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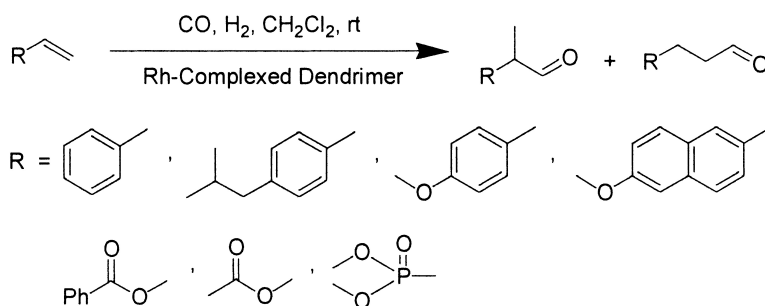
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Hydroformylation Reactions with Recyclable Rhodium-Complexed Dendrimers on a Resin

Shui-Ming Lu and Howard Alper*

Contribution from the Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada, K1N 6N5

Received June 3, 2003; E-mail: halper@uottawa.ca

Abstract: Rhodium-complexed dendrimers supported on a resin were evaluated as catalysts for the hydroformylation of aryl olefins and vinyl esters. The results showed the reactions proceeded very efficiently at room temperature with excellent yields. Outstanding selectivity for the branched aldehydes was also observed in all cases. The dendritic catalysts can be recycled by simple filtration and reused even up to the tenth cycle without loss of activity and selectivity. These results represent a dramatic improvement over those previously described for rhodium-catalyzed (dendrimer and nondendrimer based) hydroformylation reactions.

Introduction

The hydroformylation of olefins, which produces linear and branched aldehydes under carbon monoxide and hydrogen, is one of the most thoroughly investigated reactions in homogeneous catalysis.[1] From the fine chemistry viewpoint, the branched aldehydes are more important as they provide valuable intermediates for the pharmaceutical industry. For example, ibuprofen and naproxen, being two nonsteroidal antiinflammatory drugs,[2] can be obtained by the hydroformylation of 4-isobutylstyrene and 2-vinyl-6-methoxynaphthalene, respectively, followed by oxidation of the resulting branched-chain aldehydes.[3]

Although homogeneous catalytic processes often display high activity and selectivity, in most cases, the catalyst−product separation is usually nontrivial. In addition, the metal catalysts and ligands can be very expensive. These limit the practical application of many excellent catalytic systems.[1f,4] Immobilization of homogeneous catalysts on a solid support is one of the possible ways to prepare well-defined catalytic systems.[5] Unfortunately, along with the advantages of the heterogeneous catalysts, a significant loss of the catalytic activity and selectivity is often observed. From a catalytic point of view, the ideal catalyst should combine the advantages of both homogeneous and heterogeneous catalysis including high activity and selectiv-

ity under mild conditions, ease of separation from the product, and reuse as many times as possible without too much of a decrease in efficiency.[6] Introduction of a dendritic template between the support and catalyst is particularly attractive in this regard.

Dendrimers have attracted an increasing attention due to their special properties and functions.[7] An important application of dendrimers is the use of their complexes as catalysts.[6,8] Soluble dendrimers were widely utilized for a variety of catalytic reactions.[9] However, there have been only a few examples concerning heterogeneous dendritic catalysts.[10] For instance,

