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Autumn R. Flynn

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The Synthesis of Dendrimer-Bound Catalysts and Their Use in MacMillan-Type Reactions

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INTRODUCTION

Organo-catalysts are a classification of catalysts that are comprised of mostly carbon, hydrogen, oxygen, and nitrogen atoms. Organic molecules used for catalysis have a long history, but recent interest in organo-catalysis has been turned to catalysts that can produce enantioselective and diastereoselective (optically active) products. Relatively recently, in the 1970s, a revolutionary reaction called the Hajos-Parrish-Eder-Sauer-Wiechert reaction was carried out by using a naturally occurring chiral reagent, proline, as a catalyst to promote the synthesis of a chiral aldol reaction product.¹ After this asymmetric reaction catalyzed by an organo-catalyst was reported and shown to be extremely enantioselective, the field of organo-catalysis had a huge increase in the amount of attention it drew. This gain in asymmetric catalysis sparked more research into different classes of organocatalyst. During this gain in attention, another influential class of catalysts, imidazolidinone catalysts, were developed by David MacMillan² by modifying the naturally occurring chiral phenylalanine. The MacMillan research group at Princeton University in New Jersey currently works to develop different organo-catalysts to aid in a wide range of reactions, some of which are prevalent in the pharmaceutical industry and also utilized in the total synthesis of natural products.³

Dendrimers—highly branched macromolecules—present an attractive option for use as a catalytic framework because of their large size and their availability for functionalization. In addition, the use of organocatalysts to form asymmetric products has become an increasingly studied field in the pharmaceutical industry and cancer research. Organocatalyst terminally functionalized dendrimers present the possibility of both catalytic utility and increased recovery in MacMillan-type asymmetric reactions. Terminal sites of generations 2.0, 3.0, and 4.0 PAMAM dendrimers have been functionalized with the MacMillan group’s (2S, 5S)-5-benzyl-2-tert-butyl-3-methyl-imidazolidin-4-one catalyst. These functionalized PAMAM dendrimers were characterized by NMR and MALDI-TOF MS analysis. The organocatalyst functionalized dendrimers show promising yield, enantioselectivity, and recoverability in MacMillan-type organocatalytic reactions.
The organo-catalysts developed by the MacMillan group are important for a variety of organic syntheses. These syntheses include high enantioselectivity for various commonly observed asymmetric organocatalytic reactions (diels-alder, aldol addition, and nucleophilic addition) as well as cascade catalysis. The catalysts developed for these reactions produce enantioselective and diastereoselective products, which are of interest to many organizations and research efforts. Most commonly, optically active molecules are extremely important in pharmaceutical applications where different stereoisomers can play very different roles in the body. Because of their wide variety of uses and the procedure used in synthesizing the organo-catalysts, the organo-catalysts developed by MacMillan are relatively expensive to purchase. As of now, the catalysts are difficult to recover and purify for reuse, leading to disposal and therefore making any synthesis involving the catalyst expensive and inefficient.

By modifying how MacMillan’s catalysts are introduced into a reaction and building multiple catalytic units onto a large organic framework instead of introducing them into a reaction as discrete molecules, the effective size of the catalytic unit increases. This increase in size leads to more recoverability options for the catalysts, and can make syntheses involving MacMillan’s catalysts more efficient since the catalysts can be recovered and reused. This project focuses on using dendrimers as an organic scaffold onto which the catalyst can be synthesized.

Dendrimers are synthetic polymers that have a treelike structure—whose “branches” emanate from a single point called a core. PAMAM (poly(amido amine)) dendrimers are a common class of dendrimer used in many different materials science and biotechnology applications due to their physical properties. Dendrimers can be synthesized with different cores and terminal end groups. The synthetic route being taken in this project utilizes specific generations of PAMAM dendrimers, which have an ethylene diamine core, branches that contain amide groups, and terminate in amine groups (Figure 1). PAMAM dendrimers are symmetrical and adopt a relatively spherical shape. The terminal amine ends of the “branches,” or end groups, are relatively monodisperse over the molecule’s spherical surface. These amine groups are reactive as nucleophiles and therefore present a unique opportunity as a site for functionalization (addition of molecules to the amine end groups) of the PAMAM end groups. PAMAM dendrimer solubility also typically mimics the solubility of their terminal groups, which is important for keeping reaction conditions relatively consistent when investigating the use of dendrimers in catalysis. PAMAM dendrimers can be purchased or synthesized in multiple generations as well—Generations 2.0, 3.0, and 4.0 PAMAM dendrimers will be used for this project, which have 16, 32, and 64 amine-
Dendritic catalysis has become an increasingly important and studied field. Three structural motifs that utilize the dendritic macromolecule as a catalyst delivery system have been investigated (Figure 2). In the first motif, the core of the dendrimer is the single catalytic unit in dendrimer 1. The second, the “dendritic box” motif 2, utilizes pockets inside the dendrimer formed by the placement of its branches to capture and deliver the catalytic unit. The third motif 3, incorporating the largest number of catalytic units, covalently binds catalytic units to the terminal ends of the dendrimer. Using the motif in 3 and covalently binding the catalyst to the amine end groups of the PAMAM dendrimer framework is ideal for our method of dendritic catalysis because it allows separation of the catalyst with any method of separation that could be utilized with dendrimers or other similar macromolecules.

