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“Green” Synthesis of Compounds with Biomedical Significance Facilitated by Water-Soluble Dendritic-Palladium Complexes

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“Green” Synthesis of Compounds with Biomedical Significance Facilitated by Water-Soluble Dendritic-Palladium Complexes

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Abstract

The Suzuki-Miyaura cross-coupling reaction (Suzuki reaction) is a highly efficient method of Carbon-Carbon bond formation, making it widely used in the synthesis of biaryl intermediates of pharmaceuticals. The coupling is conventionally performed at elevated temperatures and in organic solvents leading to adverse economic and environmental impacts. Previous studies in our group suggest that water soluble dendrimers, able to complex palladium, are viable Suzuki catalysts able to afford quantitative yields of the target compounds in water at close to ambient temperatures. They are, however, not ideal for catalyzing the reaction between hydrophobic reagents due to lack of contact with water-insoluble substrates. The goals of this study are to design and test water-soluble dendritic-palladium complexes containing a hydrophobic core, able to solubilize and selectively bind hydrophobic substances, in an attempt to improve the spatial arrangement of the catalyst and reagents in water. The structure of these novel "green" catalysts consists of calix[n]arene (n= 4,6,8) as the central core with water soluble poly(ester-ether) dendrons attached at the upper rim of the cycle (see figure below). The progress in the synthesis of these unique macromolecules by Williamson ether synthesis and Cu(I)-catalyzed alkyne-azide cycloaddition is reported. Our ability to reproducibly form the depicted compound with chemical and structural purity is confirmed by diverse analyses (NMR, MALDI-TOF, DLS, ICP and TEM). Upon completion, this work aims to achieve unprecedented yields for the Suzuki reaction in water and produce the first Suzuki catalyst to mimic enzymatic character by selectively incorporating reagents.

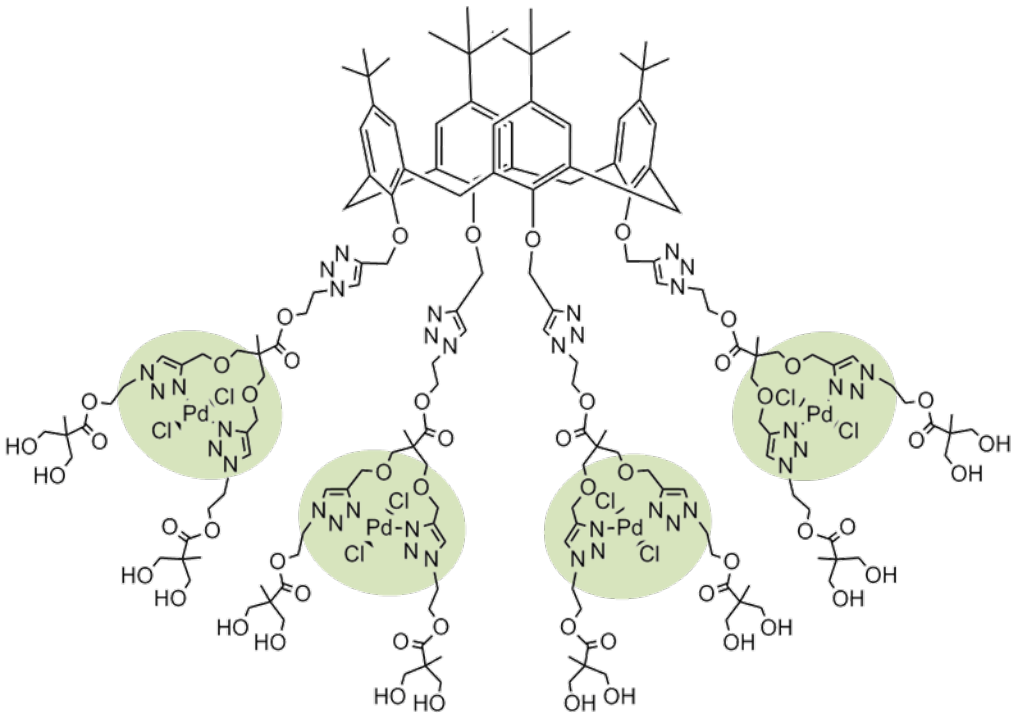

Table of Contents

List of Figures

List of Schemes

List of Tables

Acknowledgements

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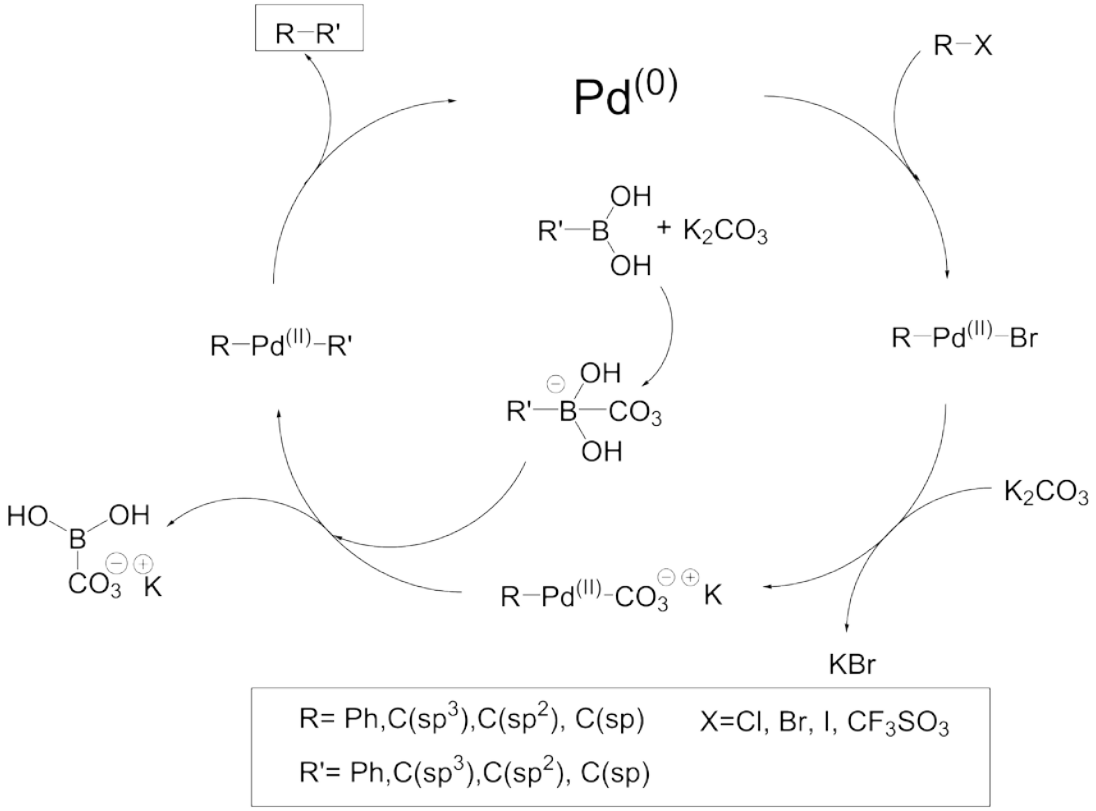
Introduction

The Suzuki-Miyaura cross-coupling reaction (Suzuki reaction), developed in 1979, provides one of the most efficient protocols for Carbon-Carbon bond formation, acknowledged with the Nobel Prize in Chemistry for 2010.[1,2] The reaction occurs between a nucleophilic organoboron compound and an electrophilic organic halide or triflate in the presence of base and a Pd(0) catalyst (Scheme 1).[2] This methodology has long been applied for the effective coupling of a wide range of substituted alkyl-, aryl-, and alkenyl-boron compounds to organic electrophiles, and has more recently been successfully employed for the coupling of alkynyl-boron compounds. In addition to its versatility, the Suzuki reaction employs readily available reagents, is compatibility with a wide variety of functional groups, has the advantage of being a one-pot process.[2] These optimal characteristics make the reaction a trade mark step in the synthesis of complex natural products, pharmaceuticals, and polymers in both academic and industrial laboratory settings.[2,3,4] From an environmental perspective, the reaction has several desirable qualities including relatively non-toxic byproducts and the need for only trace amounts of Pd (0) catalyst. On the other hand, considerable energy consumption and waste results from performing these reactions at elevated temperature and in organic solvents on a large scale. In lieu of organic solvents, water can act as an economical, environmentally friendly solvent which is highly attractive for both industrial and small scale synthesis.[5] Fortunately, the reagents are stable in water and the reaction can be executed under heterogeneous conditions allowing for modification of the reaction to run in aqueous media.

Scheme 1. General catalytic cycle and reaction mechanism for the coupling of an organohalide or triflate and an organoboronic acid in the presence of base (K_2CO_3)



Modification of the Pd (0) catalyst is the most promising way to reduce the environmental impacts of the Suzuki reaction. Pd (0) is unstable on its own, and prefers to form inactive aggregates in aqueous or organic solvents.[6] Catalyst immobilization is necessary in order to stabilize Pd (0), creating nanoparticles with high surface to volume ratio, resulting in increased activity.[7] Initially, a variety of active homogeneous catalysts were developed by employing phosphine based ligands to stabilize palladium.[8] Currently, conventional protocols for the Suzuki reaction, including industrial methods, utilize these phosphine ligands.[4] Unfortunately, phosphine based homogeneous catalysts are only active in organic solvents at elevated temperatures, and are difficult to remove from the reaction mixture for potential reuse.[3] Such drawbacks have increased interest in the development of recyclable catalysts that function in water and at low temperature. To be considered for large scale implementation, these new catalytic systems must be able to catalyze the Suzuki reaction using a wide variety of reagents, especially hydrophobic organoboranes in water.

Early studies on alternatives to phosphine based catalytic supports demonstrate a focus on producing homogeneous catalysts that operate efficiently in organic solvents but are more easily recycled.[9] While these catalysts improve upon traditional phosphine based ligands, they retain several disadvantages of homogeneous catalysts and are only active in organic solvents. In an attempt to make the Suzuki reaction more environmentally friendly, a vast accumulation of heterogeneous catalysts able to function in water have been produced. Water soluble phosphine derivatives,[10] natural and synthetic solid supports,[11] macromolecular stabilizers,[7,12] and other non-

conventional ligands[13] have been developed to create active Pd(0) catalysts in water. All of the previously mentioned catalytic systems suffer from either poor activity at low temperature (<80˚C) or inability to be recycled. Additionally, none of these Suzuki catalysts are active for the reaction for hydrophobic organoboranes. Leaching of Pd(0) from the catalyst support and restricted orientation of the reagents to the active site in these ligands are some probable causes of hindered performance.

Dendrimers are promising templates for catalyst immobilization because they have been shown to decrease palladium leaching and provide accessible active sites for reagent diffusion.[14] The pioneering work of Crooks and Tomalia first established evidence for the stabilization of metal nanoparticles using a dendritic template.[15,16] El Sayed first reported the use of dendrimer supported palladium nanoparticles as catalysts for the Suzuki reaction,[17] which was followed by a rise in the development of new more efficient dendrimer templates. Currently, there is an extensive assortment of dendrimers serving as palladium supports,[14,18] however, few water soluble dendritic-palladium catalysts exist.[7,12a,e,f] While these dendritic catalysts are efficient for the Suzuki reaction in water, to our knowledge none have been successfully applied to the reaction of non-water-soluble organoboranes. This is likely due to their insufficient selectivity towards hydrophobic substrates as a result of the hydrophilic character of the dendrimers. Without the presence of a hydrophobic binding region within these dendrimers, there is no apparent driving force for the hydrophobic substrates to come into contact with the Pd (0) catalyst.

Our group previously synthesized novel water-soluble dendrimers able to efficiently complex palladium via coordination bonds to adjacent triazole rings at each branching point (Figure 1).[12e] These dendritic catalysts have been shown to catalyze the Suzuki reaction in water at notably lower temperatures (Table 1) compared to other non-conventional Pd (0) supports. Despite this improvement they do not perform well with hydrophobic organoboranes and exhibit poor recyclability. Introduction of a hydrophobic binding site to our water-soluble dendritic-palladium complex would improve its selectivity towards hydrophobic reagents, thus increasing coupled product yields in water at low temperature. In addition to increasing yields for Suzuki reactions with hydrophilic organoboranes, this hydrophobic binding region may allow for the efficient coupling of hydrophobic organoboranes in water. A promising hydrophobic binding candidate to incorporate in our water soluble dendritic catalysts is calix[n]arene (n=4, 6, 8).