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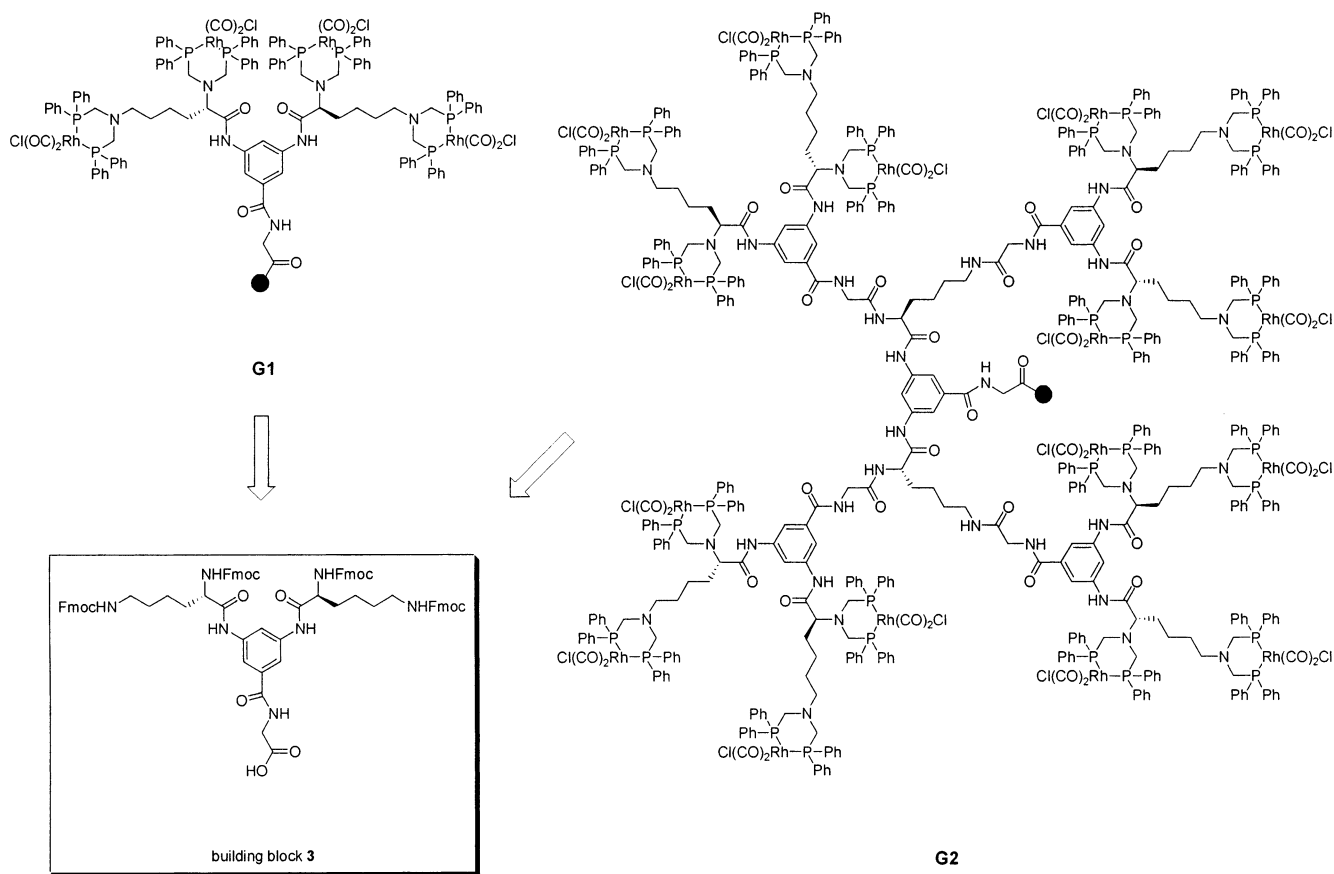
Figure 1. Retrosynthetic analysis: solid-phase synthesis of rhodium-complexed dendrimers on a resin.

Rhee has employed dendrimers supported on silica for the addition of diethylzine to benzaldehyde.[10a] Palladium dendrimers on polystyrene catalyze Heck reactions as reported by Portnoy.[10b] Recently, we described the immobilization of dendritic ligands on a resin in which the ligands were placed on the outer[11a] and inner[11b] arms of dendrimers and used for hydroformylation reactions. The environment of complexed ligands on the arms played an important role in this transformation. In contrast to the known heterogeneous catalysts, our systems showed good activity and selectivity. These results inspired us to explore the

synthesis of heterogeneous dendritic catalysts having both interior and exterior functional groups for metal coordination and their applications for hydroformylation reactions. We now report the interesting and useful results from this investigation.

Results and Discussion

Preparation of Rhodium-Complexed Dendrimers on a Resin. Solid-phase synthesis was used for the construction of dendrimers.[11] In comparison to the traditional solution chemistry suffering from difficulties associated with long reaction time and nontrivial purification,[12] the solid-phase method enables the use of excess reagents to drive the reaction to completion, turning purification steps into the simple washing of resin.[13] The dendrimers were prepared starting from the building block **3**, which contains a reactive carboxyl moiety and four Fmoc-protected amino groups, allowing the carboxyl moiety of one molecule to be applied for the attachment to the deprotected amino group of another moiety and rapid growth of dendritic assemblies (Figure 1).