PAMAM dendrimers were chosen in particular for this work due to their properties for an ideal platform for catalysis. Their spherical shape, solubility properties, organic structure, and monodisperse end groups make them attractive as a framework for organocatalysis. The spherical shape and monodisperse end groups of a PAMAM dendrimer are an optimal way to deliver a catalyst to a system because the catalytic site is on the surface of the molecule, leading to ready accessibility to reagents for catalysis. Solubility properties of PAMAM dendrimers typically mimic those of the end groups, especially in higher generations. This provides the opportunity to keep solvent reaction conditions consistent between dendrimer-bound catalysis and catalysis using free, unbound catalysts. The organic structure of the PAMAM catalysts provides the option of covalently binding molecules to the terminal end-groups.
By exploiting the reactive amino end groups, functionalizing the PAMAM dendrimers with MacMillan's (2S, 5S)-5-(1-benzyl-1H-indol-3-yl)-2-tert-butyl-3-methyl-imidazolidin-4-one catalyst (therefore increasing the effective size of the catalytic delivery framework) provides a route for catalyst purification. The size of the organo-catalyst functionalized dendrimers theoretically introduce the opportunity for recovery and reuse by filtration, dialysis, or size exclusion chromatography, which makes the MacMillan group’s procedures more economically feasible and environmentally friendly. Recovery and reuse of this catalyst could impact the fields of green chemistry as well as the pharmaceutical industry.

**DISCUSSION**

*Catalyst Functionalization of Dendrimers*

A set of three PAMAM dendrimers 4-6 were functionalized with a MacMillan-type imidazolidinone catalyst known to perform enantioselective catalysis (Figure 3). Although the dendrimer bound catalysts illustrated only show one catalytic unit per dendrimer, these schematics symbolize fully mono-functionalized dendrimers with the number of end groups functionalized respective to their generation.

Dendrimers 4-6 were functionalized using an approach adapted from a related functionalization by Koskinen and coworkers\(^\text{15}\) in order to develop the synthetic scheme to produce the desired imidazolidinone catalyst (Scheme 1). Coupling of N-fluorenylmethyloxycarbonyl (fmoc) protected L-phenylalanine with the free amine surface of each generation of PAMAM dendrimer was completed under hydroxybenzotriazole and diisopropyl-carbodiimide conditions. Deprotection of the resulting material 7 was accomplished with piperidine to reveal the phenylalanine-functionalized dendrimer 8. Treating the dendrimer with pivaldehyde in dimethylformamide resulted in the mono-functionalized dendrimers 4-6.

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**Figure 3:** Dendrimer generations 2.0-4.0 Functionalized with MacMillan’s (2S, 5S)-5-(1-benzyl-1H-indol-3-yl)—tert-butyl-3-methyl-imidazolidin-4-one catalyst.
The method that was adapted for the PAMAM dendrimer functionalization in Scheme 1 was not initially intended or optimized for varying generations of PAMAM dendrimer. Work on this project also included optimization of reagents, reaction conditions, and purification methods for the synthesis in Scheme 1. Reagent amounts were scaled appropriately for the number of amino end groups on the dendrimer, instead of a linear molar ratio. Reaction times were increased in order to allow reagents to navigate through the dendritic framework and react with terminal amino end groups. The pH of reactions were adjusted to be compatible with PAMAM dendrimer structure (pH 4-9). The first two steps in Scheme 1 were found to be able to be completed in dimethylsulfoxide (DMSO) instead of dimethylformamide (DMF) in order to minimize hazardous chemical exposure and wear on lab instruments.\textsuperscript{16,17} Pi-stacking of excess fmoc-phenylalanine with dendrimer-functionalized fmoc-phenylalanine inside the dendritic framework required that steps one and two in Scheme 1 were completed as a one-pot synthesis in order to drive all fmoc from the dendritic framework at once with an excess of piperidine in the deprotection step. This one-pot synthesis streamlined separation of fmoc from the phenylalanine-functionalized dendrimer \textbf{8}. Completing steps one and two in Scheme 1 as a one-pot synthesis also maximized recovery of \textbf{8} due to no loss of \textbf{7} in an unnecessary and time consuming purification step.

