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A General Diversity Oriented Synthesis of Asymmetric Double-Decker Shaped Silsesquioxanes†

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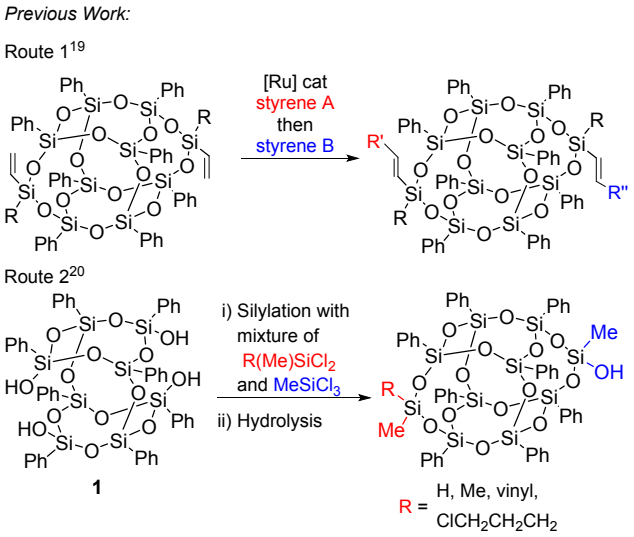
A strategically novel synthesis of nano-sized, asymmetrically functionalized double-decker shaped silsesquioxanes (DDSQ) is reported. Selective protection with a boronic acid affords the crucial mono-protected intermediate *en route* to the asymmetric products. Generation of symmetric by-products is minimized by judicious choice of base, and high recovery of recylable starting DDSQ tetraol is achieved.

Silsesquioxanes have attracted significant research interest for the synthesis of materials with properties that have met medicinal, synthetic, industrial and materials science demands.[1-5] Over the years, explorations in this field have been dominated by the manipulation of cubic-like silsesquioxanes for the synthesis of hybrid polymers.[3, 6-8] This is due to the well-defined spatial dimensions, the presence of seven inert peripheral organic moieties to accommodate solubility and processability, and one polymerizable reactive organic group.[9-11] Such silsesquioxane frameworks are accessed by corner-capping incompletely condensed R_7-trisilanol POSS with R'-trichlorosilanes.[12] The resulting condensed structure bears a polymerizable R' group that can be incorporated as a pendant nanostructure to a linear polymer chain. After the first synthesis of DDSQ-tetraol (**1**),[13] two reactive edges could be accessed via the condensation of **1** with various chlorosilane capping agents.[14] Unlike the monofunctionalized POSS where the nano-precursor acts as a pendant, this framework allows incorporation into a linear polymer backbone.[15-17] Incorporating silsesquioxanes in this manner may provide more effective retardation to the backbone motion of a linear polymer, which in turn would allow a more efficient approach to property enhancement.[18] It is noteworthy, however, that in all the cases above the two lengths of polymer bridged by the silsesquioxane linker are from the same monomer. This results from the fact that **1** is symmetrically capped. We believe that silsesquioxanes bridging two distinct polymers will offer an interesting new class of materials, but to produce and explore such materials requires the symmetry in **1** to be broken. Certainly, synthetically accessing such asymmetric DDSQ systems offers a significant challenge due to the nanometer scale distance between capping sites.



Scheme 1: Previous methodology for the synthesis of asymmetric DDSQs

Recently, two routes to asymmetric DDSQs have been reported (Scheme 1). In 2018 the Zak and Marciniec team developed an olefin metathesis catalyst able to selectively couple one vinyl group on a symmetrically capped divinyl-substituted DDSQ with various styrene derivatives.[19] After this mono-functionalization, a second styrene derivative is added to afford an AB system. While this ground-breaking work effectively provided an AB system, major limitations include the necessity of the vinyl and styryl coupling partners and the requirement of ruthenium-based catalyst. A more general synthetic route must be one that is amenable to a broader range of functionalities. Thus, in our previous attempt to

