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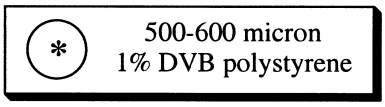

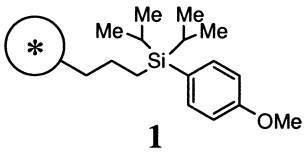

1

200 nmol of Si/bead
> 100 g scale

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An Alkylsilyl-Tethered, High-Capacity Solid Support Amenable to Diversity-Oriented Synthesis for One-Bead, One-Stock Solution Chemical Genetics

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The synthesis and use of an alkylsilyl-tethered large (500−600 μm) polystyrene resin (**1**) are disclosed. An optimized Suzuki coupling of bromine-functionalized polystyrene and a silicon-functionalized alkylborane generates the silicon-substituted polystyrene **1** in large scale (>100 g). Resin loading is accomplished by activation as the silyl triflate, which can accommodate even sterically encumbered secondary alcohols and phenols. Treatment with HF/pyridine for linker cleavage is mild, efficient, and amenable to an automated, large-scale distribution system. This platform delivers, minimally, 50 nmol of each small molecule derived from a diversity-oriented, split-pool synthesis on a *per bead* basis for use in both forward and reverse chemical genetic assays. This technology satisfies many requirements of a one bead−one stock solution approach to chemical genetics.

Introduction

Currently we are using diversity-oriented split-pool synthesis to prepare structurally complex and diverse small molecules as vehicles to induce specific and novel biological phenotypes.[1] Once a small molecule has demonstrated biological activity and the protein target identified, researchers can infer a role for that target within a biological system.[2] This is analogous and complementary to methods used in classical genetics where random mutations are first generated and then screened in search of a specific cellular or physiological phenotype. This unbiased approach of using small molecules to dissect cellular circuitry is known as forward chemical genetics (FCG).[3]

In a reverse chemical genetics (RCG) assay, which is more similar to the drug discovery process, small molecules are screened for their ability to bind a preselected protein target.[4] In our laboratory, small molecule printing (SMP) has provided the means for miniaturization of this process.[5] After identification of small molecules with suitable binding properties, experiments are performed that take advantage of their ability to modulate function rapidly and conditionally. Of course, the optimal approach to using small-molecule diversity-oriented synthesis as an engine for general biological discovery is a totally integrated approach using both forward and reverse chemical genetics; this systematic approach has been given the more general name of chemical genetics.

We believe the one encoded bead−one stock solution strategy[6] is the optimal process to generate the requisite small molecules and, consequently, large databases of novel and important protein ligands. To reduce this strategy to practice and maximize its success, we surmise that it will be necessary to deliver, minimally, 50 nmol of small molecule from a single synthesis bead.[7] This quantity of reagent will allow for over 100 FCG assays and several thousand RCG assays from a single synthesis bead with enough reagent remaining for confirmation of observed biological activity.[8,9]

No solution is currently known to the problem of delivering such large quantities of small molecules on a per bead basis (typically, most large bead/linker combinations yield ≤5 nmol/bead).[10] We now report our work toward developing a novel, large (>500 μm) polystyrene bead/alkylsilyl tethered linker combination as a general solution to the problem of delivering ≥50 nmol of each product derived from a split-pool synthesis.[11] This is also an integrated solution that addresses the needs of both forward and reverse chemical genetics; the released small molecules can be both pin-transferred into FCG assays and undergo SMP (recapture of the liberated −OH group) for RCG assays. The key developments leading to this novel bead/linker combination are an improved method for functionalizing "naked" large polystyrene beads, a new silicon linker for solid-phase diversity-oriented synthesis, and a modification/optimization of the solid-phase in situ Suzuki coupling conditions reported by Ellman and co-workers to synthesize diisopropylalkylsilicon-functionalized resin **1** (Figure 1).[12]

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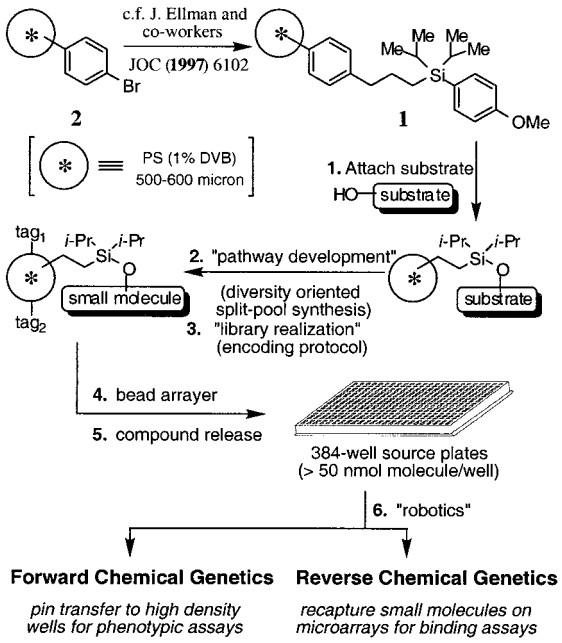


Figure 1. Integrated approach to allow any split-pool synthesis to be used in both "forward" and "reverse chemical genetic" experiments.