Functionalized dendrimer \textbf{8}, as well as functionalized dendrimers \textbf{4,5,6} were purified via dialysis in DMSO. Since DMSO was found to be trapped inside of the dendritic material, an additional step to drive solvent from the material was needed. When DMSO from dialysis is being removed via lyophilization, millipore water is added to the mixture to drive DMSO from the internal dendritic framework as well as creating diluted solution of DMSO and water that aides in the removal of solvent from the dendrimer material, as water has a higher vapor pressure (17.54 mmHg)\textsuperscript{18} than DMSO (0.42 mmHg)\textsuperscript{19}. This results in the DMSO almost completely leaving the internal dendritic framework by lyophilization to provide more accurate yields by weight as well as not interfering with any characterization methods. Additionally, in the process of developing the parameters shown in Scheme 1, it was found that cyclization of the catalyst in step 3 of Scheme 1 was sometimes not completely successful due to excess solvent, not enough reagent, or not long enough of a reaction time. In these cases, it was found that if the material was re-submitted to the reaction conditions in step 3 of Scheme 1, additional
cyclization would occur, further functionalizing the dendrimer with the desired catalyst. During the course of this work the parameters for step 3 of Scheme 1, including amounts of solvent, reagent, and reaction time, were optimized. The methods used to cyclize the catalyst are now efficient enough to produce quantitative yields of dendrimer functionalized with cyclized catalyst in one ring-closing reaction. For the purification of the resultant fully functionalized dendrimer-bound catalyst, DMF must be evaporated via lyophilization before submitting the material to dialysis, since DMF will degrade the dialysis tubing (made of regenerated cellulose) that is compatible with DMSO.

The resultant new dendrimers 4-6 were characterized using $^1$H NMR and $^{13}$C NMR spectroscopy techniques as well as matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Multiple matrices used for MALDI-TOF-MS were investigated in order to optimize dendrimer characterization, including trans-3-indoleacrylic acid (IAA) and 2,5-dihydroxybenzoic acid (DHB). Optimal MALDI-TOF-MS results were obtained using DHB as a matrix.

**Catalytic Activity of Catalyst-Functionalized Dendrimers**

Functionalized PAMAM dendrimers 4-6 were evaluated for their ability to promote enantioselective catalysis using selected reactions catalyzed by the MacMillan-type imidazolidinone catalyst that was built onto the dendritic framework (Schemes 2, 3).\textsuperscript{20,21}

\[ 	ext{Scheme 2} \]

The reactions in Scheme 2 and 3 were chosen to demonstrate the catalytic utility of the dendrimer by showing that they were within the range of what is compatible with the framework of a PAMAM dendrimer. The reactions in Schemes 2 and 3 were run at room temperature. This is advantageous as low temperatures cannot be supported for more than 8 hours in our lab, and temperatures over 30°C can degrade the framework of the dendrimer. The reactions chosen were also performed in a pH range that was adequate for the dendrimer framework, as the framework can also degrade over pH of 9, and at pHs lower than 3, the amine groups inside the dendrimer are ionized and the dendrimer can precipitate out of solution as a salt. Since these are screening reactions, the reactions in Scheme 2 and 3 were also chosen due to their readily available or relatively inexpensive reagents.

In order to gather sufficient evidence to support our dendrimer-bound catalyst’s utility, reactions...
shown in Scheme 2 and 3 were run under only acidic conditions (no catalyst), the original conditions published (free catalyst), and with the dendrimer-bound catalysts 4, 5, 6. The time until reaction completion, percent yield, optical activity, and catalyst recovery were compared to values reported by the MacMillan group. Enantiomeric excess was determined via polarimetry in chloroform.

Solvent Studies and Other Notable Observations
Although dendrimer solubility generally mimics the solubility of their end groups, lower generations of PAMAM dendrimers can exhibit different solubility properties in certain organic solvents because of their less spherical shape (compared to higher generations) and exposed internal structure. A series of control reactions for the aniline addition reaction in different solvents were used in order to determine catalyst functionality in differing solvent environments in order to broaden possible reaction conditions.

During these solvent studies, multiple things were discovered about the practical process of the procedures in Scheme 2 and 3 with dendrimer-bound material. In the reaction shown in Scheme 3, an amber vial (preferably subsequently covered in tinfoil) must be used in order to prevent light degradation of the 1-phenylpyrrolidine starting material. In the reaction shown in Scheme 3, there is also a cooling step to -10°C. When running the reaction in Scheme 3 with DMSO as a solvent, the cooling step cannot be employed because of the freezing point of DMSO at 19°C.\textsuperscript{22} Though the reaction cannot be cooled, it was found that it had no noticeable effect on the yield or enantioselectivity of the reaction. If the solvent used in the nucleophilic addition reaction is DCM, parafilm should not be used in order to prevent DCM from leeching the hard-to-separate parafilm into the reaction mixture.

Since the nucleophilic addition reaction in Scheme 3 is run in acidic conditions, there is also a reaction acidifying step. The amount of acid in the original reaction is the amount needed to acidify all of the catalyst material. However, in a system using the dendrimer-bound catalyst, some of the internal framework of the dendrimer is protonated before the catalytic groups on the surface of the dendrimer. It was found that the amount of acid needed to be increased in a dendrimer-bound catalyst system in order to protonate the catalytic groups and run the reaction successfully. However, because of the chance of the dendrimer framework being completely protonated and precipitating out of solution, the reaction must be kept above a pH of 3.

Dialysis was used to purify the dendrimer material from the reaction mixture, since the dendrimer material should stay in the dialysis tubing as the reaction mixture diffuses outside of the dialysis tubing. Dialysis in DMSO was initially tried, but the lyophilization procedure from evaporating DMSO was time consuming.
Dialysis in DCM was also attempted, but it was
found that DCM in large volumes degraded the
dialysis tubing and leached cellulose into the
reaction mixture. Removing the cellulose from
the reaction mixture added an extra
cromatography purification step (in addition to
the chromatographic method to purify product
from reagents), so DCM was discarded as a
potential solvent for dialysis and the use of
DMSO had evidence of being more efficient than
DCM in these conditions.

