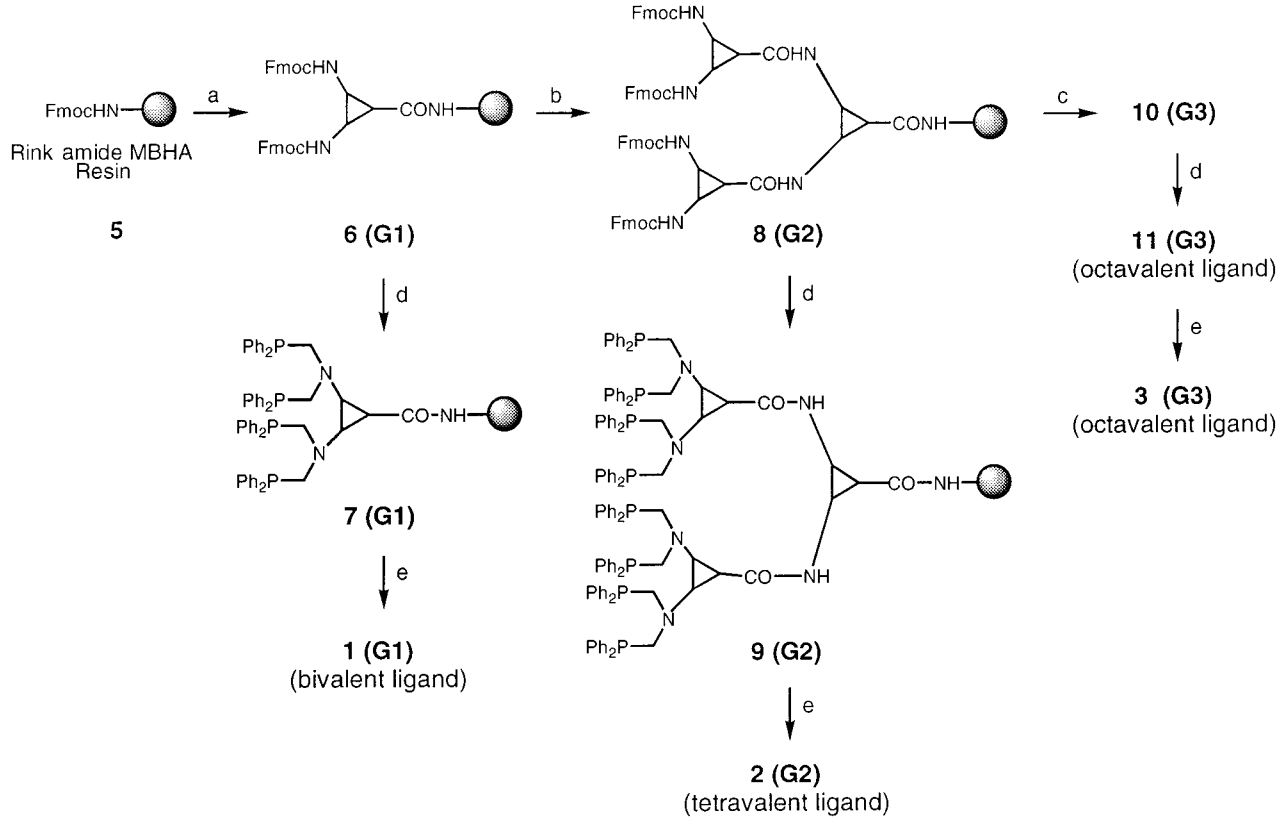


equiv of HOBt, 8.0 equiv of DIPEA in DMF, 12 h) to give compound **6** (**G1**) (Scheme 2). Compound **6** was cleaved from a known amount of resin, isolated and purified by reverse-phase HPLC. The yield of the coupling was determined to be 85% calculated from the cleavage of the known amount of the resin. Second generation based compound **8** (**G2**) was synthesized from **6** on the solid phase. Compound **6** was treated with 20% piperidine in DMF to remove the Fmoc groups. Free amino groups were then coupled with the building block **4b** as described earlier (8.0 equiv of **5**, 8.0 equiv of DIC, 8.0 equiv of HOBt, 16.0 equiv of DIPEA in DMF, 16 h) to obtain the second-generation pseudopeptidic dendrimer, **8** (**G2**). As in the case of the first-generation compound **6**, the yield was calculated to be 82% from the isolated product obtained after the cleavage from the resin followed by purification by reversed-phase HPLC. A repeat process gave the third-generation product **10 (G3)** respectively.