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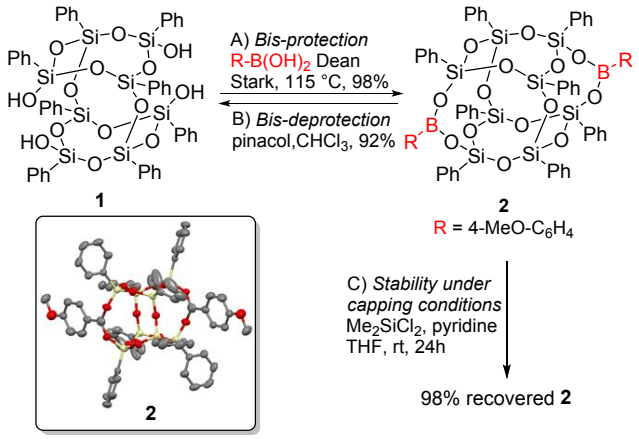
develop a methodology that supports a diverse array of functional groups we explored the capping of **1** with a premixture of two chlorosilanes.[20] In that study, we demonstrated that the AB system could be isolated if one of the chlorosilanes is a trichloromethylsilane. The latter upon workup, provided a polarity difference between the symmetric by-products and the desired asymmetric system. Again, this technique was limited in that it generated significant symmetric by-product waste and it required differences in polarity between the by-products and desired asymmetric material.

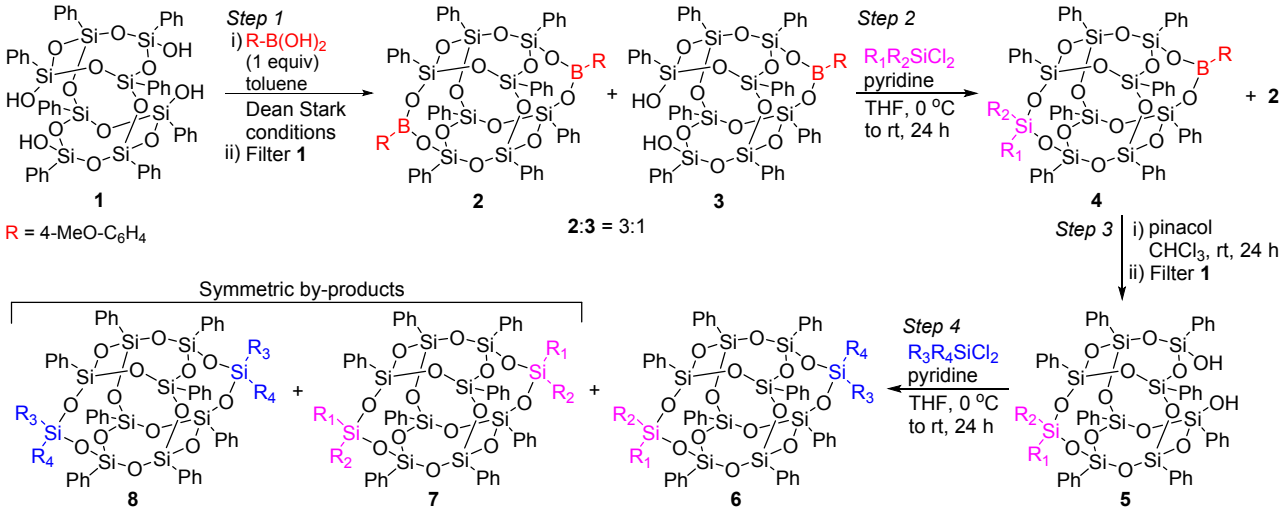


Scheme 2: (A) Bis-protection of DDSQ tetraol (**1**) with a boronic acid, (B) bis-deprotection of **2** with pinacol, and (C) stability of boronic acid protecting group under standard silylation conditions

To improve on current methodologies, we sought a synthetic route where all chlorosilane capping agents are tolerated, excess **1** can be recovered then recycled, and symmetric by-products are minimized. To this end, a protecting group strategy was envisioned. If **1** could be mono-protected by masking two silanol groups, silylation of the free silanol edge, followed by deprotection and capping with another chlorosilane would afford the desired asymmetric material. To achieve this goal, we first had to identify an effective protecting group. The desired protecting group would be able to protect two silanols simultaneously, be easily installed, and removed without impacting the DDSQ framework and tolerate standard capping conditions.