Purification of the desired products from the
reactants was performed via silica gel
chromatography. It was found that
chromatography using a Chromatotron (a
centrifugal thin-layer silica gel purification
system)\(^\text{23}\) with a hand-held UV lamp was more
efficient, used less solvent, and provided better
separation and yields than classic flash or gravity
chromatography with silica gel.

RESULTS

Three generations of dendrimer-bound (2S, 5S)-
5-benzyl-2-tert-butyl-3-methylimidazolidin-4-
one were successfully synthesized with good
functionalization yield. Phenylalanine
functionalization was completed in near
quantitative yield (Table 1, Steps 1 and 2 to
produce 8 in Scheme 1). Cyclization into the
complete catalyst (Step 3 to produce 4,5,6 in
Scheme 1) was completed in high yield when
characterized by NMR, but MALDI-TOF-MS
data shows a lower yield of cyclization (Table 1).

Because of the internal consistency of percent
functionalization found via both MALDI-TOF-
MS and NMR spectroscopy, respectively, and
due to the nature of the high-powered laser used
in MALDI-TOF-MS, it is theorized that the
laser fragments the fragile fully cyclized catalyst
functionalized dendrimer. Further investigation
is currently being conducted to determine
another method of characterization to determine
the mass of the catalyst functionalized
dendrimers to confirm this theory.

Two reactions published by MacMillan using
free (2S, 5S)-5-benzyl-2-tert-butyl-3-
methylimidazolidin-4-one were investigated by
substituting free catalyst with dendrimer-bound
catalyst, and evidence shows that the dendrimer-
bound catalyst both catalyzes these reactions and
produces the same rotation in chirality in the
desired product. (Table 2).
### Table 2: Comparison of Free Catalyst and Dendrimer-Bound Catalyst Activity

<table>
<thead>
<tr>
<th>ANILINE ADDITION (DCM)</th>
<th>FREE CATALYST</th>
<th>DENDRIMER-BOUND CATALYST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>89%</td>
<td>32%</td>
</tr>
<tr>
<td>Optical Rotation</td>
<td>-2.77°</td>
<td>-0.4° (observed rotation)</td>
</tr>
<tr>
<td>DIELS ALDER (ACN/WATER)</td>
<td>Yield</td>
<td>4%</td>
</tr>
<tr>
<td>Optical Rotation</td>
<td>-536°</td>
<td>-460°</td>
</tr>
</tbody>
</table>

Since both control and on-dendrimer catalyzed reactions ran to completion via NMR monitoring, the discrepancy in percent yield is attributed to purification error. The optical rotation for all products produced by dendrimer-bound catalyst is concurrent with the chirality observed with free catalyst, which is promising for future work because the optical rotation provides evidence the dendrimer-bound catalyst works with similar enantioselectivity to the free catalyst.

Attempts to recover the dendrimer-bound catalyst were initially successful but are currently being optimized. Purification of the dendrimer-bound catalyst by filtration was initially seemed promising because of limited dendrimer solubility in acetonitrile and water, but NMR analysis showed high levels of starting reagents trapped inside the dendrimer framework after washing of the filtrate. Dialysis against DMSO using regenerated cellulose dialysis tubing with a MWCO of 3500 kDa proved a more efficient way to purify dendrimer-bound catalyst. (Table 3).

### Table 3: Recovery of dendrimer-bound catalyst using dialysis

<table>
<thead>
<tr>
<th>TRIAL NUMBER</th>
<th>GENERATION</th>
<th>PERCENT RECOVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G (3.0)</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>G (3.0)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>G (3.0)</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>G (2.0)</td>
<td>28</td>
</tr>
</tbody>
</table>

There has not yet been any evidence of a correlation between dendrimer generation used and yield or recovery.

### CONCLUSIONS

Three generations (2.0, 3.0, and 4.0) of dendrimer-bound (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one catalyst have been successfully synthesized. The dendrimer-bound catalysts demonstrate similar yield and optical activity to free (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one catalyst as reported by MacMillan. The dendrimer-bound catalysts also demonstrate higher potential for recovery of catalyst than free catalyst. Recovery methods are currently being optimized, most promisingly through dialysis techniques. The efficiency of the dendrimer-bound catalyst after a number of uses and recoveries is also being investigated. Future work will include optimizing catalytic conditions and developing orthogonal catalysts for multistep or cascade catalysis, as well as attempting different catalytic delivery and recovery methods through the use of linking the
dendrimer-bound catalyst to a gold surface for solid-support catalysis.

ACKNOWLEDGEMENT

Thanks and appreciation are extended to Jessica Ennist and the Cloninger group at Montana State University for all of the help and guidance they provided. Carla Saunders and Asha Kopp—as other student researchers on this project—deserve special recognition for all the work they have done, as well as Dr. T. Nicholas Jones in his continual support, motivation, and encouragement for his students on this project.