Phosphonated rhodium complexed, pseudopeptide dendrimers **7**, **9**, and **11** were prepared from **6**, **8**, and **10** as follows. **General Procedure:** A solution of diphenylphosphine (10 mmol) and paraformaldehyde (10 mmol) in degassed methanol (20 mL) was stirred at 70 °C for 45 min for in situ preparation of diphenylphosphinomethanol. The reaction mixture was cooled to room temperature. A degassed toluene suspension of each generation dendrimer, **6**, **8,** and **10** with free amino groups anchored on solid support (Fmoc group was first removed from **6**, **8**, and **10** by the treatment with 20% piperidine), was added to the above mixture (6.0 equiv of diphenylphosphinomethanol per free amino group). The mixture was refluxed for 2 h and left at room temperature for 17 h. The resin was washed with degassed methanol. The resulting phosphonated dendrimers, **7**, **9**, and **11** were characterized by ^{31}P NMR (chemical shifts: −26 to −28 ppm). No sign of the phosphine oxide was detected from ^{31}P NMR. Each generation of the phosphonated dendrimer, **7**, **9**, and **11**, was then independently complexed to rhodium by the reaction with choloro(dicarbonyl)-rhodium(I) dimer in dichloromethane. Different generation-based rhodium complexed dendrimers **1** (**G1**), **2** (**G2**), and **3** (**G3**) on resins were obtained by filtration. Once again, the formation of a rhodium−phosphine complex was characterized by ^{31}P NMR (chemical shifts: 24−26 ppm). The ^{31}P NMR confirmed the complete coordination of rhodium to phosphonated ligands in all the three generations. Rhodium complex dendrimers anchored onto beads, **1** (**G1**), **2** (**G2**), and **3** (**G3**) were tested as catalysts for the hydroformylation reaction of several olefins. Initial studies were performed with styrene as a substrate (Table 1). In all the cases, the experiments were carried out on 10.0 mmol scale of the substrate with 25 mg of the catalyst in dichloromethane at 1000 psi total pressure CO/H_2 (1:1). Using catalyst **2** (**G2**) at 45 °C, complete conversion occurred to the product (>99%) with a high selectivity for the branched isomer (branched: linear, 16:1) was obtained. Second-generation dendrimer on beads, **2** (**G2**), was found to be more reactive than the first generation. The catalytic activity for the second-generation dendrimer remained the same up to the fifth cycle; however, a significant drop in the reactivity with the first generation was observed during the fifth cycle.

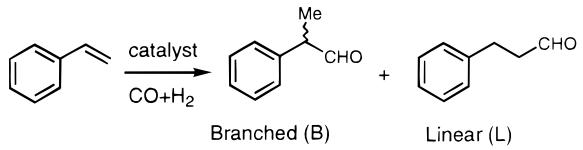
In a second set of experiments, the hydroformylation of several olefinic substrates was studied using compound **2** (**G2**) as a catalyst. The results are summarized in Table 2. Among all of the olefins tested, product formation was very high up to the third cycle. Significantly, high selectivity for the branched product (first cycle, 40:1; second cycle, 60:1; third cycle, 22:1) was obtained with vinyl benzoate as a substrate. As with styrene, the

Scheme 2. Solid-Phase Synthesis of Dendritic Ligands on Beads[a]



[a] (a) (i) 20% piperidine, DMF, (ii) 4.0 equiv of **4b**, 4.0 equiv of DIC, 4.0 equiv of HOBt, 8.0 equiv of DIPEA, DMF, 12 h; (b) repeat step a (i), (ii) 8.0 equiv of **4b**, 8.0 equiv of DIC, 8.0 equiv of HOBt, 16.0 equiv of DIPEA, DMF, 16 h; (c) repeat step a (i); (ii) 16.0 equiv of **4b**, 16.0 equiv of DIC, 16.0 equiv of HOBt, 24.0 equiv of DIPEA, DMF, 20 h; (d) repeat step a (i); (ii) 10 mmol of HCHO and Ph_2PH in degassed methanol at 70 °C, 45 min (in situ preparation of diphenylphosphinomethanol), mix with the dendrimer with free amino groups on beads, 2 h (reflux), 24 h (stirred at room temperature); (e) $[Rh(CO)_2Cl]_2$, (1.0 equiv per bisphosphinomethylamino group) dichloromethane, room temperature, 14 h.