The coupling reaction of 3,5-diaminobenzoic acid with glycine *tert*-butyl ester in the presence of 1-hydroxybenzotria-zole (HOBT) and dicyclohexylcarbodiimide (DCC) afforded *tert*-butyl ester derivative **1**, which reacted with di-Fmoc-lysine using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) as the coupling reagent to give

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Scheme 1. Synthesis of Building Block **3**
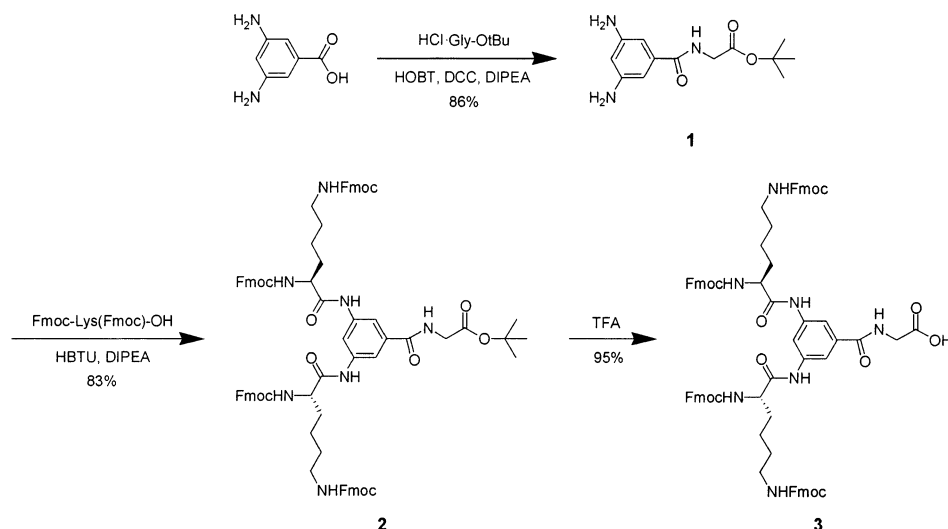
pseudopeptide *tert*-butyl ester **2**. Deprotection of *tert*-butyl group of compound **2** with trifluoroacetic acid afforded the building block **3** in 95% yield (Scheme 1).

Solid-phase synthesis of rhodium-complexed dendrimers **G1** and **G2** was carried out on Fmoc-Rink amide MBHA resin (Novabiochem, loading: 0.54 mmol/g). Treatment of the Fmoc-protected resin with 20% piperidine in dimethylformamide gave free amino resin, which reacted with the carboxyl group of the building block **3** in the presence of HBTU affording dendrimer **4**. An 86% coupling yield was determined by the cleavage and purification of the known amount of the resin. The second-generation dendrimer **5** was synthesized from dendrimer **4** in a similar manner by repeating the required steps.

The dendrimers on a resin were phosphonated prior to complexation with rhodium. Diphenylphosphinomethanol, prepared in situ from paraformaldehyde and diphenylphosphine, reacted with each terminal amino group of dendrimers. The resulting phosphonated dendrimers were characterized by ^{31}P solid-state NMR. A chemical shift of −28 ppm for the various generations compared well with the published value of −28 ppm[9d,10h,i,k,11] for the polyaminophosphonated dendrimers (loading of phosphine groups: **G1**, 2.01 mmol/g; **G2**, 2.63 mmol/g).

The phosphonated dendrimers on a resin were complexed by simply stirring with chloro(dicarbonyl)rhodium(I) dimer in degassed dichloromethane at room temperature for 3 h under argon. The resulting complexed dendrimers were characterized by ^{31}P solid-state NMR (complexed δ = 25 ppm, uncomplexed δ = −28 ppm). The ICP results showed the rhodium contents of **G1** and **G2** are 0.74 mmol/g and 0.83 mmol/g, respectively (Scheme 2).