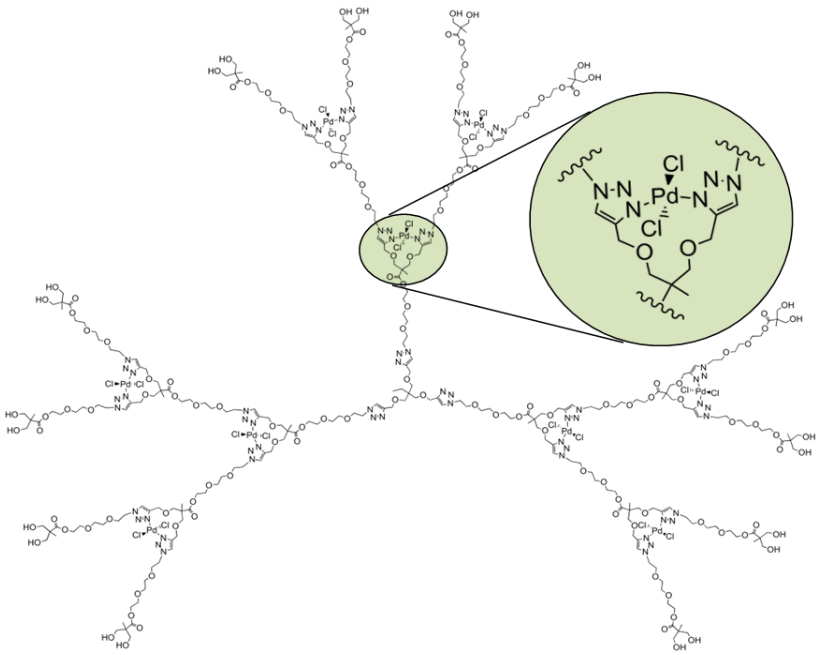


Figure 1. Previously synthesized 2nd generation dendrimer palladium complex (G2-OH-Pd) highlighting the coordination bond between adjacent triazole rings and $PdCl_2$[12e]

Table 1. Suzuki-Miyaura reaction between 4'-bromoacetophenone and phenylboronic acid, catalyzed by different Pd complexes in Water. *Performance of G1-OH-Pd highlighted (green)

Catalyst Class	Temp (˚C)	Pd (mol%)	Time (h)	Yield (%)
Dendrimer (G1-OH-Pd)	50	0.029	3	99
Polymer	60	0.01	3	92
Dendrimer	78	0.04	0.5	60
Polymer	80	0.00001-0.01	4-40	85-100
Phosphine	90	0.1	2	94-96
Phosphine	100	0.1	2	81-95
Cationic	100	0.001-0.01	1-3	94-99
Nitrogen bound	100	0.25	16	>99
Natural support	100	0.003	5	94-95
Silica Support	100	0.1	8	95
Natural support	100	0.3	4-7.5	92-94
Nitrogen bound	110	0.001-1.0	2-4	59-99
Nitrogen bound	120	0.1	1	100

Calix[n]arenes (n= 4,6,8) represent a class of host molecules, with three-dimensional structure, that can be tailored for a variety of hosts based on functionalization and the dimensions of the cavity (Figure 2).[19] Previously, there has been limited research into the development of dendrimers with a calixarene core,[20] and no studies into the use of dendrimers with a calixarene core as supports for transition metal catalysts. However, the hydrophobic binding nature of the calixarene cavity has been successfully employed in the production of multivalent ligands that selectively bind hydrophobic entities.[21] A similar approach is adopted to increase the selectivity of our dendritic palladium complexes towards catalyzing hydrophobic reagents by creating dendritic palladium complexes with a calixarene core. Modified water-soluble dendrons with ethylene glycol spacers are attached to a calixarene core using Williamson ether synthesis and copper-catalyzed azide−alkyne cycloaddition (CuAAC). The purpose shortening the triethylene glycol spacers (Figure 1) to ethylene glycol (Figures 3, 4) in the dendrons is to improve the proximity of the complex sites to the hydrophobic binding core. Produced dendritic-palladium supports containing a hydrophobic calix[n]arene (n=4,6) core are subsequently loaded with palladium to produce potentially size selective water-soluble Suzuki catalysts (Figures 3, 4). These novel dendritic-palladium complexes are analyzed for their ability to facilitate higher yields for the Suzuki reaction in water for the model reaction described in Table 1. In the future our goal is to test the ability of these catalysts to catalyze the Suzuki coupling of a hydrophobic organoborane, with potential for physiological activity, in water. Furthermore, the size of the hydrophobic cavity will be varied by changing the number of repeat units, n, in the calix[n]arene core. Lastly, the recyclability and size selectivity of the novel catalysts will be assessed.

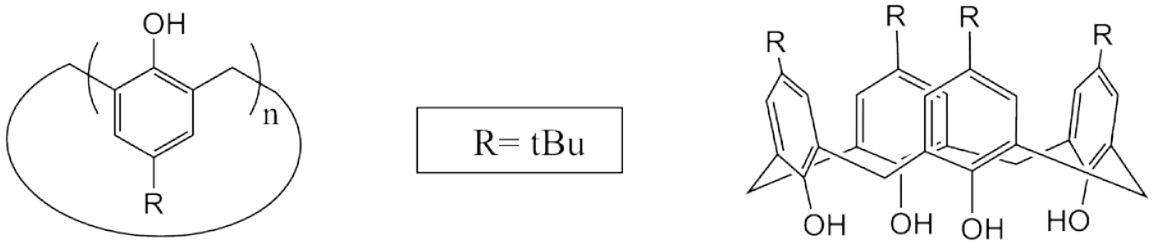


Figure 2. a) General repeat unit for the cyclic structure of calix[n]arene (n= 4,6,8) b) Three dimensional molecular skeleton of Calix[4]arene.

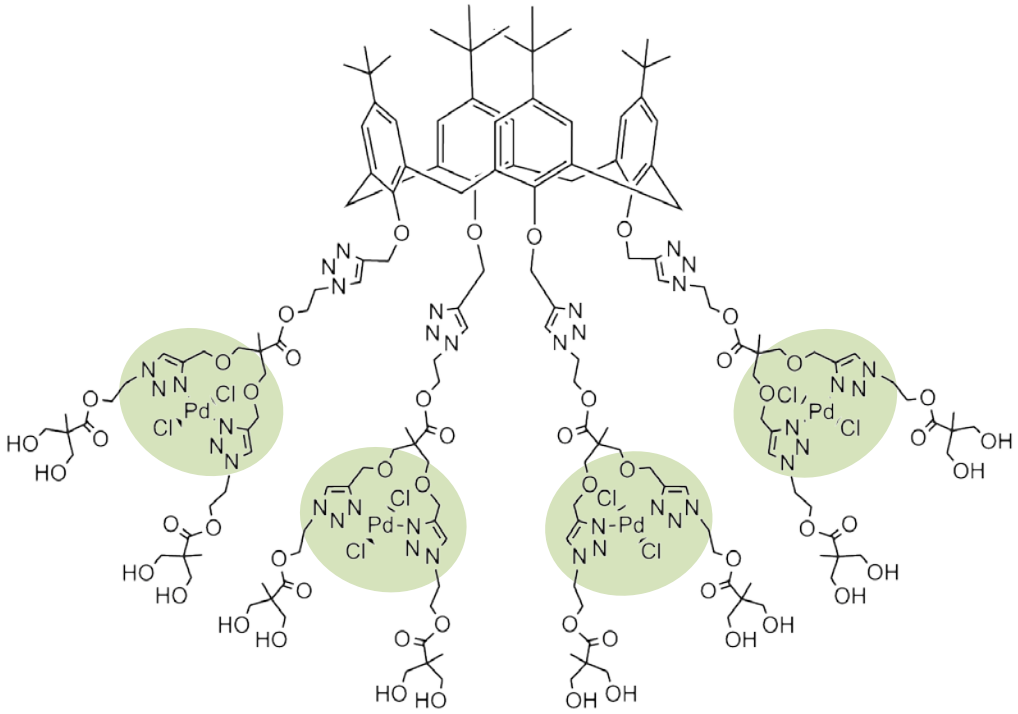


Figure 3. Tetra- SG1-tBu Calix[4]arene dendrimer complexed with $PdCl_2$ (Bis-SG1-[4]A$(OH)_{16}(PdCl2)_4$ (**13**).

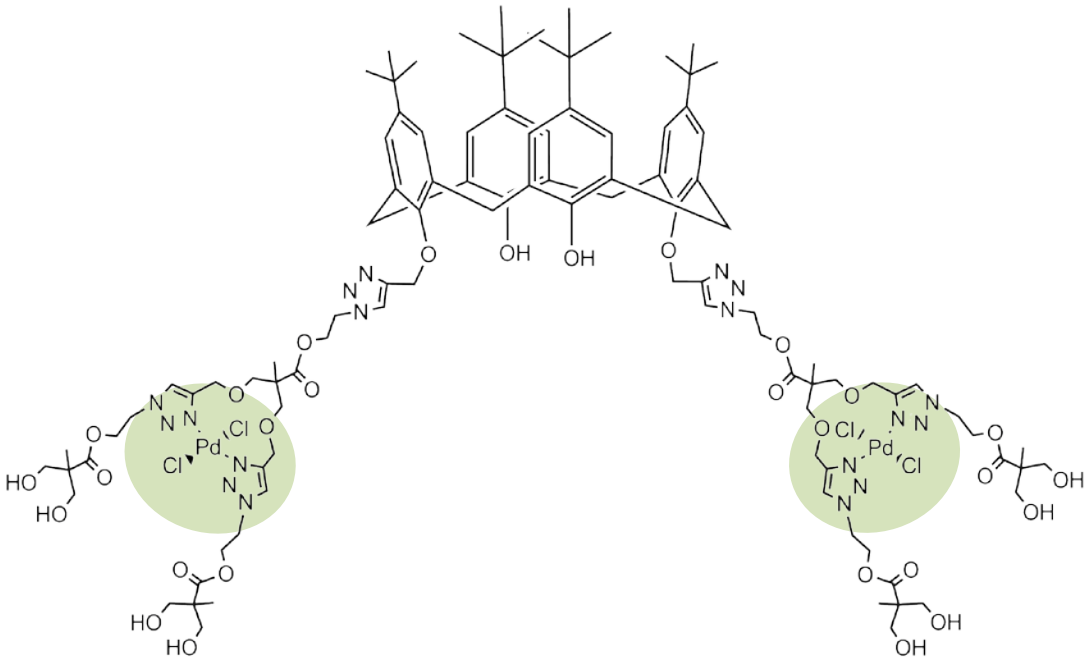


Figure 4. Bis-SG1-tBu Calix[4]arene dendrimer complexed with $PdCl_2$ (Bis-SG1-tBuC[4]A$(OH)_8(PdCl_2)_2$ (**14**)

Methods

Materials*:* 4-tert-butylcalix[4]arene (Reagent Grade); 4-tert-butylcalix[6]arene (95% containing ≤5% 4-tert-butylcalix[4]arene); propargyl bromide (80 wt % in toluene); sodium hydride, NaH (95% dry), p-toluenesulfonic acid monohydrate (≥98.5%); N, N, N', N', N'', N''-pentamethyldiethylenetriamine, PMDETA (99%); copper (I) bromide, CuBr (98%); 1,3-dicyclohexylcarbodiimide, DCC (99%); 4-(dimethylamine)pyridine, DMAP (99%); chloroform-d (99.8 atom % D); 2,2-dimethoxy propane, DMP (98%); and DOWEX 50Wx8-100 ion exchange resin (ACS grade), were all purchased from Sigma-Aldrich and used as received. 18-Crown-6 (99%); sodium azide, NaN_3 (98%, powder); 2,2-Bis(hydroxymethyl) propionic acid, Bis-MPA (≥99%); and ammonia, NH_3 (7N solution in methanol), were all purchased from Acros Organics and used as received. Tetrahydrofuran, THF (99%); acetone (99.9%); ethyl acetate, EtOAc (99.98%); reagent alcohol, 200 Proof, EtOH (90% EtOH, 5% MeOH, 5% IPA); methanol, MeOH (99%); and hexanes (99.9%), were all purchased from PHARMCO-AAPER and used as received unless dried using molecular sieves as specified in the syntheses section. Potassium carbonate, K_2CO_3 (99.5%, anhydrous); dimethyl sulfoxide, DMSO (99.9%); and magnesium sulfate, $MgSO_4$ (99%, anhydrous), were all purchased from Fisher Scientific and used as received. 2-Bromoethanol (97%); phosphorus (V) oxide, P_2O_5 (98%); and phenol (≥99%), were all purchased from Alfa Aeser and used as received. N,N-Dimethylformamide, DMF (99.8%); sodium chloride, NaCl (99%); and sodium hydroxide, NaOH (95%), were all purchased from EMD Chemicals and used as received. Acetonitrile, CH_3CN (99.9%); dichlorobis(benzonitrile) palladium (II), $(C_6H_5CN)_2PdCl_2$

(99%); and dimethyl sulfoxide-D6, DMSO-D6 (99.9%), were purchased from J.T. Baker, STREM Chemicals, Inc, and Cambridge Isotope Laboratories, Inc., respectively, and used without further purification. Dichloromethane, DCM (99.5%), was purchased from MACRON Chemicals and used as received unless dried under P_2O_5 as specified in the syntheses section.