This material is based upon work supported by the National Science Foundation under Grants No. (NSF 1057690) and (NSF-REU 1156855).
Generation 2.0 PAMAM-based nitrogen-linked phenylalanine dendrimer (8):

An aqueous solution of amine-terminated Starburst PAMAM dendrimer (Generation 2.0, 12.57% (w/w)) was lyophilized. The resulting residue (124.8 mg, 0.0383 mmol, 1 eq) was dissolved in DMSO (1.0 mL). In a separate scintillation vial, a solution of 9-fluorenylmethoxycarbonyl-L-phenylalanine (0.9442 g, 2.43 mmol, 64 eq) and hydroxybenzotriazole (0.3375 g, 2.49 mmol, 64 eq) in DMSO (4.0 mL) was added to a solution of N,N'-diisopropylcarboimide (382 uL, 2.43 mmol, 64 eq) in DMSO (0.25 mL) and allowed to stir for five minutes. The two solutions were combined and stirred (2.5 h) to form 7. This product was dialysed against DMSO (MW cutoff 1 kDa). The solution was lyophilized to give 7. This product was used without further purification.

Resulting crude product 7 was deprotected in a 20% (v/v) solution of piperidine/ DMSO by dissolving in DMSO (7.0 mL) and adding piperidine (1.75 mL). After 110 minutes of stirring, the reaction mixture was dialysed against DMSO (MW cutoff 1 kDa). The solution was lyophilized using water to drive out DMSO to give title compound (8) as a fluffy, white solid (136.6 mg). [α]D = -131.5; 1H NMR (500MHz, CD3OD) δ (ppm) 2.31 (m, 61H, PAMAM-x), 2.54 (m, 28H, PAMAM-x), 2.76 (m, 61H, PAMAM-x), 2.97, 3.01 (m, 16H, PhCH2CH), 3.21 (m, 96H, PAMAM-x), 3.50 (m, 16H, PhCH2CH), 7.20, 7.28 (m, 80H, Ph) ppm; 13C NMR (500MHz, CD3OD) δ 34.7, 38.6, 39.9, 40.4, 42.5, 51.1, 53.4, 57.9, 127.9, 129.7, 130.5, 139.0, 175.1, 176.9 ppm; MALDI-TOF-MS (pos) 5628.

Generation 2.0 PAMAM-based nitrogen-linked (2S,5S)-(−)-2-tert-butyl-3-methyl-5-benzyl-4-imidazolidinone dendrimer (4):

Phenylalanine functionalized G (2.0) PAMAM (8) (126.6 mg, 0.2256 mmol, 1 eq) was dissolved in dimethylformamide (1.5 mL) and pivaldehyde was added (490 uL, 4.51 mmol, 200 eq). N,N'-diisopropylethylamine was added until the reaction mixture reached a pH of 9. The reaction mixture was stirred for approximately 40 hours. This product was lyophilized to remove DMF, re-dissolved in DMSO and dialysed against DMSO (MW cutoff 1 kDa). The solution was lyophilized using water to drive out DMSO to give title compound 4 as a pale yellow glassy solid (89.2 mg). [α]D = -131.5; 1H NMR (500MHz, CD3OD) δ 0.85 (s, 123H, tert-butyl) 2.31 (m, 60H, PAMAM-x) 2.52 (m, 28H, PAMAM-x), 2.74 (m, 61H, PAMAM-x) 3.21 (m, 96H, PAMAM-x) 3.65, 3.69 (dd, 16H, PhCH2CH) 6.88, 7.06, 7.21 (m, 80H, Ph) ppm; 13C NMR (500MHz, CD3OD) δ (ppm) 27.2, 34.8, 37.3, 38.7, 40.1, 40.5, 41.8, 42.6, 51.2, 53.6, 58.0, 76.1, 127.7, 129.4, 129.7, 130.6, 131.2, 138.9, 174.6,
174.7, 175.1, 175.5, 176.5, 177.0 ppm; MALDI-TOF-MS (pos) 6118.

**Generation 3.0 PAMAM-based nitrogen-linked phenylalanine dendrimer (8):**
An aqueous solution of amine-terminated Starburst PAMAM dendrimer (Generation 3.0, 7.01% (w/w)) was lyophilized. The resulting residue (116.8 mg, 0.0169 mmol, 1 eq) was dissolved in DMSO (2.0 mL). In a separate scintillation vial, a solution of 9-fluorenylmethoxycarbonyl-L-phenylalanine (0.8398 g, 2.17 mmol, 128 eq) and hydroxybenzotriazole (0.2950 g, 2.18 mmol, 128 eq) in DMSO (3.0 mL) was added to a solution of N,N'-diisopropylcarboimide (340 uL, 2.18 mmol, 128 eq) in DMSO (1.0 mL) and allowed to stir for five minutes. The two solutions were combined and stirred (2.5 h) to form 7. This product was dialysed against DMSO (MW cutoff 3.5 kDa). The solution was lyophilized to give 7. This product was used without further purification.