Table 1. Hydroformylation of Styrene (10 mmol) with 25 mg of Rhodium-Complexed Dendrimers Anchored onto Beads 1 (G1), 2 (G2), and 3 (G3)[a]



catalyst	cycle	time (h)	*T* (°C)	conversion (%)	branched/linear[b]
1 (G1)	1st	5	65	42	13:1
1 (G1)	2nd	18	65	70	12:1
1 (G1)	3rd	23	65	85	10:1
1 (G1)	4th	24	65	51	15:1
1 (G1)	5th	24	65	22	9:1
1 (G1)	6th	24	65	8	10:1
2 (G2)	1st	21	25	35	35:1
2 (G2)	1st	5	65	57	14:1
2 (G2)	1st	16	45	>99	16:1
2 (G2)	2nd	22	65	>99	11:1
2 (G2)	3rd	22	65	>99	12:1
2 (G2)	4th	22	65	>99	12:1
2 (G2)	5th	22	65	98	11:1
2 (G2)	6th	22	65	88	12:1
3 (G3)	1st	22	65	99	10:1
3 (G3)	2nd	22	65	99	9:1
3 (G3)	3rd	22	65	99	12:1
3 (G3)	4th	22	65	99	10:1
3 (G3)	5th	22	65	78	12:1
3 (G3)	6th	22	65	47	12:1

[a] Reaction conditions: styrene (10.0 mmol), CO(1000 psi), H_2 (1000 psi), catalyst (25 mg). [b] Ratio of branched/linear aldehydes was determined by ^1H NMR.

Table 2. Hydroformylation of Olefins (10 mmol) with 25 mg of Rhodium Complexed Dendrimers Anchored onto Beads 2 (G2) at 65 °C[a]

substrate	cycle	time (h)	conversion (%)	B/L ratio[b]
vinyl acetate	1st	10	>99	15:1
vinyl acetate	2nd	22	>99	15:1
vinyl acetate	3rd	22	>99	15:1
vinyl benzoate	1st	10	>99	40:1
vinyl benzoate	2nd	36	>99	60:1
vinyl benzoate	3rd	22	>99	22:1
p-methoxy styrene	1st	10	>99	10:1
p-methoxy styrene	2nd	36	>99	11:1
t-butyl styrene	3rd	22	>99	8:1

[a] Reaction conditions: substrate (10.0 mmol), CO(1000 psi), H_2 (1000 psi), catalyst (25 mg). [b] Ratio of branched/linear aldehydes was determined by ^1H NMR.

reactions were carried out using 25 mg of the catalyst on 10.0 mmol substrate.

To summarize, rhodium complexes with dendritic, phosphine ligands anchored onto beads were found to be excellent catalysts for the hydroformylation of several olefins. In some cases (i.e., **2**, second generation) catalysts are reactive up to several cycles. It is generally believed that polymer supported catalysts are relatively less reactive compared to homogeneous catalysis. Contrary to this, our studies strongly support the possibility of achieving high reactivities in heterogeneous systems. The origin of the high reactivity is not clear at this stage. One may speculate that well-exposed ligands on the outer-core may account for the high reactivity as compared to the irregular-shaped polymeric materials. Cooperativity

may be the other factor playing a role for high reactivities. This will be the subject of further investigations.[11]

Experimental Section

General Remarks. All reagents (DMF, DIPEA, CH_2Cl_2, MeOH, piperidine, and hexanes) were purchased from Aldrich as anhydrous grade and used as supplied. The reactions were carried out under argon or nitrogen atmosphere. Purification of compounds by flash chromatography was performed using recycled silica gel (230−400 mesh, 60 Å) supplied by Silicycle (Québec, Canada).