Instrumentation: The mass spectrometric measurements were made on a Bruker Autoflex III MALDI-TOF MS instrument with Smartbeam ion source equipped with a Nd:YAG laser (266 and 355 nm). All spectra were acquired using a reflect-positive mode. The laser attenuation was set to the lowest value possible to get high resolution spectra. Matrix was prepared by dissolving recrystallized 2,5-dihydroxybenzoic acid (DHB) in methanol at a concentration of 40 mg/mL. Sample was prepared in methanol at a concentration of 1 mg/mL. Samples were spotted using the dried-droplet method, where sample and matrix were premixed with a ratio of 1:7. 1 µL of mixed solution was spotted on an AnchorChip target plate (MTP 384 polished steel, Bruker Daltonics). ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ or DMSO-D_6 as solvents with Bruker AVANCE 300 or 600 MHz instruments. The palladium concentration in solution was determined on a PerkinElmer Elan DRC-e inductively coupled plasma mass spectrometer (ICP-OES-MS).

Syntheses: 2,2-Bis(propargyl)propionic acid (**1**). In a one-pot two step reaction, Bis-MPA (3.0061 g, 22.41 mmol) was dissolved with 50 mL of dry DMF in an oven dried three-neck flask with the left neck capped with rubber septum, an air cooled condenser with a

DRIRIGHT adaptor on top attached to the middle neck, and an argon gas inlet is attached to the right neck. The system was cooled to 0°C, and NaH (2.0 g, 83.34 mmol) was added carefully at one gram at a time. The reaction mixture was stirred until hydrogen evolution was complete. Then, propargyl bromide (80 wt % in toluene, 13.021 g, 109.46 mmol) was added slowly. The mixture was stirred at 0 °C for 30 min and then at room temperature (RT) for 12 h. After completion, 20 mL H_2O and 1g NaOH were added to the reaction mixture and stirred at room temperature overnight to hydrolyze undesired ester linkage. The reaction mixture was then extracted with $CHCl_3$ (3 × 50 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to give a dark brown oily product (1.602g, 34%). The crude product was purified by column chromatography on silica gel with gradient elution using EtOAc/hexane (20/80→33/67 v/v) to give **1** as an almost colorless oily product with a slight yellow hue. ^{1}H NMR(300 MHz, $CDCl_3$) δ: 4.17 (d, J = 2.4 Hz, 4H), 3.67 (d, J = 0.8 Hz, 4H), 2.43 (t, J = 2.3 Hz, 2H), 1.25 (s, 3H). 13C NMR (75 MHz, $CDCl_3$) δ: 179.87, 79.34, 74.58, 71.46, 58.70, 47.77, 17.79.

2,2-Bis(propargyl)-2-bromoethyl propionate (**2**). **1** (2.517 g, 11.98 mmol), 2-bromoethanol (2.3237, 18.60 mmol), and DCC (3.55g, 17.21 mmol) were dissolved in 25 mL CH_2Cl_2 (dried under P_2O_5 and filtered). After the addition of solvent, 0.7463 g of DMAP (6.11 mmol) was added. The reaction mixture was stirred at RT overnight. After the reaction was completed, the dicyclohexyl urea (DCU) formed, was filtered, and washed with 50/50 v/v EtOAc/hexane. The crude product was purified by column chromatography on silica gel with gradient elution using EtOAc/hexane (17/83→25/75,

v/v) to give **2** as colorless oily product (2.5121g, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.429 (t, J = 6 Hz, 2H), 4.167 (d, J = 3 Hz, 4H), 3.64 (s, 4 H), 3.525 (t, J = 6 Hz, 2H), 2.436 (t, J = 3 Hz, 2H), 1.26 (s, 3H).

Isopropylidene-2,2-bis(methoxy)propionic acid (IBPA) (**3**). Bis- MPA (10.00319 g, 74.58 mmol), 2,2-dimethoxypropane (12.0039 g,115.26 mmol), and p-toluenesulfonic acid monohydrate (572.23 mg, 3.01 mmol) were dissolved in 50 mL of dry acetone (molecular sieves). The reaction mixture was stirred overnight at RT. Then 0.5 mL of 7N NH_3/MeOH was diluted to 10 mL with MeOH and the solution was added to quench the catalyst. The solvent was evaporated, and the crude product was then dissolved in 125 mL of CH_2Cl_2 and extracted three times with a brine of NaCl/ deionized H_2O (50 mL). The organic layer was dried over MgSO4 and concentrated to give target compound **3** as white solid (9.62056 g, 74%). ^{1}H NMR (600 MHz, DMSO) δ: 4.177 (d, J = 6 Hz, 2H), 3.688 (d, J = 6 Hz, 2H), 1.456 (s, 3H), 1.425 (s, 3H), 1.214 (s, 3H).

Isopropylidene-2,2-bis(methoxy)-2-bromoethyl propionate (**4**). **3** (2.503 g, 14.37 mmol), 2-bromoethanol (2.314 g, 17.0 mmol), and DCC (3.552 g, 17.22 mmol) were dissolved in 20 mL of CH_2Cl_2 (dried under P_2O_5 and filtered). Excess DMAP (0.7256 g, 5.94 mmol) was added to act as a ligand and neutralize any P_2O_5 remaining in the DCM after filtration. The reaction mixture was stirred at RT overnight. After the reaction was completed, DCU was filtered and washed with CH_2Cl_2. The crude product was purified by column chromatography on silica gel using gradient elution with EtOAc/ hexane (17/83→25/75, v/v). The solvent was removed to obtain **4** as colorless oil (3.112 g, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.46 (t, J = 6.3 Hz, 2H), 4.22 (d, J = 12 Hz, 2H), 3.667 (d, J = 12 Hz, 2H), 3.554 (t, J = 6.3 Hz, 2H), 1.44 (s, 3H), 1.399 (s, 3H), 1.22 (s, 3H).

Isopropylidene-2-azide-ethyl propionate (**5**). **4** (4.0501 g, 14.36 mmol) and NaN_3 (2.82223 g, 43.42 mmol) were dissolved in 20 mL of DMSO. The reaction was allowed to proceed at RT for 12 h. The reaction slurry was quenched by adding 15 mL of deionized water. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed twice with 20 mL of brine and dried over $MgSO_4$. EtOAc was removed under vacuum to yield **5** (3.1258 g, 89%) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.319 (t, J = 5.4, 2H), 4.202 (d, J = 11.4 Hz, 2H), 3.658 (d, J = 11.4 Hz, 2H), 3.490 (t, J = 5.4, 2H), 1.426 (s, 3H), 1.383 (s, 3H), 1.212 (s, 3H).

Synthesis of Br-[SG1] (**6**). In a typical "click" reaction, a flask sealed with a rubber septum was charged with **2** (1.280 g, 4.04 mmol), **5** (2.414 g, 9.89 mmol), and PMDETA (1.372 g, 7.93 mmol) in 25 mL of THF. The reaction system was degassed by three freeze−pump−thaw cycles and backfilled with argon. Then, CuBr (1.184 g, 8.16 mmol) was added under argon and the reaction mixture was stirred at RT for 24 h. After completion, the reaction was quenched with 20 mL of H_2O and extracted three times with $CHCl_3$/EtOAc (50/50, v/v). The organic layers were combined, washed twice with brine solution and concentrated under vacuum. The crude product was further purified by column chromatography on silica gel using a gradient elution of methanol/EtOAc (3.3/96.7→9.1/90.9, v/v). **6** was obtained as a colorless oil (3.266 g, 68%) after removing the solvent. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.7779 (s, 2H), 4.669-4.567 (m, 12H), 4.388 (t, J

= 6 Hz, 2H), 4.168 (s, 2H), 4.129-4.095 (m, 4H), 3.651 (d, J = 3Hz, 4H), 3.618 (s, 2H), 3.485 (t, J = 4 Hz, 2H), 1.442 (s, 6H), 1.3718 (s, 6H), 1.212 (s, 3H), 1.084 (s, 6H). MS (MALDI-TOF MS, positive mode): calculated for $C_{33}H_{51}N_6O_{12}Br$: $[M]^+$ m/z = 803.69. Found: $[M]^+$ m/z = 803.068, and $[M+Na]^+$ m/z = 825.053.

Synthesis of N_3-[SG1] (**7**). **6** (1.0362 g, 1.29 mmol) and NaN_3 (0.253 g, 3.927 mmol) were dissolved in 6 mL of DMF. The reaction was left at 60°C for 24 h under argon. Then, the system was cooled down to RT followed by adding 10 mL of water and extracted with ethyl acetate (3 × 30 mL). All organic layers were combined, washed with 30 mL of brine twice, and dried over $MgSO_4$. The solvent was evaporated to give product as colorless oil (0.8787 g, 89%). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.093 (s, 2H), 4.669 (t, J = 5.4 Hz, 4H), 4.508 (s, 4H), 4.473 (t, J = 5.4 Hz, 4 H), 4.171 (t, J = 4.2 Hz, 2H), 3.965 (d, J = 12 Hz, 4 H), 3.566 (d, J = 12 Hz, 4H), 3.52 (dd, J = 8.64, 4H) 3.488 (t, J = 4.2 Hz, 2H), 1.35 (s, 6H), 1.248 (s, 6H), 1.104 (s, 3H), 0.994 (s, 3H). MS (MALDI-TOF MS, positive mode): calculated for $C_{33}H_{51}N_9O_{12}$: $[M]^+$ m/z = 765.81. Found: $[M]^+$ m/z = 766.147, and $[M+Na]^+$ m/z = 788.136.

Synthesis of tetrapropargyl p-tert-butylcalix[4]arene (**8**). Protocol adopted from Chetcuti et al.[22] 4-tert-butylcalix[4]arene (0.60 g, 0.925 mmol), propargyl bromide (80 wt % in toluene, 0.85097g, 5.722 mmol), anhydrous K_2CO_3 (0.7166 g, 5.19 mmol), and 18-Crown-6 (0.015 g, 0.0568 mmol) are all dissolved using 20 mL of dry acetonitrile (molecular sieves) in a 100 mL round bottom flask fixed with a water cooled condenser. The reaction was stirred under reflux (90 ˚C) for 48 h. The reaction mixture was filtered

and dried under vacuum. The crude product was dissolved in $CHCl_3$ and concentrated to 2 mL followed by the addition of 20 mL MeOH. This solution was cooled to -15˚C for 15 h to facilitate crystallization of the product. The solid was collected by cold filtration using MeOH. The product was further purified by column chromatography on silica gel using gradient elution of $CHCl_3$/hexane (25/75→50/50, v/v) and the solvent was removed under vacuum to yield **8** as a clear viscous liquid (0.33 g, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.808 (s, 8H), 4.820 (d, J = 2.4 Hz, 8H), 4.269 (d, J = 13.5 Hz, 4 H), 3.186 (d, J = 13.5, 4 H), 2.490 (t, J = 2.4 Hz, 4 H), 1.099 (s, 36H). MS (MALDI-TOF MS, positive mode): calculated for $C_{56}H_{64}O_4$: $[M]^+$ m/z = 801.10. Found: [M+Na] M/z = 823.628, and $[M+K]^+$ m/z = 839.598.