After initial evaluation it was found that **1** could be bis-protected with a variety of boronic acids under Dean-Stark conditions in high isolated yields. Among the boronic acids explored, 4-methoxyphenylboronic acid allowed simple spectroscopic analysis due to its distinct methoxy protons while also affording a high yield (98%, Scheme 2A). Recrystallization of this material from DCM/hexane (1:3) provided single crystals suitable for X-ray analysis. The boronic ester protecting group in **2** was removed by stirring with pinacol providing a high yield of pure **1** (Scheme 2B). To our knowledge, this is the first report of a boronic acid used as a protecting group for silanols; however, borosiloxane cages have been reported before.[21] Excitingly, compound **2** was stable under the capping reaction conditions with one alteration. Using pyridine as opposed to the more common triethylamine provided a nearly quantitative recovery of bis-protected material (Scheme 2C). In our hands, pyridine had no adverse effects on the capping of **1**.

With a suitable protecting group determined, optimal conditions leading to mono-protected **1** were sought (see SI for details). Although all conditions screened could not exclusively afford mono-protected **1**, it was found that addition of 1 equivalent of *p*-MeO-$C_6H_4B(OH)_2$ under Dean-Stark conditions for 2 h afforded 42% recovered **1** and 58% of an inseparable mixture that by ^1H and ^{29}Si NMR spectroscopy consisted of mono-borylated **3** and bis-borylated **2** in a ratio of 1:3 (Scheme 3, step 1). While the ratio of compound **3** to compound **2** is not optimal, it was reasoned this mixture could be carried forward without significant loss of material as compound **2** could be recovered as starting material, **1**, after global deprotection in step 3 of Scheme 3. Note that in both steps 1 and 3 compound **1** is recovered by filtration which is enabled by the poor solubility of **1** in chloroform. See the supporting information for a more complete solubility study. With this route, the identity of the chlorosilanes used in steps 2 and 4 is unrestricted unlike

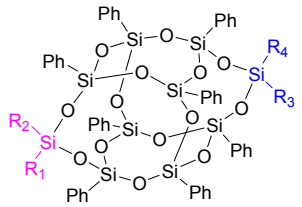


Scheme 3: Synthetic route for the synthesis of asymmetrically functionalized DDSQ compounds

prior synthetic routes.[12,13] Furthermore, symmetric by-products will only arise from inefficiencies in removing **1** in steps 1 and 3.

In our efforts to explore the scope of this multistep route, the reactions were scaled to DDSQ tetraol **1** (1.96 mmol, 2g), *p*-MeO-$C_6H_4B(OH)_2$ (1 equiv), chlorosilane (1 equiv based on **3**), pyridine (2 equiv based on **3**), and pinacol (1 equiv based on original *p*-MeO-$C_6H_4B(OH)_2$ added). All reactions were followed using ^{1}H, ^{11}B, and ^{29}Si spectroscopy and the final asymmetric products were purified by flash chromatography (see SI for details). The asymmetrically functionalized DDSQs **6** were obtained almost exclusively with minor symmetric AA **7** and BB **8** by-products. The by-products were separated by flash column chromatography, and the ^{29}Si NMR of the symmetric products matched previous reports of these materials or were independently synthesized to confirm structural assignments.

Table 1: Isolated asymmetric and symmetric DDSQ products

Entry	Asymmetric Product **6**[a]	By-products[b] AA (**7**), BB(**8**), **1**
		
1) R_1 = Me R_2 = Me R_3 = Me R_4 = H	**6a:** 79% (22%)	**7a:** 2% **1:** 62% recovered
2) R_1 = Me R_2 = Me R_3 = Me R_4 = OH	**6b:** 61% (16%)	**7b:** 4% **1:** 66% recovered
3)[c] R_1 = Me R_2 = H R_3 = Me R_4 = (3-CNPr)	**6c:** 52% (14%)	**7c:** 5% **8c:** 6% **1:** 69% recovered
4) R_1 = Me R_2 = Me R_3 = Me R_4 = (3-CNPr)	**6d:** 81% (21%)	**7d:** 4% **8d:** 6% **1:** 71% recovered
5) R_1 = Me R_2 = (3-CNPr) R_3 = Me R_4 = Me	**6e:** 74% (19%)	**7e:** 4% **8e:** 5% **1:** 68% recovered
6)[c] R_1 = Me R_2 = vinyl R_3 = Me R_4 = (3-CNPr)	**6f:** 65% (17%)	**7f:** 3% **8f:** 6% **1:** 61% recovered
7)[c] R_1 = Me R_2 = vinyl R_3 = Me R_4 = H	**6g:** 50% (13%)	**7g:** 3% **8g:** 2% **1:** 60% recovered
8)[c] R_1 = Me R_2 = H R_3 = vinyl R_4 = OH	**6h:** 68% (18%)	**7h:** 3% **1:** 63% recovered
9)[c] R_1 = Me R_2 = vinyl R_3 = isopropyl R_4 = OH	**6i:** 56% (15%)	**7i:** 4% **1:** 70% recovered