Optimization of Hydroformylation Reaction Conditions. The hydroformylation reactions were optimized by using styrene as a model substrate and **G1** as the catalyst. The effects of the reaction time, temperature, pressure of carbon monoxide and hydrogen, and solvent were investigated; the results are listed in Table 1. Table 1 showed that the reaction time played an important role in this transformation (Table 1, entries 1−5). The reaction was carried out by treating 2 mmol of styrene with 500 psi of carbon monoxide and 500 psi of hydrogen in the presence of catalyst **G1** in 10 mL of anhydrous dichloromethane

at room temperature for 2 h, at which time there was 30% conversion to aldehydes (Table 1, entry 1). Increasing the reaction time to 6 and 10 h gave 83% and 90% conversions, respectively (Table 1, entries 2 and 3). Performing the reaction under the same conditions for 16 h resulted in 96% conversion to product (Table 1, entry 4). However, a >99% conversion of styrene to aldehydes was observed when prolonging the reaction time to 22 h at room temperature (branched:linear = 36:1; Table 1, entry 5).

Clearly, the reaction temperature and the total pressure of carbon monoxide and hydrogen also affected the hydroformylation of styrene. Treatment of styrene with catalyst **G1** at 500 psi of carbon monoxide and 500 psi of hydrogen in dichloromethane at 45 °C and 65 °C for 22 h afforded 18:1 and 13:1 ratios of branched-to-linear aldehydes (>99% conversions), respectively (Table 1, entries 6 and 7). The results are in accordance with our previous observation that high temperature decreased the selectivity for the branched aldehyde.[10h,11a] Increasing the total pressure favored hydroformylation to give the branched aldehydes (Table 1, entries 8−11). A 38:1 ratio of branched-to-linear aldehydes was obtained under 600 psi of carbon monoxide and 600 psi of hydrogen (Table 1, entry 8). When the total pressure was changed to 800 and 600 psi, the ratios of branched-to-linear aldehydes were reduced to 34:1 and 32:1, respectively (Table 1, entries 9 and 10). A decrease in the conversion occurred when hydroformylation proceeded at a total pressure of 400 psi (branched:linear = 32:1; Table 1, entry 11). These results indicate the selectivity may be due to thermodynamic effects (linear aldehydes pack more efficiently).

The solvent was another key factor for successful hydroformylation. Dichloromethane proved to be the best solvent for this transformation, and the reaction also worked well in chloroform, benzene, toluene, and ethyl acetate with >99% conversions, but a slight decrease in selectivity for the branched aldehydes was observed (Table 1, entries 12−15). Other solvents, such as tetrahydrofuran, ether, and hexane, gave >80% conversions (Table 1, entries 16−18). Apparently, no solvent is as effective as dichloromethane.

Hydroformylation of Aryl Olefins and Vinyl Esters. Rhodium-complexed dendrimers were assessed as catalysts for the hydroformylation of styrene, 4-isobutylstyrene, 4-vinylani-