Synthesis of tetra-SG1-(isopropylidine) p-tert-butylcalix[4]arene (Tetra-SG1-tBu-C[4]A) (**9**). In a typical "click" reaction, a flask sealed with a rubber septum was charged with **8** (0.047 g, 0.059 mmol), PMDETA (0.102 g, 0.589 mmol), and **7** (0.548 g, 0.715 mmol) dissolved in 10 mL dried THF (molecular sieves). The mixture in THF is degassed was degassed by three freeze−pump−thaw cycles and backfilled with argon. Then, CuBr (1.032 g, 0.719 mmol) was added under argon. The mixture was stirred under argon at 50 ˚C for 96 h. After completion, the mixture was extracted with EtOAc (3 x 15mL) and the combined organic layers were washed twice with brine, dried under $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography using gradient elution of EtOAc/MeOH (9/91→12.5/87.5, v/v) to yield **9** as a thick oily liquid (30 mg, 13%) after removing the solvent under vacuum. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.940 (s, 4H), 7.829 (s, 8H), 6.720 (s, 8H), 4.986 (s, 8H), 4.668 (t, J =

4.8 Hz, 24H), 4.558 (t, J = 6 Hz, 16 H), 4.534 (s, 16H), 4.486 (t, J = 4.2 Hz, 8H), 4.142 (m, 24H), 3.636 (d, J = 6.6 Hz, 16H), 3.553 (s, 16H), 1.435 (s, 24H), 1.365 (s, 24H), 1.119 (s, 12H), 1.087 (s, 36H), 1.054 (s, 12H). MS (MALDI-TOF MS, positive mode): calculated for $C_{188}H_{268}N_{36}O_{52}$: $[M]^+$ m/z = 3864.34. Found: $[M + Na]^+$ m/z = 3887.091, and $[M + Cu]^+$ m/z = 3928.075.

Synthesis of bis-1,3-propargyl p-tert-butylcalix[4]arene (**10**). Protocol adopted from Chetcuti et al.[22] 4-tert-butylcalix[4]arene (0.60 g, 0.925 mmol), propargyl bromide (80 wt % in toluene, 0.4726 g, 3.03 mmol), anhydrous K_2CO_3 (0.7166 g, 5.19 mmol), and 18-Crown-6 (0.015 g, 0.0568 mmol) are all dissolved using 20 mL of dry acetone (molecular sieves) in a 100 mL round bottom flask fixed with a water cooled condenser. The reaction was stirred under reflux (90 ˚C) for 24 h. The reaction mixture was filtered and dried under vacuum. The crude product was dissolved in $CHCl_3$ and concentrated to 2 mL followed by the addition of 20 mL MeOH. This solution was cooled to -15 ˚C for 15 h to facilitate crystallization of the product. The solid was collected by cold filtration using MeOH. The product was further purified by column chromatography on silica gel using gradient elution of $CHCl_3$/hexane (25/75→50/50, v/v) and the solvent was removed under vacuum to yield **9** as a clear viscous liquid (0.479 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.100 (s, 4H), 6.748 (s, 4H), 6.471 (s, 2H), 4.772 (d, J = 2.4 Hz, 4H), 4.405 (d, J = 13.5 Hz, 4H), 3.362 (d, J = 13.5, 4H), 2.563 (t, J = 2.4 Hz, 2H), 1.340 (s, 18H), 0.97 (s, 18 H). * MALDI-TOF-MS data not available

Synthesis of bis-1,3-SG1(isopropylidine) p-tert-butylcalix[4]arene (Bis-SG1-tBuC[4]A) (**11**). In a typical "click" reaction, a flask sealed with a rubber septum was charged with **10** (0.2 g, 0.275 mmol), PMDETA (0.102 g, 0.589 mmol), and **7** (0.548 g, 0.715 mmol) dissolved in 10 mL dried THF (molecular sieves). The mixture in THF is degassed was degassed by three freeze−pump−thaw cycles and backfilled with argon. Then, CuBr (1.032 g, 0.719 mmol) was added under argon. The mixture was stirred under argon at 50˚C for 96 h. After completion, the mixture was extracted with EtOAc (3 x 15mL) and the combined organic layers were washed twice with brine, dried under $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography using gradient elution of EtOAc/MeOH (8.3/91.7→10/90, v/v) to yield **11** as a thick oily liquid with a yellow hue (0.3985,64%) after removing the solvent under vacuum. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.064 (s, 2H), 7.787 (s, 4H), 7.061 (s, 4H), 7.0173 (s, 2H), 6.794 (s, 4H), 5.136 (s, 4H), 4.636-4.496 (m, 48 H), 4.262 (d, J = 6.6 Hz, 4H), 4.142 (m, 20H), 3.635 (d, J = 3.64, 12H), 3.525 (d, J = 1.8 Hz, 6H), 3.306 (d, J = 7.0 Hz, 4H), 1.439 (s, 12H), 1.367 (s, 12H), 1.295 (s, 18H), 1.098 (s, 6H), 1.083 (s, 12H), 0.964 (s, 18H). MS (MALDI-TOF MS, positive mode): calculated for $C_{122}H_{166}N_{18}O_{28}$: $[M]^+$ m/z = 2332.272. Found: $[M + Na]^+$ m/z = 2278.664.

General Procedure for the Deprotection of Dendrimer Peripheral Acetonide Protecting Groups (12, 13). The peripheral acetonide groups were readily removed using Dowex ion exchange resin (50W x 8-100). The dendrimers were dissolved in MeOH and a 1/1 w/w portion of Dowex resin was added. The reaction is stirred at RT for 48 hours monitoring products using TLC throughout. The reaction mixture is filtered and

concentrated under vacuum to afford the hydroxyl terminated dendrimers in high yield. The purity of the compounds after deprotection was confirmed by ^{1}H NMR.

General Procedure for the Palladium Complexation of Dendrimers (14, 15). Acetonide- terminated dendrons or dendrimers were dissolved in acetone followed by adding 3 equiv of $Pd(PhCN)_2Cl_2$ according to the number of potential chelating sites. The complexation was conducted at RT using vortex to mix the solutions and is complete within 5 min as monitored by ^{1}H NMR. The excess of $Pd(PhCN)_2Cl_2$ was isolated by cold filtration and washed with cold $CHCl_3$. The products were obtained by removing the solvent under vacuum.

General Procedure for Suzuki–Miyaura Coupling Reactions. 5 mL of conical reaction vial was charged with 4-bromoacetophenone (48.42 mg, 0.24 mmol), phenylboronic acid (45.49 mg, 0.37 mmol), potassium carbonate (71.36 mg, 0.514 mmol), and 800 µL of H_2O. The appropriate amount of Bis-SG1-tBuC[4]A$(OH)_{16}(PdCl_2)_4$ stock solution (0.029 mol %) was withdrawn and added to the mixture. The reaction mixture was kept at 50°C for 3 h. After completion, the product was extracted with $CDCl_3$ and transferred directly to a NMR tube for analysis on a 300 MHz ^{1}H NMR. The percent conversion is calculated by comparing the acetyl group CH_3 peak for the product compared to the 4' bromoacetophenone. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 6.9 Hz, 2H), 7.53− 7.44 (m, 2H), 7.42 (dd, J = 5.0, 3.6 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.79, 145.89, 140.00, 136.02, 129.07, 129.02, 128.34, 127.38, 127.33, 26.74.

Results and Discussion

This study aims to design and synthesize a variety of dendrimers, containing hydrophobic calixarene cores, which have potential to function as highly selective macromolecular frameworks in "green" synthesis and biomedical applications. The structure of these dendrimers resembles previously synthesized water-soluble dendrimers that were shown to efficiently catalyze the Suzuki reaction when complexed with $PdCl_2$. Two essential modifications were made to improve the dendrimers' selectivity for hydrophobic substrates (a) and shorten the distance from the hydrophobic binding site to the $PdCl_2$ complex site (b). The first improvement (a) was achieved by replacing the triacetylene core (Figure 1) with calixarene which has been shown to preferentially bind hydrophobic substrates. To optimize the spatial arrangement of the hydrophobic substrates to the $PdCl_2$ catalytic sites (b), the triethylene glycol spacers (Figure 1) were replaced with ethylene glycol. Ethylene glycol spacers may also act to increase the density of the dendritic architecture reducing the potential for palladium leaching. These shorter spacers will decrease the flexibility of the branches which may affect reagent diffusion, but should also add to the selectivity of the dendritic interior. 2,2-bis(hydroxymethyl) propionic acid, bis MPA, remains the parent branching fragment in the new dendritic species due to its proven versatility in dendrimer synthesis[23] and potential biodegradability and biocompatibility.[24]

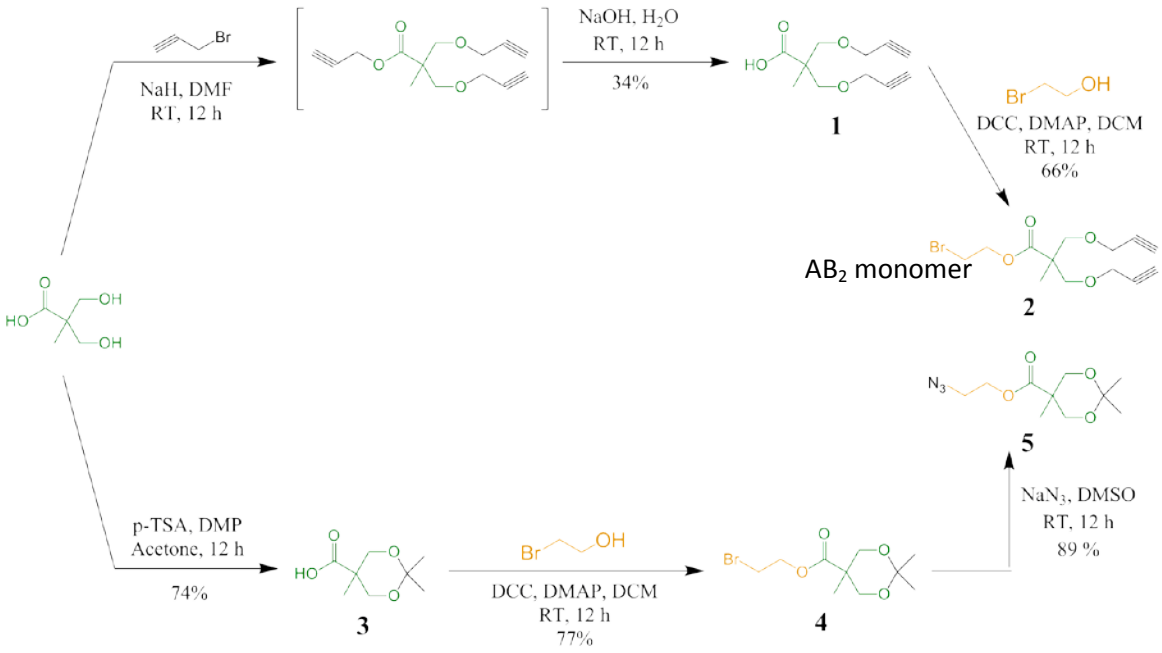
The synthetic strategy for the AB_2 monomer is depicted in Scheme 2. A bis-alkyne-modified bis-MPA derivative **1** is synthesized via Williamson ether synthesis. The yield of the reaction after the necessary hydrolysis of the intermediate is regrettably low

and results as the limiting step in the overall yield of the reaction. A brominated derivative of ethylene glycol, 2-bromoethanol, is then linked as a shorter spacer to **1** via DCC-mediated esterification reaction yielding the AB_2 ether ester monomer **2**. Compound **2** will act as the branching point in the dendrons produced by convergent synthesis.

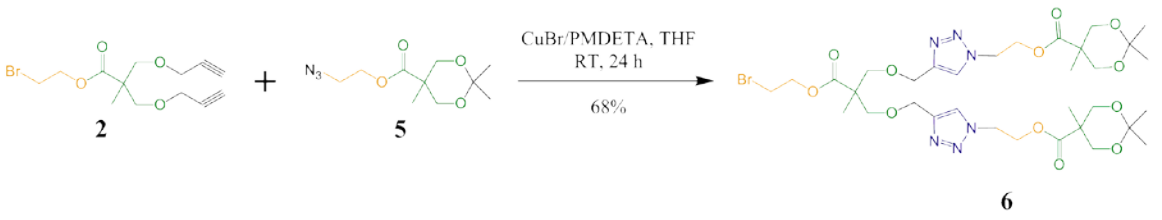
The corresponding azide derivative of bis-MPA EG **5** is synthesized by DCC coupling of the same 2-bromoethanol spacer with isopropylidene protected bis-MPA and the subsequent conversion of the $-CH_2Br$ end group into the resultant azide. The azide terminated structure **5** has similar assembly to the AB_2 monomer and serves as the starting material in the convergent synthetic scheme. The isopropylidine protected termini offer the ability to later functionalize the dendrimer periphery with hydroxyl groups, which are formed and available for further modification after a simple acid hydrolysis deprotection.