Resulting crude product 7 was deprotected in a 20% (v/v) solution of piperidine/ DMSO by dissolving in DMSO (5.5 mL) and adding piperidine (1.4 mL). After 60 minutes of stirring, the reaction mixture was dialysed against DMSO (MW cutoff 3.5 kDa). The solution was lyophilized using water to drive out DMSO to give title compound 8 as a fluffy, white solid (122.2 mg). $^1$H NMR (300MHz, CD$_3$OD) δ (ppm) 2.33 (m, 124H, PAMAM-x), 2.56 (m, 57H, PAMAM-x), 2.77 (m, 119H, PAMAM-x), 2.96 (m, 61H, PhCH$_2$CH), 3.21 (m, 182H, PAMAM-x), 3.51 (m, 32H, PhCH$_2$CH), 7.21, 7.28 (m, 169H, Ph); $^{13}$C NMR (500MHz, CD$_3$OD) δ (ppm) 34.8, 28.6, 40.0, 40.4, 42.5, 128.0, 129.6, 130.6, 139.1, 174.6, 175.1, 176.9 ppm; MALDI-TOF-MS (pos) 10606.

**Generation 3.0 PAMAM-based nitrogen-linked (2S,5S)-(–)-2-tert-butyl-3-methyl-5-benzyl-4-imidazolidinone dendrimer (5):**
Phenylalanine functionalized G (3.0) PAMAM 8 (122.2 mg, 0.012 mmol, 1 eq) was dissolved in dimethylformamide (2.0 mL) and pivaldehyde was added (228 uL, 2.05 mmol, 200 eq). N, N'-diisopropylethylamine was added until the pH of the reaction mixture reached 9. The reaction mixture was stirred for approximately 40 hours. This product was lyophilized to remove DMF, re-dissolved in DMSO and dialysed against DMSO (MW cutoff 3.5 kDa). The solution was lyophilized using water to drive out DMSO to give title compound 5 as a pale yellow glassy solid (126.1 mg). $^1$H NMR (500MHz, CD$_3$OD) δ 0.89 (s, 252H, tert-butyl), 2.35 (m, 120H, PAMAM-x), 2.57 (m, 56H, PAMAM-x) 2.78 (m, 121H, PAMAM-x), 3.25 (m, 185H, PAMAM-x), 3.71, 3.74 (dd, 31H, PhCH$_2$CH), 6.93, 7.09, 7.24 (m, 163H, Ph) ppm; $^{13}$C NMR (500MHz, CD$_3$OD) δ ppm 25.1, 25.8, 33.4, 35.9, 37.3, 38.7, 39.1, 40.4, 41.2, 49.8, 52.2, 56.6, 74.6, 126.3, 128.0, 128.3, 129.2, 129.8, 137.5, 173.7, 174.1, 175.1; (500MHz,
An aqueous solution of amine-terminated Starburst PAMAM dendrimer (Generation 4.0, 13.12% (w/w)) was lyophilized. The resulting residue (123.7 mg, 0.0087 mmol, 1 eq) was dissolved in DMSO (2.0 mL). In a separate scintillation vial, a solution of 9-fluorenylmethoxycarbonyl-L-phenylalanine (0.8622 g, 2.23 mmol, 256 eq) and hydroxybenzotriazole (0.3067 g, 2.27 mmol, 256 eq) in DMSO (4.0 mL) was added to a solution of N,N'-diisopropylcarboimide (346 uL, 2.22 mmol, 256 eq) in DMSO (0.5 mL) and allowed to stir for five minutes. The two solutions were combined and stirred (2.5 h) to form 7. This product was dialysed against DMSO (MW cutoff 3.5 kDa). The solution was lyophilized to give title compound 8 as a fluffy, white solid (161.4 mg). °H NMR (500MHz, CD3OD) δ (ppm) 2.29 (m, 240H, PAMAM-x), 2.52 (m, 112H, PAMAM-x), 2.73 (m, 243H, PAMAM-x), 2.98 (m, 63H, PhCH2CH), 3.21 (m, 368H, PAMAM-x), 3.51 (m, 64H, m, PhCH2CH), 7.19,7.25 (m, 319H, Ph) ppm; 13C NMR (500MHz, CD3OD) δ (ppm) 34.8, 38.7, 40.0, 40.5, 42.6, 51.3, 53.6, 57.8, 127.9, 129.6, 130.6, 139.0, 175.2, 176.8 ppm; MALDI-TOF-MS (pos) 21164.

Generation 4.0 PAMAM-based nitrogen-linked (2S,5S)-(-)-2-tert-butyl-3-methyl-5-benzyl-4-imidazolidinone dendrimer (6):