Scheme 2. Solid-Phase Synthesis of Rhodium-Complexed Dendrimers on a Resin[a]
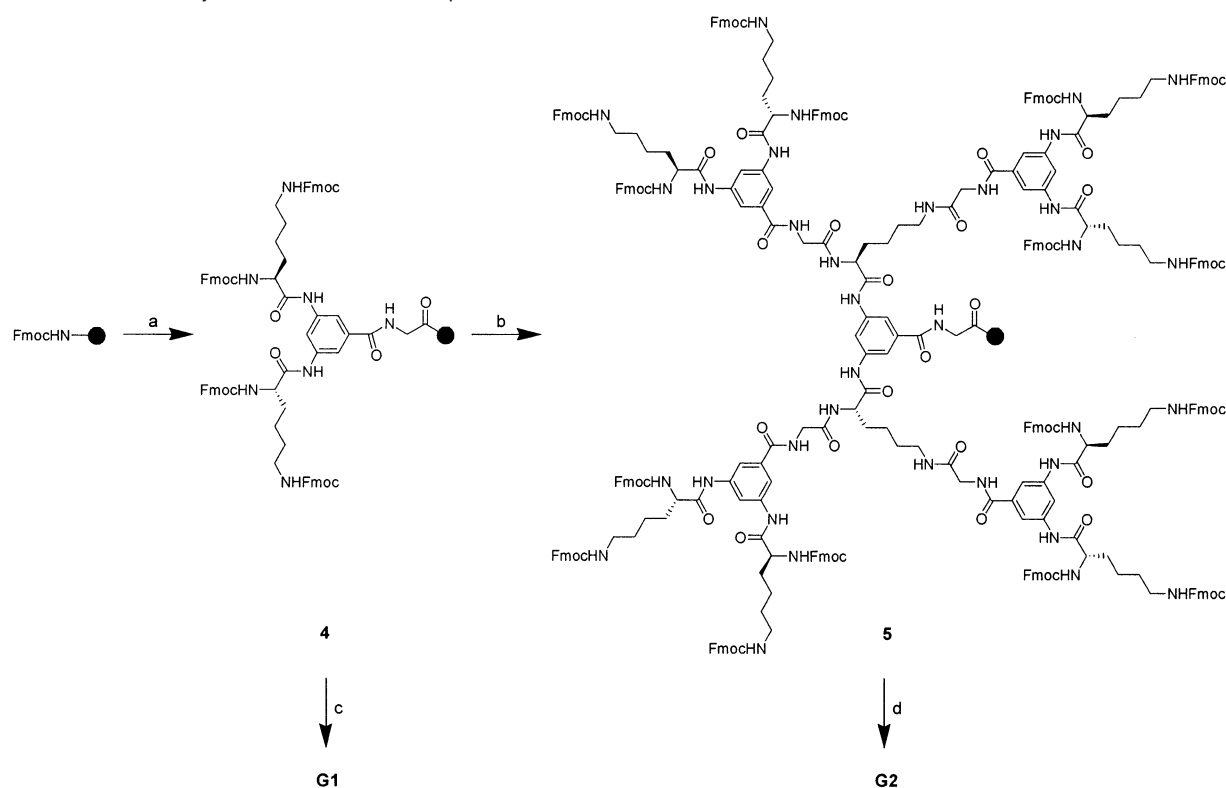
[a] (a) (i) 20% piperidine, DMF; (ii) 4 equiv of **3**, 4 equiv of HBTU, 8 equiv of DIPEA, DMF, 16 h. (b) 20% piperidine, DMF; (ii) 16 equiv of **3**, 16 equiv of HBTU, 24 equiv of DIPEA, DMF, 24 h. (c) (i) 15 equiv of Ph_2PCH_2OH with respect to NH_2, prepared from $(HCHO)_n$ and Ph_2PH in degassed toluene, 70 °C 2 h, stirred rt 16 h; (ii) 0.25 equiv of $[Rh(CO)_2Cl]_2$ with respect to PPh_2, CH_2Cl_2, rt, 3 h. (d) repeat steps in part c.

Table 1. Hydroformylation of Styrene with Rhodium-Complexed Dendrimers under Different Reaction Conditions[a]

entry	pressure (psi)	solvent	temp (°C)	time (h)	conversion[b] (%)	selectivity[c] B:L ratio
1	1000	CH_2Cl_2	25	2	30	32:1
2	1000	CH_2Cl_2	25	6	83	34:1
3	1000	CH_2Cl_2	25	10	90	34:1
4	1000	CH_2Cl_2	25	16	96	35:1
5	1000	CH_2Cl_2	25	22	>99[d]	36:1
6	1000	CH_2Cl_2	45	22	>99	18:1
7	1000	CH_2Cl_2	65	22	>99	13:1
8	1200	CH_2Cl_2	25	22	>99	38:1
9	800	CH_2Cl_2	25	22	>99	34:1
10	600	CH_2Cl_2	25	22	>99	32:1
11	400	CH_2Cl_2	25	22	97	32:1
12	1000	$CHCl_3$	25	22	>99	33:1
13	1000	Benzene	25	22	>99	32:1
14	1000	Toluene	25	22	>99	30:1
15	1000	Ethyl acetate	25	22	>99	32:1
16	1000	THF	25	22	93	32:1
17	1000	Ether	25	22	87	26:1
18	1000	Hexane	25	22	89	25:1

[a] 2 mmol of styrene, 10 mL of solvent, 1:1 ratio of $CO:H_2$, 25 mg of catalyst. [b] Determined by ^1H NMR and GC. [c] Determined by ^1H NMR. [d] 99% isolated yield.