The convergent strategy, employed in the synthesis of the novel dendrons is shown in Scheme 3. The dendron is formed by the "click" reaction of the AB_2 monomer **2** with minor stoichiometric excess (1.1 equiv) of the azide segment **5**. The product is easily purified by column chromatography (see Experimental Section for separation conditions) due to the significant molecular weight difference between the starting materials and the new macromolecular product. Generation 1 dendrons are produced in relatively high yields and structural purity as confirmed by MALDI-TOF- MS (Figure 5), and NMR analyses (Figure 6).

Scheme 2. Synthesis of AB_2 Monomer and Corresponding Azide



Scheme 3. Convergent Growth of the SG1 dendron



The high purity and monodisperse nature of the dendrons is proven through convincing evidence provided by the MALDI-TOF mass spectrum (Figure 5). The presence of molecular ion is observed as $[M]^+$ and $[M + Na]^+$ peaks and the m/z values match the theoretical molecular mass for the Br-SG1 dendron. Similarly, the presence of N_3-SG1 dendron is confirmed by the presence of molecular ion as $[M]^+$ and $[M + Na]^+$ peaks which match its theoretical mass.

The chemical structure of the SG1 dendron is verified by ^{1}H NMR analysis (Figure 6). Formation of the triazole rings is supported by the disappearance of the acetylene protons (Figure 6, **2**, t and u) and the presence of a clean singlet at ~7.75 ppm (e) corresponding to the triazole proton. Additionally, a general downshift is observed for the methylene protons (t→d and l→f) as a result of the creation of the electron-rich triazole structure. The intact nature of the ester bonds after the CuAAC to produce the SG1 dendron is evidenced by the ester methylene protons (b and g) shown as triplets that remain in a similar region to their precursors (r and m) respectively. With the exception of minor solvent residue, the ^{1}H NMR spectra are quite clean and the integrations follow the correct number of protons in the SG1 theoretical structure.

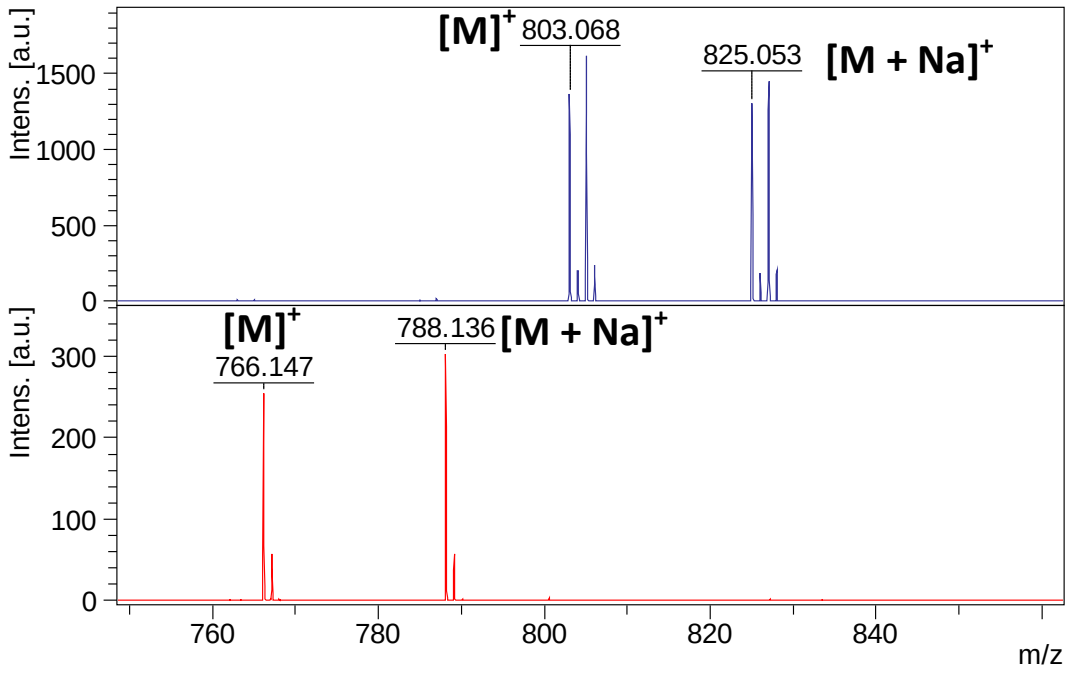


Figure 5. MALDI-TOF spectrum of Br-SG1 dendron (top) $[M]^+$ m/z = 803.206, $[M+ Na]^+$ m/z = 825.235, and N_3-SG1 dendron (bottom) $[M]^+$ m/z = 766.147, $[M + Na]^+$ m/z = 788.136.

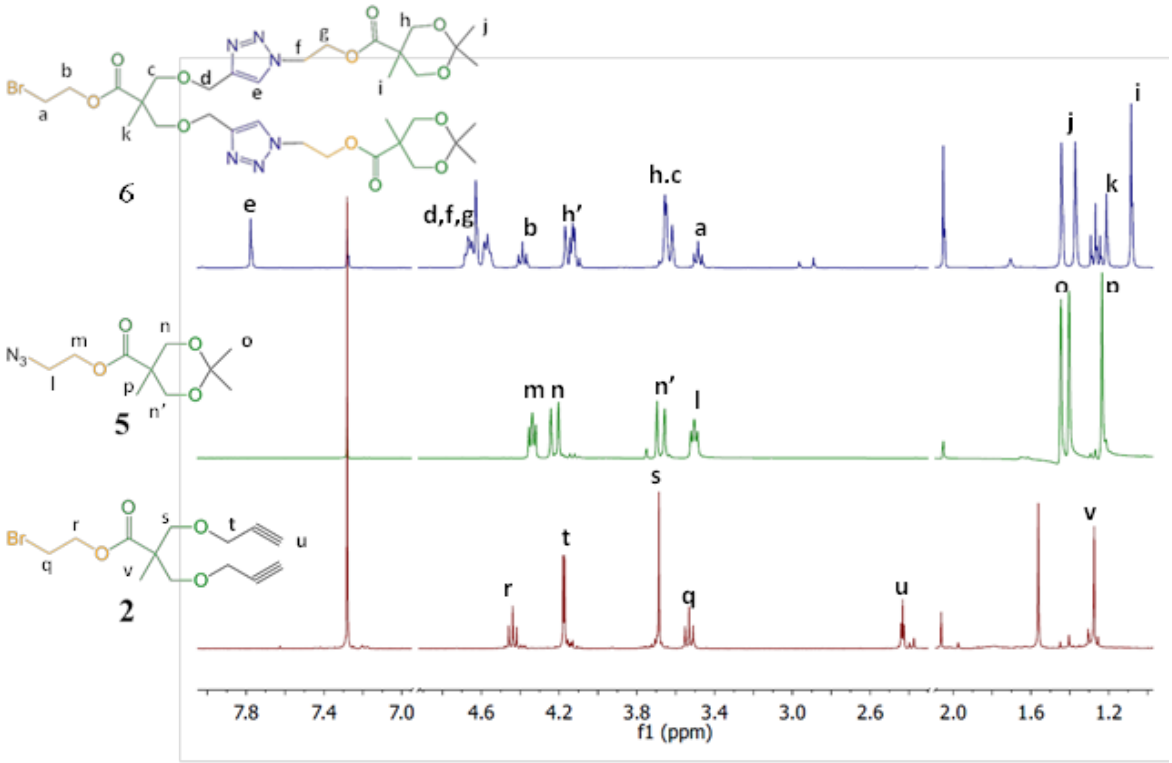
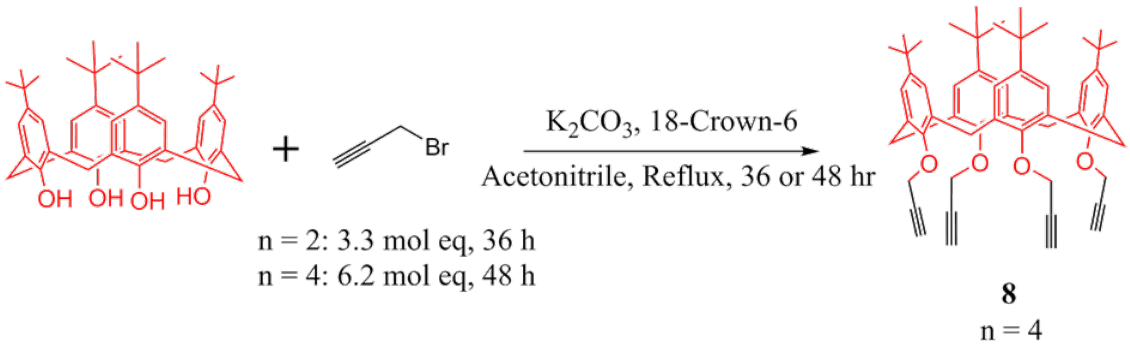


Figure 6. 600 MHz ^{1}H NMR Spectra of **5**, **2** , and Br-[SG1] **6**, recorded in $CDCL_3$ at 298 K

To form dendrimers, containing a hydrophobic core, from the SG1 dendrons, multifunctionalized calixarene cores were first created (Scheme 4). Both tetra and bis substituted propargyl p-tert-butylcalix[4]arenes were exclusively synthesized using protocols adopted from Chetcuti et al. The Williamson ether synthesis using 3.3 equiv. of propargyl bromide and a 24 h reaction time yielded the bis species while the tetra functionalized calixarene was formed using a 6.2 molar excess of propargyl bromide in a 48 h reaction. Both bis and tetra molecules were synthesized at yields consistent with those reported by Chetcuti et al.

Exclusive formation of the bis and tetra products is evidenced by MALDI-TOF-MS analysis. The mass spectrum for tetrapropargyl p-tert-butylcalix[4]arene (Figure 7) shows molecular ion as $[M + Na]^+$ and $[M + K]^+$ peaks which have m/z values that agree with the theoretical molecular mass of the analyte. While the MALDI-TOF-MS spectra for bis-1,3-propargyl p-tert-butylcalix[4]arene is unavailable, its purity is evidenced later by the MALDI-TOF-MS for the subsequently formed Bis-SG1-tBuC[4]A (Figure 9, b). Since Bis-SG1-tBuC[4]A is isolated in purity it supports that we exclusively formed bis-1,3-propargyl p-tert-butylcalix[4]arene with the procedure described.

Scheme 4. Synthesis of bis (n = 2) and tetra (n = 4) propargyl substituted tert-butylcalix[4]arene