Phenylalanine functionalized G (4.0) PAMAM 8 (151.8 mg, 0.0066 mmol, 1 eq) was dissolved in dimethylformamide (1.5 mL) and pivaldehyde was added (143 uL, 1.32 mmol, 200 eq). N, N'-diisopropylethylamine was added until the pH of the reaction mixture reached 9. The reaction mixture was stirred for approximately 40 hours. This product was lyophilized to remove DMF, re-dissolved in DMSO and dialysed against DMSO (MW cutoff 3.5 kDa). The solution was lyophilized using water to drive out DMSO to give title compound 6 as a pale yellow glassy solid (99.3 mg). [α]D = -47.4; °H NMR (500MHz, CD3OD) δ 0.89 (s, 521H, tert-butyl), 2.35 (m, 239H, PAMAM-x), 2.56 (m, 119H, PAMAM-x), 2.78 (m, 239H, PAMAM-x), 3.25 (m, 366H, PAMAM-x), 3.71 (dd, 62, PhCH2CH), 6.92, 7.08, 7.22 (m, 320H, Ph) ppm; 13C NMR (500MHz, CD3OD) δ 25.4, 26.4, 27.4, 35.0, 37.4, 40.2, 40.3, 40.7, 42.0, 51.3, 53.8, 58.1, 76.2, 127.9, 129.6, 129.9, 131.4, 139.0, 139.3, 174.7,
174.8, 175.2, 176.6, 177.0 ppm; MALDI-TOF-MS (pos) 22700.

**Acid-Catalyzed in Dichloromethane 3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)propionaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added 4-nitrocinnamaldehyde (13.7 mg, 0.077 mmol, 1.0 equiv) dichloromethane (0.2 mL), and HCl (as a 4N solution in 1,4-dioxane, 5 uL). The solution was cooled to -10°C in a salt/ice bath before addition of 1-phenylpyrrolidine (35.1 uL, 0.244 mmol, 3.0 equiv). After 48 h, the crude reaction mixture was analyzed by NMR and product was found to be formed in a 4-nitrocinnamaldehyde:product ratio of 1:1.2, providing evidence that any additional product formed after the 16 d mark in the on-dendrimer catalyst is due to catalytic activity, and not acid catalysis.

**Dendrimer-Bound Catalyst in Dichloromethane (S)-3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)-propionaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added 4-nitrocinnamaldehyde (13.7 mg, 0.077 mmol, 1.0 equiv) dichloromethane (0.2 mL), and HCl (as a 4N solution in 1,4-dioxane, 5 uL). The solution was cooled to -10°C in a salt/ice bath before addition of 1-phenylpyrrolidine (35.1 uL, 0.244 mmol, 3.0 equiv). After 48 h, the crude reaction mixture was analyzed by NMR and product was found to be formed in a 4-nitrocinnamaldehyde:product ratio of 1:1.2, providing evidence that any additional product formed after the 16 d mark in the on-dendrimer catalyst is due to catalytic activity, and not acid catalysis.

**Dendrimer-Bound Catalyst in Dimethylsulfoxide (S)-3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)-propionaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added G(3.0) dendrimer-bound (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one (14.0 mg, 0.0013 mmol, 0.20 equiv catalyst), dimethylsulfoxide (0.2 mL), HCl to acidify the solution to pH ~4 (as a 4N solution in 1,4-dioxane, 30 uL), and 4-nitrocinnamaldehyde (24.1 mg, 0.136 mmol, 1.0 equiv). 1-phenylpyrrolidine was then added to the vial (57.3 uL, 0.398 mmol, 2.98 equiv). After 20 d, the reaction mixture was transferred into dialysis tubing (MWCO 3500) and dialyzed against DMSO. The DMSO outside the dialysis tubing was concentrated under reduced pressure in a lyophilizer and subjected to silica gel chromatography via chromatotron. Gradient elution with 25-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 32.4% yield (8.6 mg, 0.027 mmol); $[\alpha]_{obs} = -0.4$.
a bright orange oil in 26.97% yield (11.9 mg, 0.037 mmol); apparent \([\alpha]_D = -1.89 \, (c=0.030 \, \text{mmol}, 1 \, \text{mL CHCl}_3)\), 45% ee.

**Free Catalyst in Acetonitrile and Water (2R)-Bicyclo[2.2.2]oct-5-ene-2-carboxyaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one (24.2 mg, 0.098 mmol), acetonitrile/water (95/5 v/v, 0.13 mL), acrolein (500 \, \text{uL}, 7.48 mmol), and cyclohexadiene (240 \, \text{uL}, 2.52 mmol). The solution was stirred for 24 h, after which time the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (10 mL). The aqueous layer was extracted with diethyl ether (5 mL x 4) and the combined organics were dried (\text{Na}_2\text{SO}_4) and concentrated. Purification by silica gel chromatography (10% ether/pentane) afforded the title compound as a colorless oil in 4% yield (14.0 mg, 0.10 mmol); apparent \([\alpha]_D = -535^\circ \, (c=5.1*10^{-6} \, \text{mmol}, 1 \, \text{mL CHCl}_3)\)

**Dendrimer-Bound Catalyst in Dichloromethane (2R)-Bicyclo[2.2.2]oct-5-ene-2-carboxyaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one (24.1 mg, 0.099 mmol, 0.20 equiv) dichloromethane (1.0 mL), HCl (as a 4N solution in 1,4-dioxane, 25 \, \text{uL}), and 4-nitrocinnamaldehyde (88.5 mg, 0.500 mmol, 1.0 equiv). The solution was cooled to -10°C in a salt/ice bath before addition of 1-phenylpyrrolidine (216 \, \text{uL}, 1.485 mmol, 3.0 equiv). After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 25-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 89% yield (162.1 mg, 0.500 mmol); apparent \([\alpha]_D = -2.77 \, (c=0.37 \, \text{mmol}, 1 \, \text{mL CHCl}_3)\), 67%ee.