sole, 2-vinyl-6-methoxynaphthalene, vinyl benzoate, vinyl acetate, and dimethyl vinylphosphonate. In a typical reaction, a mixture of 2 mmol of the olefin in 10 mL of dichloromethane with 25 mg of the catalyst was treated with a mixture of 500 psi of carbon monoxide and 500 psi of hydrogen gas at room

temperature for 22 h. The results, summarized in Tables 2−8 of the Supporting Information, indicate that the room temperature hydroformylation reactions give quantitative conversion to aldehydes, with a remarkable preference for the branched-chain products using **G1** and **G2** as the catalysts (styrene, 36 ± 3:1; 4-isobutylstyrene, 33.5 ± 2.5:1; 4-vinylanisole, 45 ± 3:1; 2-vinyl-6-methoxynaphthalene, 38 ± 4:1; vinyl benzoate, 32 ± 1:1; vinyl acetate, 21.5 ± 1.5:1; dimethyl vinylphosphonate, 43.5 ± 1.5:1). Both catalysts are easily recovered by simple filtration and reusable for at least six more cycles without loss of activity and regioselectivity. For example, hydroformylation of styrene using the catalyst **G1** exhibited >99% conversion to aldehydes (the ratios of branched-to-linear aldehydes ranged from 36:1 to 33:1) up to the seventh cycle. The conversion to the aldehydes decreased to 95% for the eighth cycle, but prolonging the reaction time to 32 h gave >99% conversion for the ninth cycle. Catalyst **G2** was found to be more reactive than catalyst **G1** for the hydroformylation of styrene, the ratios of branched-to-linear aldehydes ranging from 39:1 to 36:1 with >99% conversions observed, even up to the tenth cycle, without loss of activity and selectivity (Table 2, Supporting Information).

Similar results were obtained for the hydroformylation of 4-isobutylstyrene, 4-vinylanisole, and 2-vinyl-6-methoxynaphthalene. The presence of the isobutyl group at the 4-position of the phenyl ring slightly decreased the selectivity (Table 3, Supporting Information). However, the high preference for the branched aldehydes was observed when the methoxyl group is at the 4-position of the phenyl ring or the 6-position of the naphthyl ring (Tables 4 and 5, Supporting Information). Compared to other olefins, reactivity was modestly reduced for

the hydroformylation of vinyl benzoate and vinyl acetate. For example, with vinyl benzoate, catalyst **G1** exhibited >99% conversion up to the fifth cycle, but the conversion to product decreased to 93% for the sixth cycle. Employing **G2** as the catalyst, >99% conversion was obtained up to the sixth cycle, whereas 98% conversion resulted for the seventh cycle (Table 6, Supporting Information). When vinyl acetate was examined as a substrate, the ratios of branched-to-linear aldehydes varied from 20:1 to 23:1 (Table 7, Supporting Information). To our surprise, high activity and selectivity resulted from the hydroformylation of dimethyl vinylphosphonate; both **G1** and **G2** exhibited >99% conversions with about 43:1 ratios of branched-to-linear aldehydes up to the seventh cycle (Table 8, Supporting Information).

Summary

In conclusion, dendrimer rhodium complexes having both interior and exterior functional groups are found to be very efficient catalysts for the hydroformylation of a variety of olefins, affording exceptionally high selectivity for the branched aldehydes with excellent yields even up to the tenth cycle. Moreover, the reactions occur under remarkably mild conditions (room temperature) and are simple in execution and workup. These results indicate a dramatic improvement over previously described rhodium-complexed dendrimers for the hydroformylation reactions.[10h,i,11] This may be attributed to cooperative catalytic behavior of the multiple coordination sites on the interior and exterior functional groups of rhodium-complexed dendrimers. Our studies also demonstrate that it is possible to achieve high reactivity in the heterogeneous catalytic systems. Of particular note are 2-(4-isobutylphenyl)propanal and 2-(6-methoxy-2-naphthyl)propanal as important intermediates for the synthesis of ibuprofen and naproxen.