8
n = 4

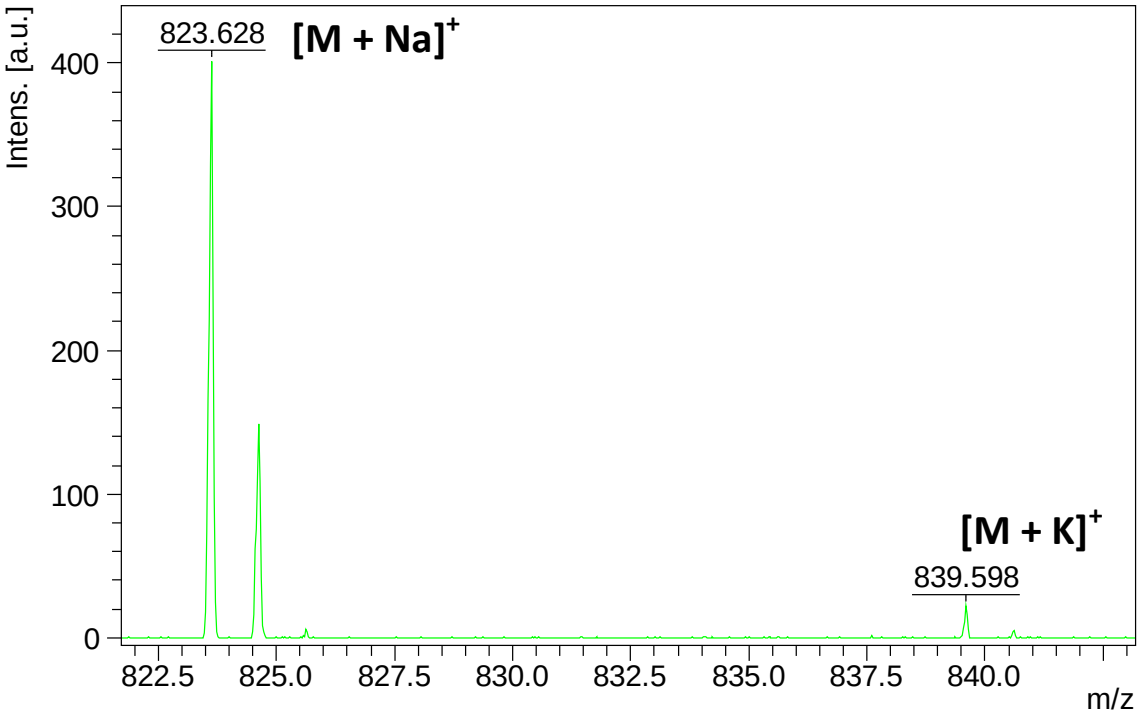
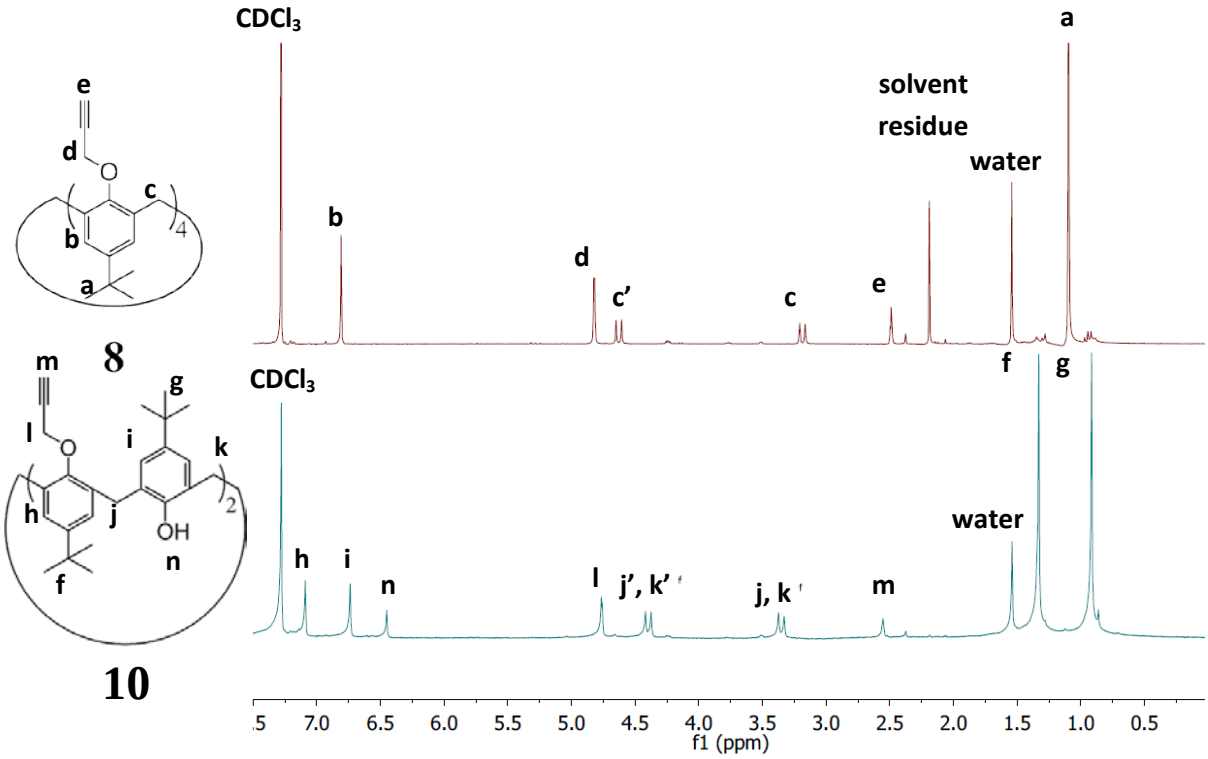


Figure 7. MALDI-TOF spectrum of tetrapropargyl p-tert-butylcalix[4]arene core. $[M + Na]^+$ m/z = 823.628, $[M+ K]^+$ m/z = 839.598

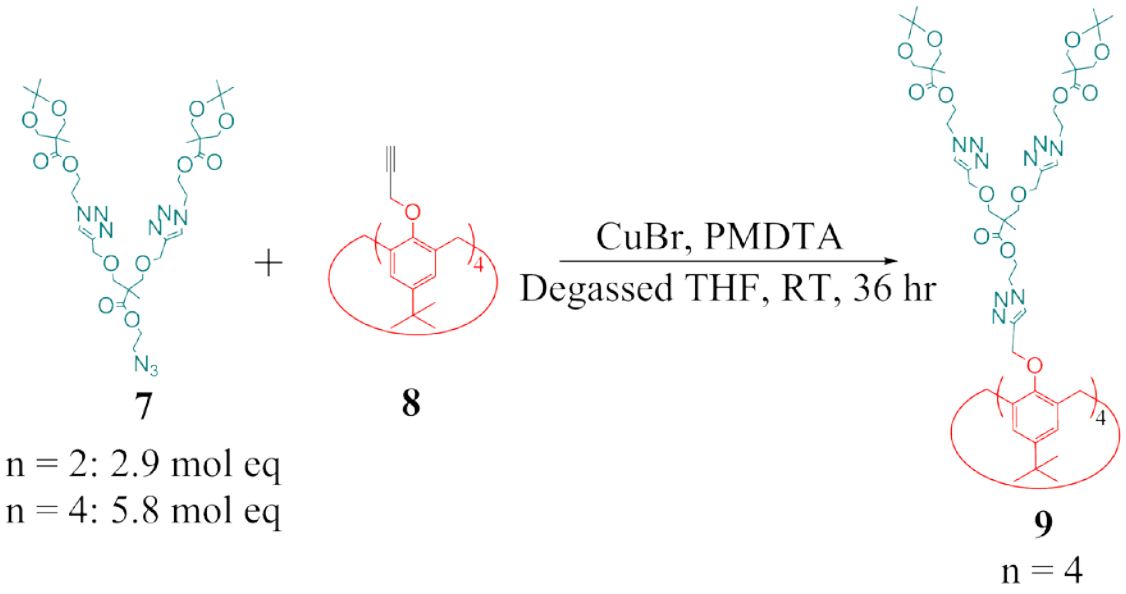
The chemical composition of both tetrapropargyl p-tert-butylcalix[4]arene and bis-1,3-propargyl p-tert-butylcalix[4]arene is verified by ^{1}H NMR (Figure 8). The peaks in the spectrum of **8** are assigned to the structure. In this spectrum, the presence of peak **e** is indicative of a terminal alkynyl hydrogen and peak **d** corresponds well to the expected chemical shift of methylene protons flanked by -OR and -CΞC groups. Additionally, the ratio of peak **d** to **b** is 1:1 which again supports that the calixarene is fully functionalized. Surprisingly, the spectrum of bis-1,3-propargyl p-tert-butylcalix[4]arene seems to indicate that the molecule may adopt a flipped orientation as depicted in Figure 8. The peaks in the spectrum of **10** are assigned to the structure. As expected peaks **l** and **m** are present in a similar region as **d** and **e** and the ratio is 1:1 with peaks **h**, **i**, **f**, and **g,** further supporting that the calixarene is bis functionalized. Additionally, the integration of peak **n** has a ratio of 1:1 compared to peak **m** verifying that two hydroxyl groups in the calix[4]arene structure are preserved. What we did not anticipate is the non-chemically shift equivalent nature of peaks **h** and **i,** and **f** and **g.** We hypothesize that this difference could not due to the formed ether linkage alone due to its distant proximity. Instead we believe that **10** may have a flipped orientation where protons **f** and **h** are more shielded by the OH (**n**) compared to their counterparts **g** and **i**, which interact with the OR group. Further work must be done to prove that this is the case, including a model reaction with t-Bu phenol to see if there is a noteworthy chemical shift observed in the t-Bu protons of the product vs the starting material. Furthermore, single crystal X-Ray analysis needs to be performed on **10** before any concrete conclusions can be made regarding a potential flipped orientation.

Bis-SG1-tBuC[4]A and Tetra-SG1-tBu-C[4]A, generation 1 dendrimers, were formed in the last step of the synthetic process by linking azide terminated dendrons **7** with alkyne functionalized calixarene cores (**8,10**), by employing similar “click” chemistry (Scheme 5). A 2.9 and 5.8 stoichiometric excess of the SG1 dendron is used to generate the bis and tetra substituted calixarenes respectively. Due to time constraints, the synthesis has currently only been performed once leading to limited yields of 64% for the bis and 13 % for tetra structures. The reaction has been shown to proceed yielding a pure bis product and nearly pure tetra product as monitored by MALDI-TOF MS. Optimization of the reaction conditions will likely lead to drastically improved yields in future runs making the process more economically viable.

Figure 8. 600 MHz ^{1}H NMR Spectra of tetra **8** and bis **10** propargyl t-Bu calix[4]arene,recorded in $CDCL_3$ at 298 K



Scheme 5. Synthesis of Bis-SG1-tBuC[4]A (n = 2) and Tetra-SG1-tBu-C[4]A (n = 4)



Selective production of the bis and tetra products is evidenced by their MALDI-TOF mass spectra (Figure 9). The predominant peak observed in the spectrum for the tetra substituted dendrimer (a) is $[M + Cu]^+$ with a less intense $[M + Na]^+$ peak. The inclusion of copper in the analyte is likely a result of complexation between triazole rings of excess Cu(I) from the "click" chemistry used to form the dendrimers. Examples of triazole rings forming copper complexes have been previously reported in the literture[25]. A graphic depicting the green color of the tetra dendrimer dissolved in $CDCl_3$ in an NMR tube is shown to support the presence of Cu(I). It is important to note that the green color and copper complexation was easily removed by washing the product solution with water. A minor peak at 3644.914 results from deprotection of the dendrimer to form hydroxyl groups caused by the high intensity of the UV laser. A final trace peak at 3121.672 represents a small amount of tri substituted dendrimer. The spectrum of the bis substituted dendrimer (b) is much cleaner and only one $[M + Na]^+$ peak is observed. Interestingly no Cu (I) complexation seems to be present in the bis dendritic species.

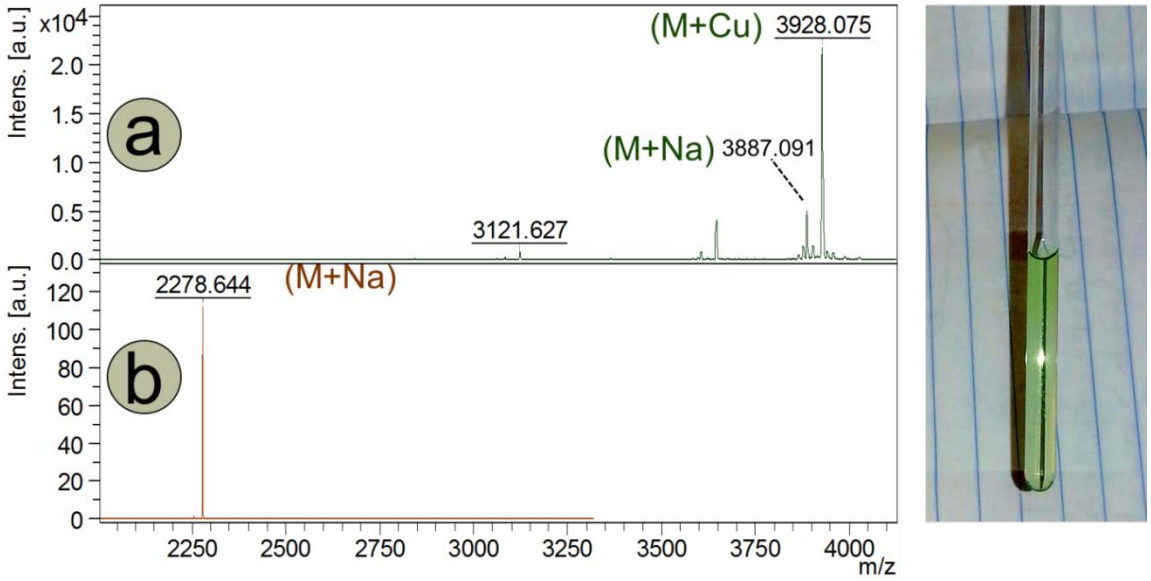


Figure 9. MALDI-TOF spectra of Tetra-SG1-tBu-C[4]A (a) $[M + Na]^+$ = 3887.091, $[M + Cu]^+$ = 3928.075 and Bis-SG1-tBuC[4]A (b) $[M+Na]^+$ = 2278.664 m/z. *Note: Green solution in $CDCl_3$

The chemical composition of the tetra and bis products is characterized by ^{1}H NMR (Figure 10 and 11). Upon formation of the tetra substituted dendrimer **9** a new triazole ring is generated and its proton is seen as peak **e** at a 1:2 ratio with peak **j**, which represents the two other triazole ring protons at the branching point. Additionally, the disappearance of the acetylene proton peak ~ 2.5 ppm also supports the formation of our proposed product. Characteristic peaks are observed in the spectrum, which are also present in the tetrapropargyl t-Bucalix[4]arene precursor (Figure 8). These include doublets **c** and **c',** singlet **a**, along with singlet **b**, which all have similar chemical shifts (Figure 8) and integrations matching their theoretical number of protons. Furthermore, all protons in the dendron portion of the molecule have been labeled in the structure. In the bis substituted dendrimer **11**, similar observations hold true. In addition to the presence of **ee** in a 1:2 ratio to **jj** and the absence of any acetylene proton peaks, the -O*H* signal (**tt**) is preserved in the calixarene structure and has a ratio of 1:1 with peak **ee**. This provides evidence that the bis dendrimer has been selectively generated. All signals, resulting from calixarene protons, have been successfully assigned in the spectrum. Moreover, the trend of splitting in the tert butyl peaks (**aa** and **qq**) and aryl proton peaks (**bb** and **rr**) resembles what was observed in the spectrum of the bispropargyl t-Bucalix[4]arene precursor (Figure 8). The protons associated with the dendron portion of the molecule have been assigned. Signals **ff**, **gg**, **ii**, **kk**, and **ll** make an exception due to the similarities in their chemical shift resulting in a multiplet at ~4.45-4.7 ppm. Future analysis in DMSO-d_6 may help distinguish the peaks.