**Free Catalyst in Dimethylsulfoxide (S)-3-(4-Nitrophenyl)-3-(4-pyrrolidin-1-yl-phenyl)propionaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one (3.0 mg, 1.07*10^{-4} \, \text{mmol}), dichloromethane, acrolein (6.5 \, \text{uL}, 0.097 mmol), and cyclohexadiene (5.0 \, \text{uL}, 0.052 mmol). The solution was stirred for 8 d, after which time the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (10 mL). The aqueous layer was extracted with diethyl ether (5 mL x 4) and the combined organics were dried (\text{Na}_2\text{SO}_4) and concentrated. Purification by silica gel chromatography (10% ether/pentane) afforded the title compound as a colorless oil in 24% yield (17.4 mg, 1.3*10^{-4} \, \text{mmol}); apparent \([\alpha]_D = -460^\circ \, (c=3.7*10^{-2} \, \text{mmol}, 1 \, \text{mL CHCl}_3)\)
2-tert-butyl-3-methylimidazolidin-4-one (27.6 mg, 0.112 mmol, 0.20 equiv) dimethylsulfoxide (0.5 mL), HCl (as a 4N solution in 1,4-dioxane, 25 μL), and 4-nitrocinnamaldehyde (99.3 mg, 0.500 mmol, 1.0 equiv). The solution was cooled to -10°C in a salt/ice bath before addition of 1-phenylpyrrolidine (241.8 μL, 1.68 mmol, 3.0 equiv). After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 25-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 69.5% yield (126.4 mg, 0.390 mmol); apparent [α]D = -3.9 (c=0.34 mmol, 1 mL CHCl3), 94%ee

**Free Catalyst in Dichloroethane (S)-3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)-propionaldehyde**

To a 5 mL amber scintillation vial equipped with a magnetic stir bar was added (2S, 5S)-5-benzyl-2-tert-butyl-3-methylimidazolidin-4-one (25.6 mg, 0.104 mmol, 0.20 equiv) dichloroethane (1.0 mL), HCl (as a 4N solution in 1,4-dioxane, 30 μL), and 4-nitrocinnamaldehyde (92.2 mg, 0.512 mmol, 1.02 equiv). The solution was cooled to -10°C in a salt/ice bath before addition of 1-phenylpyrrolidine (223.0 μL, 1.55 mmol, 3.0 equiv). After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 25-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 47.6% yield (80.3 mg, 0.248 mmol); [α]D = -2.36 (c=0.13 mmol, 1 mL CHCl3), 57%ee

**Characterization Notes**

1H NMR and 13C NMR for all functionalized dendrimer characterization was carried out in deuterated methanol. 13C NMR was optimized by running 8,000-9,000 scans on samples with a 3 second relaxation delay.

Optimum MALDI-TOF-MS characterization can be carried out in both trans-3-indolacrylic acid (IAA) or 2,5-dihydroxybenzoic acid (DHB) with dimethylformamide (DMF) as a solvent with the concentrations used in Table 4. It was found that DHB provided more consistent success in MALDI-TOF-MS analysis attempts. Myoglobin was used as a standard for calibration purposes.

Myoglobin standards were prepared by adding 10 μL of myoglobin solution (1.6 mg/mL H2O) to 10 μL of DHB solution (20 mg/mL DHB in 80% ACN/H2O).

<table>
<thead>
<tr>
<th>Desired Concentration (Dendrimer:Matrix)</th>
<th>uL 1mM Dendrimer Solution</th>
<th>uL 1M Matrix Solution</th>
<th>uL 0.1M Matrix Solution</th>
</tr>
</thead>
<tbody>
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<td>1:250</td>
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<td>10</td>
</tr>
<tr>
<td>1:500</td>
<td>2</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>1:1000</td>
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</tr>
<tr>
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</tr>
<tr>
<td>1:30k</td>
<td>1</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>
1M DHB Matrix solution was prepared by adding 0.0231g of DHB to 150 uL of DMF.

0.1M DHB Matrix solution was prepared by adding 20 uL of 1M DHB solution to 180 uL of DMF.

1 mM dendrimer solutions were prepared according to their theoretical mass based on functionalization and generation (Table 5).

<table>
<thead>
<tr>
<th>Generation</th>
<th>Concentration Dendrimer 8 in DMF</th>
<th>Concentration Dendrimers 4,5,6 in DMF</th>
</tr>
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<tr>
<td>G (2.0)</td>
<td>5.5mg/mL</td>
<td>6.7 mg/mL</td>
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<tr>
<td>G (3.0)</td>
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<td>14 mg/mL</td>
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<td>G (4.0)</td>
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<td>28 mg/mL</td>
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</table>
REFERENCES


12. Pittlekow, M.; Moth-Poulsen, K.; Boas, U.; Christensen, J. B. “Poly(amideamine)-Dendrimer-Stabilized Pd(0) Nanoparticles as a Catalyst for the Suzuki Reaction” Lagmuir 2003, 19, 7682-7684.