Experimental Section

Materials. 4-Isobutylstyrene[14] and 2-vinyl-6-methoxynaphthalene[15] were prepared according to literature procedures. Other chemicals were purchased from commercial sources. All solvents were dried and distilled prior to use.

Coupling Reaction of 3,5-Diaminobenzoic Acid with Glycine *tert*-Butyl Ester Hydrochloride. Glycine *tert*-butyl ester hydrochloride (3.5204 g, 21 mmol), 1-hydroxybenzotriazole monohydrate (2.8377 g, 21 mmol), 3,5-diaminobenzoic acid (3.0430 g, 20 mmol), and *N,N*-diisopropylethylamine (2.7143 g, 3.66 mL, 21 mmol) were dissolved in dry *N,N*-dimethylformamide (40 mL), and the solution was stirred and cooled in an ice−water bath while dicyclohexylcarbodiimide (4.3329 g, 21 mmol) was added. Stirring was continued for 2 h at 0 °C and an additional 12 h at room temperature. The 1,3-dicyclohexylurea which separated was removed by filtration and washed with *N,N*-dimethylformamide (3 × 5 mL), and the solvent was evaporated under reduced pressure. The oily residue was dissolved in dichloromethane (100 mL), which was washed with 10% aqueous sodium hydrogen-carbonate solution (3 × 80 mL) and saturated sodium chloride solution (3 × 80 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The resulting oil was purified by silica gel chromatography with a mixture of hexane and ethyl acetate as the eluant to give a pale-yellow solid as compound **1** (4.5527 g, 86%). ^{1}H NMR (200 MHz, CD$_3$SOCD$_3$) δ 1.40 (s, 9H), 3.76 (d, 2H), 4.89 (ws, 4H), 5.94 (s, 1H), 6.22 (s, 2H), 8.27 (t, 1H); ^{13}C NMR (200 MHz,

CD$_3$SOCD$_3$) δ 27.76, 41.79, 80.41, 101.98, 102.18, 135.65, 149.07, 168.07, 169.24. MS (EI), *m/z*: 265 [M$^+$].

Coupling Reaction of *N*-α,ε-di-Fmoc-L-Lysine with Compound 1. To a solution of *N*-α,ε-di-Fmoc-L-lysine (6.4977 g, 11 mmol), 3,5-diamino-*N*-benzamide glycine *tert*-butyl ester (**1**) (1.3266 g, 5 mmol) and *N,N*-diisopropylethylamine (1.4218 g, 1.92 mL, 11 mmol) in dry *N,N*-dimethylformamide (30 mL) was added to 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (4.1723 g, 11 mmol) in an ice−water bath. The reaction mixture was stirred for 2 h at 0 °C and an additional 18 h at room temperature. The solvent was removed under reduced pressure, and the oily residue was dissolved in dichloromethane (100 mL), which was washed with 10% aqueous citric acid solution (2 × 80 mL), saturated sodium chloride solution (2 × 80 mL), 10% aqueous sodium hydrogencarbonate solution (2 × 80 mL), and saturated sodium chloride solution (2 × 80 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting oil was purified by silica gel chromatography with a mixture of hexane and ethyl acetate as the eluant to give a white solid as compound **2** (5.8541 g, 83%). ^{1}H NMR (300 MHz, CD$_3$SOCD$_3$) δ 1.22−1.70 (m, 21H), 2.97−3.00 (m, 4H), 3.85 (d, 2H), 4.12−4.34 (m, 14H), 7.27−7.87 (m, 38H), 8.15 (s, 1H), 8.76 (t, 1H), 10.22 (s, 2H); ^{13}C NMR (300 MHz, CD$_3$SOCD$_3$) δ 23.84, 28.58, 30.10, 32.24, 42.82, 47.55, 56.30, 66.03, 66.50, 81.42, 110.63, 120.90, 122.24, 125.98, 126.17, 127.89, 128.14, 128.44, 128.48, 129.77, 138.27, 140.18, 141.57, 143.41, 144.62, 144.75, 156.96, 167.69, 169.78, 172.27. MS (ESI), *m/z*: 1410 [MH$^+$].