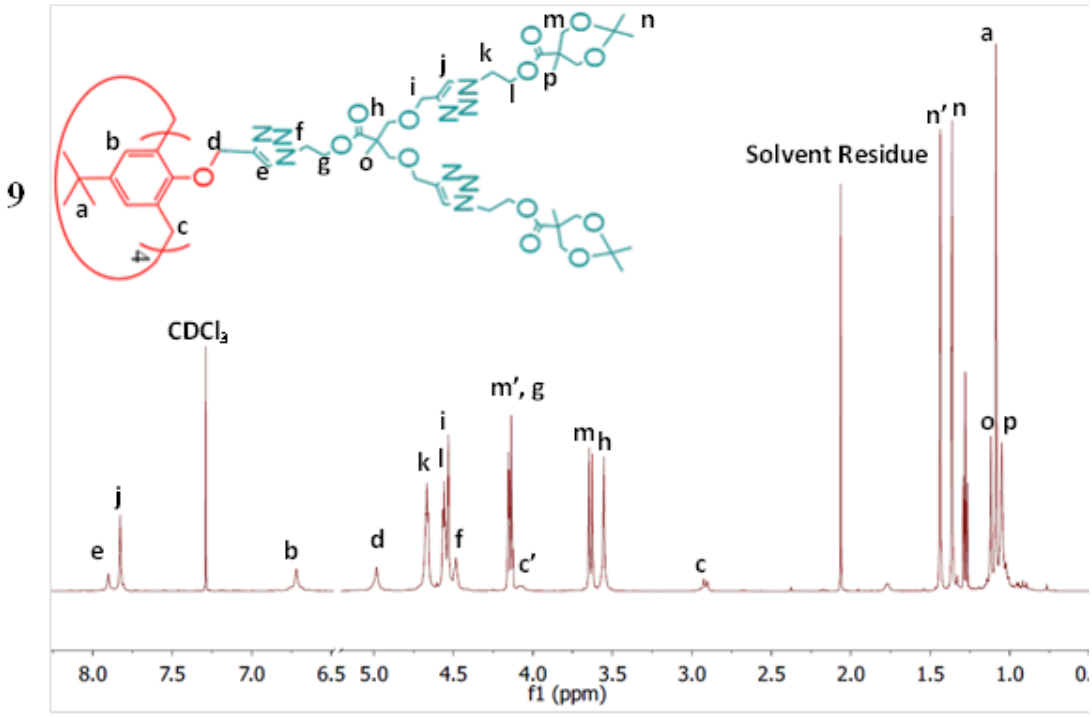


Figure 10. 600 MHz ^{1}H NMR Spectra of Tetra-SG1-tBu-C[4]A **9**, recorded in $CDCL_3$ at 298 K

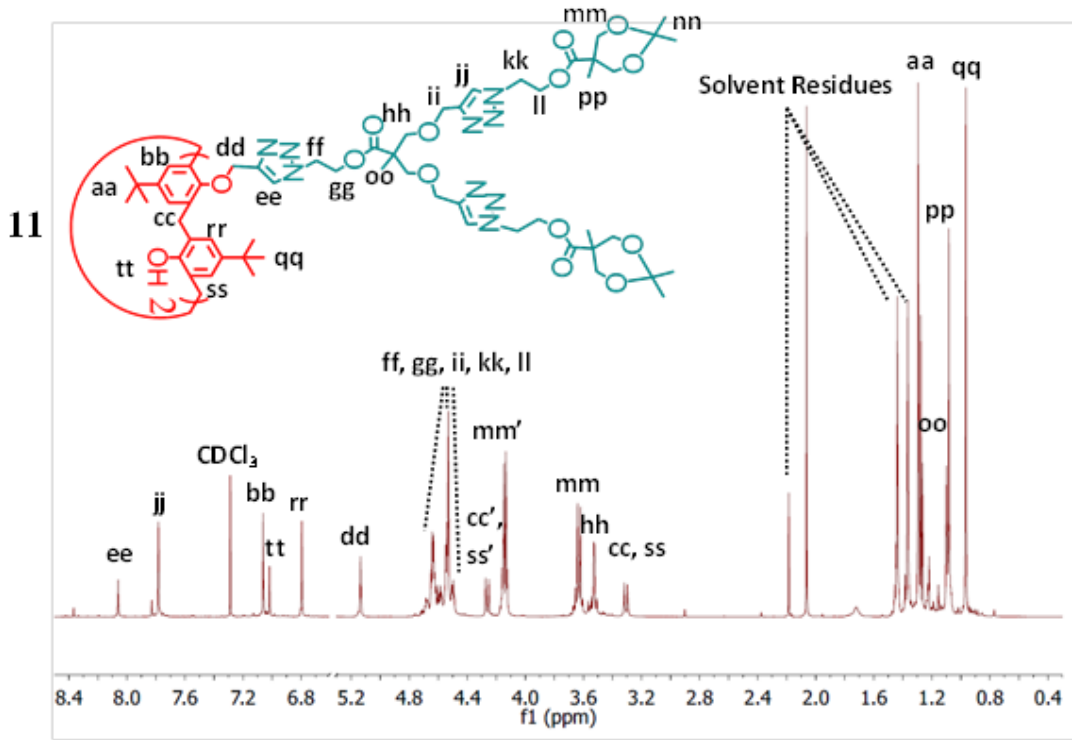


Figure 11. 600 MHz ^{1}H NMR Spectra of Bis-SG1-tBuC[4]A **11,** recorded in $CDCL_3$ at 298 K

Our results demonstrate that both Bis-SG1-tBuC[4]A and Tetra-SG1-tBu-C[4]A can be effectively produced in high purity using the protocol described. The bis structure is has 8 protected primary hydroxyl groups, 6 hydrolysable esters and 2 potential metal binding sites. The tetra structure has 16 protected primary hydroxyl groups, 12 hydrolysable ester linkages and 4 potential metal binding sites. Subsequent deprotection of the dendrimers affords bis and tetra compounds with 8 and 16 terminal hydroxyl groups respectively, which surround the periphery of the molecules likely increasing their water solubility. While the tetra substituted dendrimer has not yet been tested for its water solubility, it is interesting that the bis substituted dendrimer is not soluble in water but is in 50 % EtOH. While further testing into the solubility, biodegradability, and biocompatibility of these dendrimers is necessary, it is believed that these potentially size-selective macromolecules will have a wide variety of biomedical and catalytic functions. For the sake of time, only preliminary coordination and catalytic performance studies were performed on the Bis-SG1-tBuC[4]A compound.

Previously, molecular dynamics simulations were performed on a model compound consisting of bis- MPA branching unit linked to two triazole rings by the primary hydroxyl groups.[11g] The study showed that the N1/N4 and N3/N6 pairs are the most likely place for $PdCl_2$ complexation (Figure 12). With this in mind, the Br-SG1 dendron was employed as a model compound to determine the potential of the triazole moieties to complex $PdCl_2$ by mixing with ($Pd(PhCN)_2Cl_2$) in acetone or DMSO. The formed square planar complex leads to a twelve membered ring with restricted rotation

at each branching point in the dendrimers. The coordination in both solvents is monitored *in situ* by ^{1}H NMR and shown to be complete within 5 min (Figure 13).

The ^{1}H NMR spectra (Figure 13) of N_3-SG1 (**7**) before (a) and after complexation with $PdCl_2$ (b) depict several differences that indicate that coordination of $PdCl_2$ between two triazole rings occurs. In the spectrum of **7** prior to complexation, chemically shift similar protons on **c** and **d** lead to what appears as single peaks labeled **c** and **d.** After complexation, it is observed that peaks **c** and **d** both split into two separate doublets of doublets. This is an effect of the limit on rotation in the complexed structure which makes the methylene protons on **c** and **d** non-chemically shift similar to each other. Another effect of the coordination of $PdCl_2$ is increased shielding of protons in the vicinity of the $PdCl_2$ leading to a general downshift of protons **a**, **b**, and **e**.

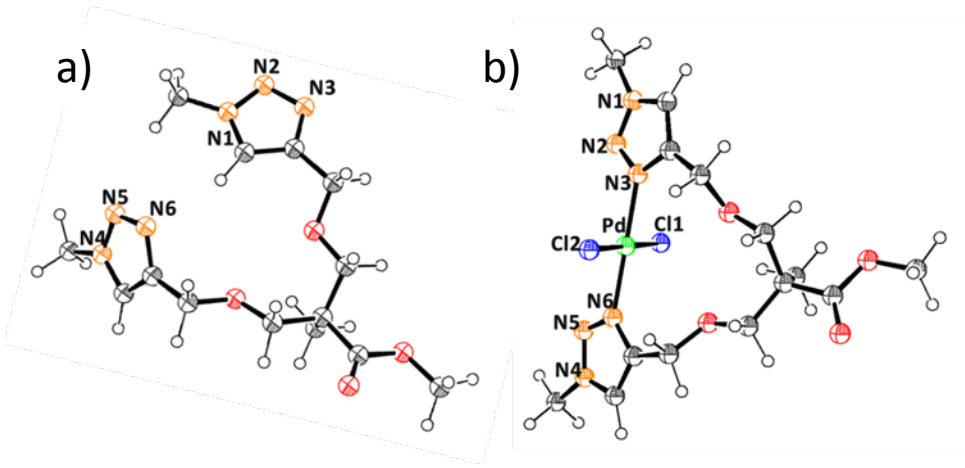


Figure 12. ORTEP diagrams for the chemical structure (a) and of the palladium (II) complex (b) for the model compound representing the metal binding sites in the SG1 dendrimer. C atoms (grey spheres), H atoms (white spheres), N atoms (orange spheres), O atoms (red spheres), Cl atoms (blue spheres), and Pd atom (green sphere).