[a]Yields reported are based on the calculated amount of compound **3** generated in step 1. Yields in parenthesis are based on the total amount of compounds **2** and **3** generated in step 1. [b]Yields for **7** and **8** are based on the total amount of compounds **2** and **3** generated in step 1. The percentage of recovered **1** includes material from steps 1 and 3. [c]Isolated as a cis/trans mixture.

To demonstrate the synthetic scope, asymmetric products (Table 1) were synthesized and characterized following the route from Scheme 3. Two yields are reported for the asymmetric material. The first yield is based on the amount of compound **3** after step 1 in Scheme 3. This yield shows the overall efficiency of the route from the monoprotected material to the desired asymmetric product. The yield in parenthesis and the yields of symmetric by-products are based on the combined amount of compounds **2** and **3** generated in step 1. Finally, the reported yield compound **1** is based on the amount of material recovered in steps 1 and 3. It is worth commenting that the high amount of recovered **1** is not due to inefficient chlorosilane capping. Rather high recovery of **1** is a key element of this strategy; namely the recyclability of compound **2** back to **1**.

Overall, moderate to high isolated yields were achieved with an average relative isolated yield of 65%. The ^{29}Si NMR spectra of compounds **6a-6i** exhibited six or eight characteristic peaks depending on if cis/trans isomers were present, and the high-resolution mass spectrometry are in excellent agreement with calculated theoretical masses (See SI for full characterization details). While some of the AB cages contain moieties that can bind as a polymer end-cap (**6a**, **6b**, **6d**, **6e**, and **6i**), others possess the moieties that enable them to bridge two distinct monomers (**6c**, **6f**, and **6g**). Asymmetric product **6h** is quite unique in that it bears three reactive polymerizable groups. Interestingly, reversing the order in which chlorosilanes were added had little effect on isolated yields and had no observed effect on the amounts of symmetric by-products isolated (**6d** and **6e**). This experiment suggests the symmetric by-products can only be attributed to the small amounts of **1** passing through the filtration in steps 1 and 3 and is independent of the capping agent used. The variation of isolated symmetric materials throughout Table 1 is attributed to the ability of the symmetric material to pass through the flash chromatography after the final step. It was observed that asymmetric products with a significant difference in polarity at the capping site afforded better yields of the isolated asymmetric products (**6b**, **6d**, **6e**, **6g**, and **6h**). This is not surprising as the success in separating the mixture by column chromatography relies on the interaction of the various components in the mixture with the stationary phase and the eluting solvent (mobile phase). It is also noteworthy that in entries 2, 8, and 9 the corresponding symmetric by-product **8** was not isolated. This is likely because these symmetric products are quite polar thus will only slowly pass through the silica column. The symmetric product **8a** in entry 1, on the other hand, should readily pass through the silica. We expect in this case the mass of generated symmetric material maybe low enough it is difficult to detect.

In conclusion, this strategically novel synthetic route leading to asymmetrically functionalized DDSQ compounds was successfully demonstrated. The technique relied on the protection of two silanol groups on DDSQ tetraol (**1**) using boronic acid. Importantly, the protocol discloses the effectiveness of pyridine as a base, which unlike the more commonly used triethylamine is inert to the boron protected cage. Additionally, pinacol chemoselectively demasks the boron protecting group without compromising the cage architecture.

The protocol is general, robust and allows the assemblage of a wide range of functionalized asymmetrically functionalized DDSQs. Eight asymmetric compounds were synthesized and characterized as pure compounds by ^{1}H, ^{13}C, and ^{29}Si NMR and mass spectroscopy. Over 50% of the starting DDSQ tetraol (**1**) that could have otherwise contributed toward the synthesis of unwanted side products is recovered with a high purity and can be used in another cycle of synthesis. Efforts to use these compounds as nano-linkers to two different block copolymers are underway in our lab.

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Conflicts of interest

There are no conflicts to declare.

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