Synthesis of Building Block 4b. (i) A solution of 3,5-Diaminobenzoic acid (50 mmol), GlyOBn (60 mmol), DCC (60 mmol), HOBt (60 mmol) and DIPEA (60 mmol) in CH_2Cl_2/DMF (1:1, 100 mL) was stirred under nitrogen at room temperature for 14−16 h. The precipitated solid was filtered and washed thoroughly with CH_2Cl_2 and the mother liquor collected, washed with saturated solution of $NaHCO_3$, and evaporated to give the crude product. 3,5-Diamino-*N*-benzamide glycine benzyl ester was obtained (72% yield) after purification by flash chromatography (CH_2Cl_2/MeOH, 20:1): ^{1}H NMR (DMSO-d_6) δ 7.35 (m, 5H, Ar-H), 5.75 (s, 2H, $-OCH_2Ar$), 4.95 (bs, 1H, O=CN*H*CH_2), 3.95 (bs, 4H, $ArNH_2$) and 3.3 (m, 2H, $-NHCH_2C=O-$); LRMS (FAB, positive ion mode, *m*/*z*) $C_{16}H_{17}N_3O_3$ 299.1 (M^+). **(ii)** To a solution of Fmoc-Phe-OH (60 mmol) in CH_2Cl_2 (100 mL) were added DCC (60 mmol), HOBt (60 mmol) and 3,5-diamino-*N*-benzamide glycine benzyl ester (20 mmol). The mixture was stirred under nitrogen at the room temperature for 30−40 h. The precipitated solid was filtered and washed thoroughly with CH_2Cl_2 and the mother liquor collected, washed with a saturated solution of $NaHCO_3$, and evaporated to give the crude product. The benzyl ester derivative of the building block **(4a)** was obtained in 76% isolated yield after purification: ^{1}H NMR (DMSO-d_6) δ 2.89 (m, 2H), 3.05−3.10 (m, 2H), 4.00−4.24 (m, 2H), 4.42−4.48 (m, 2H), 5.17 (s, 2H), 7.08−7.88 (m, 34H), 8.31 (bs, 2H) and 10.34 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 38.2, 42.4, 47.4, 60.6, 66.6, 66.7, 114.5, 120.9, 126.1, 126.2, 127.3, 127.9, 128.5, 128.7, 128.9, 129.0, 129.3, 136.1, 136.8, 138.8, 140.0, 141.5, 141.5, 144.6, 144.6, 156.8, 167.8, 170.6 and 171.7; LRMS (electrospray, positive ion mode, *m*/*z*) for $C_{64}H_{55}N_5O_9$ 1038 (MH^+). This was subjected to the debenzylation conditions to obtain the building block **4b**, required for solid-phase synthesis. **(iii)** The benzyl derivative of the building block **4a** (10 mmol) was dissolved in DMF (50 mL) and hydrogenated in the presence of 10% Pd over carbon (10 mol %) for 30−45 min. The catalyst was filtered over Celite, and the solvent was evaporated to give the building block **4b** in 95% yield: ^{1}H NMR (DMSO-d_6) δ 2.88−2.94 (m, 2H), 3.08−3.17 (m, 2H), 3.76 (s, 2H), 4.10−4.18 (m, 6H), 4.45−4.54 (m, 2H), 7.08−7.94 (m, 29H), 8.31 (bs, 2H) and 10.60 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 39.8, 45.0, 47.4, 58.0, 66.6, 114.1, 120.9, 122.3, 128.9, 129.7, 130.2, 138.2, 140.2, 141.5, 141.5, 144.5, 144.6, 156.8 and 171.7; LRMS (electrospray, positive ion mode, *m*/*z*) for $C_{57}H_{49}N_5O_9$ 948 (MH^+).

General Procedure for Solid-Phase Synthesis. Rink amide MBHA resin (loading 0.4−0.5 mmol/g, **5**) was suspended in DMF for 30−45 min under argon. After filtration, a solution of 20% piperidine in DMF was added and the mixture strirred for 40 min (two cycles). This was followed by the addition of the building block (**4b**, 4.0 equiv), DIC (4.0 equiv), HOBt (4.0 equiv), and DIPEA (8.0 equiv), and it was stirred for 12 h. After filtration, compound **6** (G1) was subjected to the Fmoc group removal as discussed before. In a separated reaction flask, formaldehyde (10 mmol) and diphenylphosphine (10 mmol) in degassed MeOH (20 mL) were stirred at 70 °C for 45 min under argon (in situ preparation of diphenylphosphinomethanol). Beads from the solid-phase synthesis were transferred to this solution, and the mixture was stirred for 24 h at room temperature. The beads were filtered under argon and further stirred with $[Rh(CO)_2Cl_2]$ (1.0 equiv per bisphosphinomethylamino group) in CH_2Cl_2 for 14 h at room temperature. The synthesis of the higher generation dendritic compounds anchored on to beads **8** (G2) and **9** (G3) was obtained from **6** (G1), followed by the alkylation of the amino groups to obtain phosphonated ligands, and subsequently, complexation with the Rh as discussed before.

General Procedure for Hydroformylation of Styrene and Other Substrates. A solution of styrene (10.0 mmol) in CH_2Cl_2 (10−20 mL) was treated with a 1:1 mixture of carbon monoxide and hydrogen in the presence of Rh-based catalytsts (25 mg) at 1000 psi total pressure. The reaction was studied at several temperatures with variation in time period, and the ratio of the products(s) was determined by ^{1}H NMR and GC (see, Table 1 for the effect of the temperature and time on the product-(s) yields as well as for the ratio of the branched vs linear aldehydes as products).

Acknowledgment. We thank DuPont Canada and NRC/NSERC Research partnership for the financial support.

JO991621H