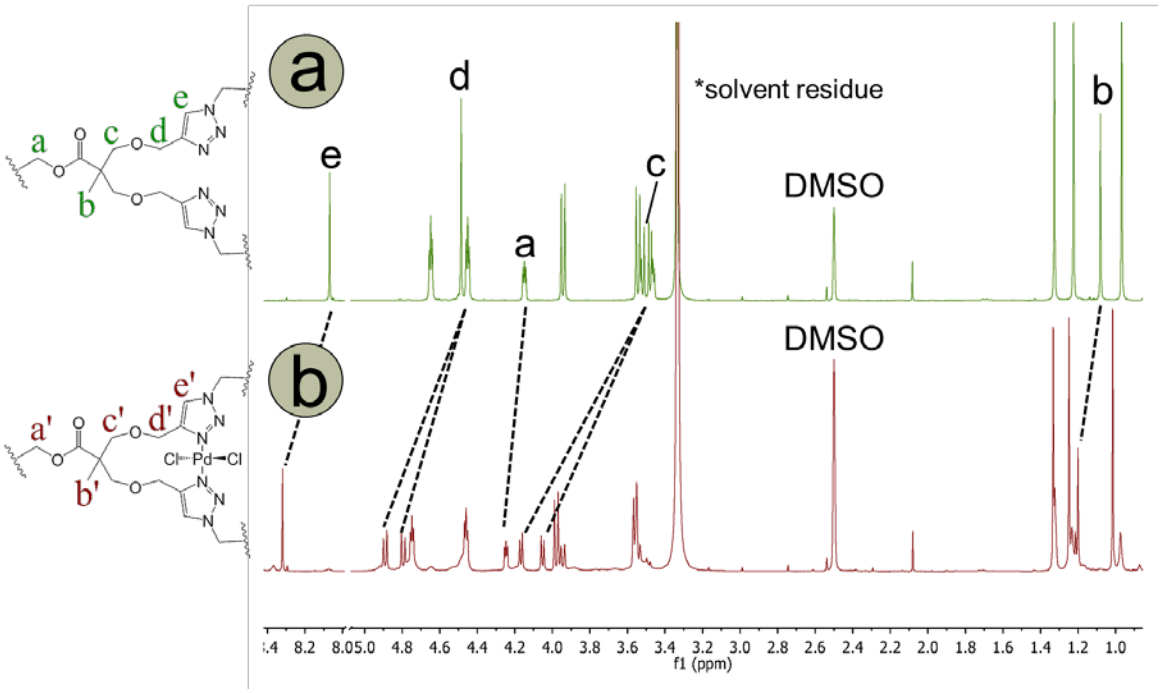


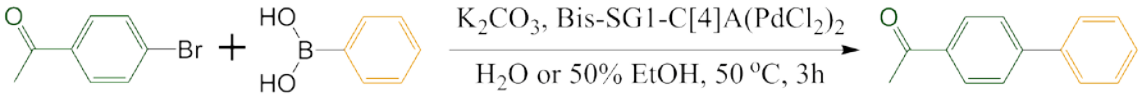
Figure 13. ^{1}H NMR spectra of (a) Br-SG1 and (b) palladium (II) complex of Br-SG1. Analysis conditions: 600 MHz, DMSO-d_6, 298 K.

The formation of active Suzuki catalysts from novel dendritic supports **9** and **11** is achieved by first deprotecting the dendrimers using acid hydrolysis. Currently, the deprotection has only been performed on bis-1,3-SG1(isopropylidine) p-tert-butylcalix[4]arene (11) to yield bis-1,3-SG1(OH)$_8$ p-tert-butylcalix[4]arene (Bis-SG1(OH)C[4]A). Interestingly, the water solubility of this deprotected dendrimer with a hydroxyl periphery is very limited; however, the compound is soluble in 50% ethanol. Following deprotection, the Bis-SG1(OH)C[4]A dendrimer was loaded with $PdCl_2$ via ligand substitution of (C_6H_5CN) with N3/N6 as shown in Figure 11. The complexation was performed in acetone-d_6 and was shown to be complete, yielding bis-1,3-SG1(OH)$_8$-($PdCl_2$)$_2$ p-tert-butylcalix[4]arene (Bis-SG1-C[4]A (OH)(Pd)) (Figure 4), within 5 min by monitoring the reaction with ^{1}H NMR. The spectrum of the Bis-SG1-C[4]A (OH)(Pd) is not included due to significant peak broadening and insufficient resolution of peaks using 600 MHz ^{1}H NMR. Fortunately, the complexed dendrimer, Bis-SG1-C[4]A (OH)(Pd), exhibits high water solubility upon mild agitation and heating. The solubilization of palladium into water using the Bis-SG1-C[4]A (OH)(Pd) catalyst is confirmed by ICP-OES.

An aqueous solution of Bis-SG1-C[4]A (OH)(Pd) was employed as a catalyst for the Suzuki reaction in water at close to ambient temperature. As of the writing of this thesis, the bis catalyst has only been used in two Suzuki reactions (Scheme 6) using analogous conditions to the optimal reaction for the G1-dendritic catalyst (Table 1) found in our previous study. The bis catalyst was employed in both pure water and 50% EtOH as solvent and the percent conversion achieved was compared to the average of our previously synthesized catalyst (G1-OH-Pd) and the ligand precursor (C_6H_5CN)$_2PdCl_2$

(Figure 14). It is important to note that the ligand precursor had no activity in water because if it were active then there would be little motivation for this study. The Bis-SG1-C[4]A (OH)(Pd) catalyst afforded a comparable percent conversion to the average for G1-OH-Pd which indicates that is a promising catalyst to study further. Optimization of the reaction conditions and repeated trials will be necessary before any significant conclusions can be made about this new dendritic catalyst containing a calix[4]arene core. It was unexpected that Bis-SG1-C[4]A (OH)(Pd) was virtually inactive in 50% EtOH especially because the non-complexed bis dendrimer had higher solubility in this solvent. The results indicate that Bis-SG1-C[4]A (OH)(Pd) is sensitive to its environment and further studies on its dynamics are required to fully understand how the catalyst functions. Dynamic light scattering could be a future avenue for testing how the catalyst expands or contracts in various solvent systems.

Scheme 6. Model Suzuki-Miyaura reaction catalyzed by Bis-SG1-tBuC[4]A $(OH)_8(PdCl_2)_2$



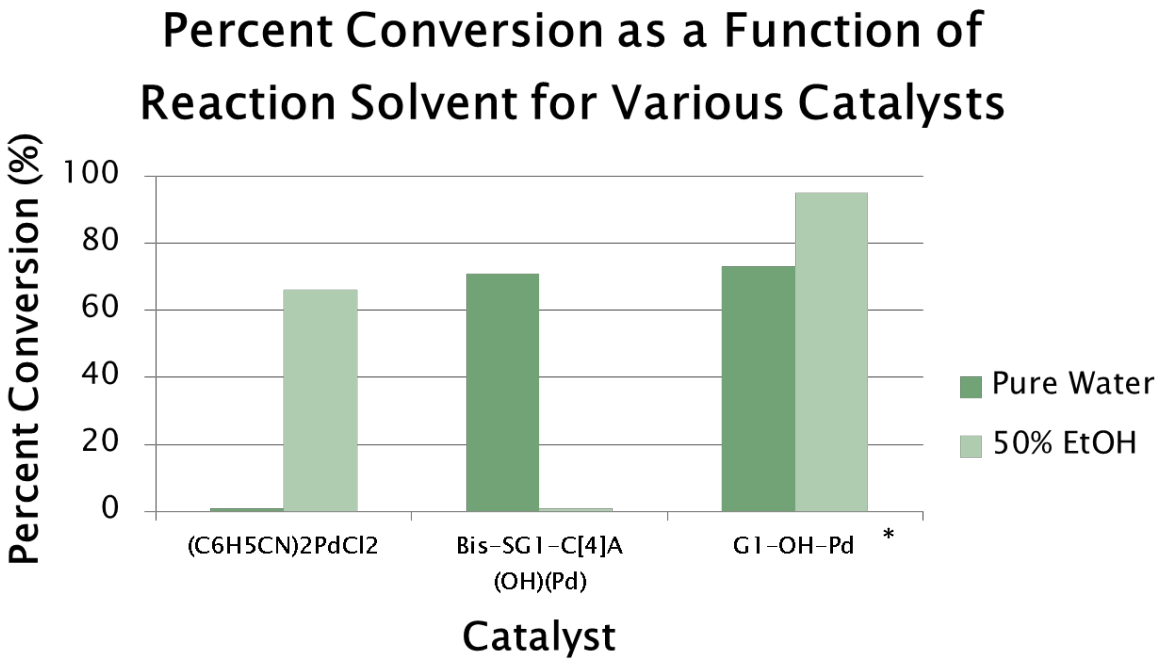


Figure 14. Catalytic performance of Bis-SG1-tBuC[4]A $(OH)_8(PdCl_2)_2$ in both pure water and 50% ethanol vs. the catalytic performance of the ligand precursor ($(C_6H_5CN)_2PdCl_2$) and the G1-OH-Pd dendrimer with triacetylene core from previous study.[12e] * Average values included

Conclusions

To review, we have successfully and reproducibly synthesized a new class of more dense poly(ether-ester) dendrimers with triazole ring metal binding moieties at the branching points and a hydrophobic calixarene based core. The components of these dendrimers were tailored to increase the selectivity of the scaffolds for hydrophobic substrates, and decrease the distance from the substrate binding site to the catalytically active palladium complex. Compounds **9** and **11** were exclusively produced and characterized by NMR and MALDI-TOF-MS. An active Suzuki catalyst was synthesized by loading deprotected **9** with $PdCl_2$ to yield Bis-SG1-C[4]A (OH)(Pd). Initial results support that this compound is a very promising catalyst for the Suzuki reaction in water at low temperatures.

This work will continue well beyond this thesis as numerous further investigations into these novel catalysts remain necessary. In the immediate future, the Suzuki reaction conditions must be optimized for the Bis-SG1-C[4]A (OH)(Pd) catalyst. Subsequently, Tetra-SG1-tBu-C[4]A needs to be complexed with $PdCl_2$ in a similar manner and employed as a catalyst in similar reactions as a comparison. It is hypothesized that the tetra catalyst will be more soluble in water, due to more hydrophilic dendrons, potentially improving on the performance of the bis catalyst. Next we must attempt to achieve one of our main goals, which is to catalyze the Suzuki reaction for a hydrophobic organoborane with potential in drug discovery. Such a compound has been ordered and will be available to our group shortly. If successful, we will be the first of my knowledge to catalyze the Suzuki reaction for a hydrophobic

organoborane increasing the potential for water soluble catalysts to be implemented in large scale pharmaceuticals. A variety of new tri- and hexa- substituted calix[6]arene core dendrimers will also be produced and compared to their calix[4]arene core analogs. Finally, the size selectivity of the calixarene core must be analyzed. Catalysts that selectively incorporate substrates based on size have huge potential to act as synthetic enzymes (Figure 15) which could be used in one pot Suzuki cascade reactions. Modified dendrimers using a similar model could also be applied as “nanosponges”, which could be employed to remove toxins from the body. Our group will continue to take on these significant challenges in the future.

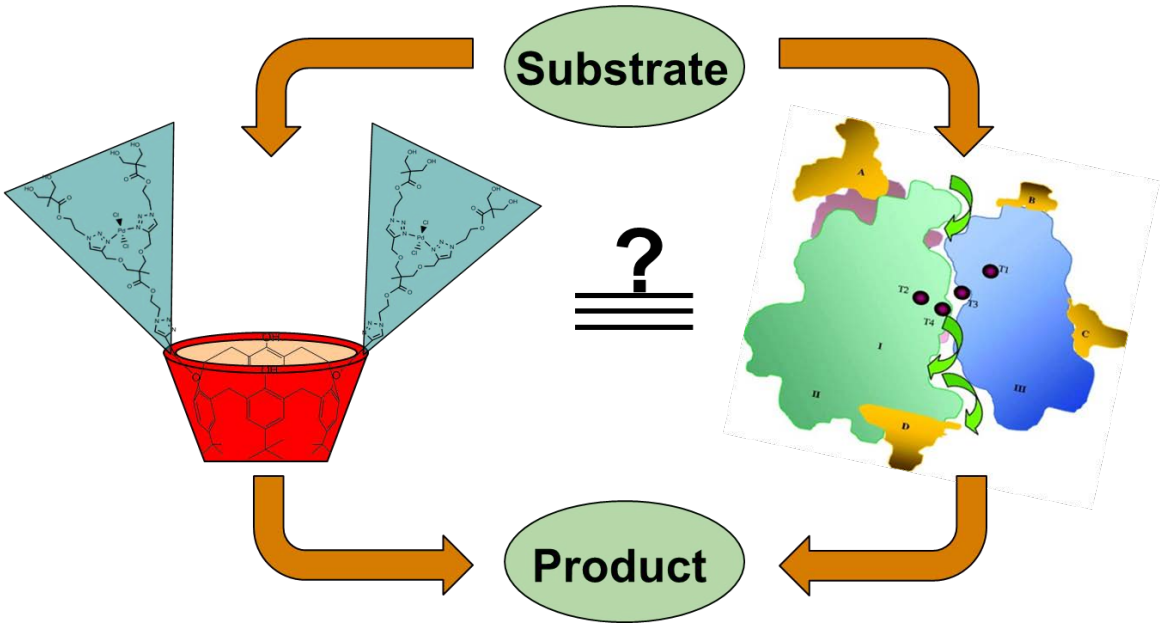


Figure 15. Comparison of the catalytic process of Bis-SG1-tBuC[4]A $(OH)_8(PdCl_2)_2$ to an enzyme.

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