Deprotection of Compound 2. Trifluoroacetic acid (15 mL) was added dropwise to a solution of compound **2** (4.2319 g, 3 mmol) in dichloromethane (15 mL) at 0 °C, and the resulting mixture was stirred for 3 h at room temperature. The solution was concentrated by rotary evaporation and washed with diethyl ether (3 × 10 mL, followed by reconcentration) to give a white solid as product **3** (3.8604 g, 95%). ^{1}H NMR (300 MHz, CD$_3$SOCD$_3$) δ 1.21−1.71 (m, 12H), 2.96−2.99 (m, 4H), 3.88 (d, 2H), 4.11−4.29 (m, 14H), 7.27−7.87 (m, 38H), 8.14 (s, 1H), 8.74 (t, 1H), 10.21 (s, 2H); ^{13}C NMR (300 MHz, CD$_3$SOCD$_3$) δ 23.84, 29.96, 32.23, 42.12, 47.54, 56.29, 66.02, 66.49, 111.22, 120.96, 125.98, 126.17, 127.89, 128.44, 128.49, 136.22, 140.07, 141.57, 144.62, 144.72, 144.76, 156.96, 167.57, 172.10, 172.27. MS (ESI), *m/z*: 1354 [MH$^+$].

General Procedure for the Solid-Phase Synthesis. Rink amide MBHA resin (400 mg, 0.54 mmol/g) was swollen with dimethylformamide (15 mL, 30 min, 3×) and treated with a solution of 20% piperidine in dimethylformamide (10 mL, 30 min, 3×) to remove the Fmoc protecting group. After washing with dimethylformamide (3 × 15 mL) and dichloromethane (5 × 15 mL), a solution of compound **3** (1.1703 g, 0.864 mmol), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (0.3277 g, 0.864 mmol), and *N,N*-diisopropylethylamine (0.2234 g, 1.728 mmol) in dimethylformamide (10 mL) was added, and the mixture was reacted for 16 h. The resin was washed with dimethylformamide (3 × 15 mL) and dichloromethane (5 × 15 mL) and subsequently treated with 20% piperidine in dimethylformamide (15 mL, 30 min, 3×). After washing with dimethylformamide (3 × 15 mL) and dichloromethane (5 × 15 mL), a light yellow resin was obtained as the first-generation dendrimer.

The second-generation dendrimer was prepared in a similar manner by repeating the required steps.

General Procedure for the Phosphonation Reaction. The mixture of paraformaldehyde (0.2253 g, 7.5 mmol) and diphenylphosphine (1.74 mL, 10 mmol) in degassed toluene (15 mL) was heated at 110 °C for 2 h under argon and then cooled to room temperature. The resin (0.5 mmol with respect to NH$_2$) from the solid-phase synthesis was added to the above solution. The reaction was stirred at 70 °C for 2 h and at room temperature overnight. After filtration under a stream of argon, the product was washed with methanol (5 × 15 mL) and dried in vacuo.

General Procedure for the Complexation Reaction. The resin (0.4 mmol with respect to PPh$_2$) was added to a solution of chloro(dicar-

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bonyl)rhodium(I) dimer (0.0389 g, 0.1 mmol) in freshly distilled dichloromethane (20 mL). The mixture was stirred for 3 h at room temperature under argon. After filtration under a stream of argon, the product was washed with dichloromethane (5 × 15 mL) and dried in vacuo.

General Procedure for the Hydroformylation Reaction. A glass liner containing the substrate (2 mmol), catalyst (25 mg), and dichloromethane (10 mL) was placed in a 45 mL autoclave equipped with a magnetic stirring bar. The autoclave was flushed 3 times with carbon monoxide and pressurized to the desired level. The hydrogen line was then attached to the autoclave and purged before pressurizing the autoclave up to the desired level. The autoclave was placed in an oil bath preset to the desired temperature on a stirring hot plate. After the appropriate reaction time (see Table 1), the autoclave was removed from the oil bath and cooled to room temperature prior to the release

of the excess carbon monoxide and hydrogen. The resulting solution was filtered to remove the catalyst, and the solvent was evaporated in vacuo. The product aldehydes were analyzed by ^{1}H NMR and gas chromatography and identified by comparison with literature data. The recovered catalyst was washed with dichloromethane and reused in subsequent cycles.

Supporting Information Available: Tables 2−8. This material is available free of charge via the Internet at http://pubs.acs.org.

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