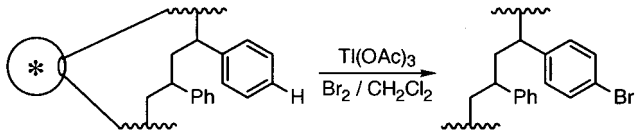
Initial Analysis. Our initial analysis of the linker problem was primarily concerned with the end result of a diversity-oriented split-pool library synthesis; it required a quantitative linker cleavage process that is amenable to large-scale production (many beads treated simultaneously in a spatially arrayed format), does no damage to the final product(s), and leaves no impurities that are difficult to remove. Guided by similar principles used in target-oriented organic synthesis, we chose a silicon-based linker for the above as well as for the following reasons.[13]

(1) The attachment of starting materials is readily accomplished in high yield. Activation of silicon as a silyl chloride or silyl triflate for silyl ether synthesis is straightforward and general. For diversity-oriented synthesis, ease and efficiency of substrate loading to solid support are critical, particularly with the intended goal of delivering ≥50 nmol of small molecule/bead.

(2) Silicon is compatible with the widest array of modern synthetic chemistries. Because no commercially available bead/linker systems satisfied our needs, we were not encumbered with the use of known approaches that include heteroatom bond formation (typically C−O and C−N bonds) as the method of grafting the linker onto the solid support backbone.[14] After removal of the heteroatom(s), the linker can now be considered a bulky trialkylsilyl protecting group amenable to most modern synthetic chemistries.[15] In this particular example, a strong parallel can be drawn between the chemical stability of solid support linker **1** (Figure 1) and the known methyldiisopropylsilyl ether protecting group.[16]

With a diisopropylalkyl-substituted silyl ether chosen as a flexible method of linking small molecules to the solid support, commercially available unfunctionalized 500−560 μm polystyrene macrobeads were selected principally because this was the only solid support known in which each bead in a population of beads has the physical capacity to deliver ≥50 nmol of each small molecule.[17]

Table 1. Bromination of Polystyrene



1% DVB cross-linked PS **2**

entry	resin size, μm	Br loading, mequiv/g (theoretical)[a]	nmol/bead	% yield
1	500−560	0.97 (1.00)	92	97
2	500−560	1.31 (1.36)	127	96
3[b]	500−560	1.43 (1.49)	147	96
4[c]	500−560	1.74 (1.84)	176	95
5	400−450	1.86 (1.93)	95	96

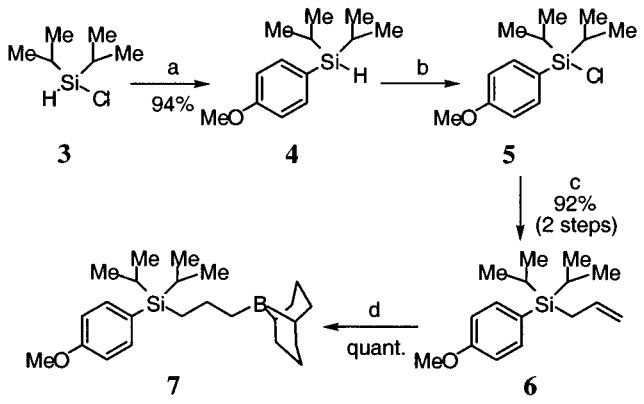
[a] Determined by elemental analysis (ref 21). [b] Performed on >80 g scale. [c] This loading is identical on a per bead basis to commercially available 500−600 μm beads (after factoring in size distribution) at 2 mequiv of Br per gram (ref 25).

Results and Discussion

Synthesis of Bead/Linker System. Although an extensive body of literature concerning silicon-derived solid-phase linkers already existed,[18] to the best of our knowledge, there was no precedent for the use of large polystyrene beads (>500 μm) grafted with a "heteroatom-free" aliphatic linker. Inspired by the work of Woolard et al.,[12] we chose to adapt the Suzuki coupling reaction for C−C bond formation as a route to the desired linker system. To carry this experiment forward, it was necessary to synthesize the Suzuki coupling partners de novo, the bromine-functionalized 1−2% dvinylbenzene (DVB) cross-linked polystyrene resin (500−560 μm) **2** and the silicon-containing alkylborane **7**.

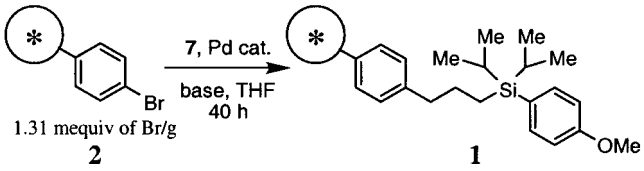
(a) Bromination of Polystyrene. On the basis of the method of Frechet,[19] we subjected unfunctionalized 1−2% DVB cross-linked polystyrene, both 400−450 and 500−560 μm beads, to thallium acetate-catalyzed electrophilic aromatic bromination conditions in CCl_4.[20] Unfortunately, experimental results using this protocol were inconsistent, yielding highly colored resins with lower than expected levels of bromine incorporation.[21] These products were also brittle, which is unacceptable for library synthesis.[22] Increasing the amount of thallium catalyst (from 9 to 18 mol % relative to bromine) and switching to CH_2Cl_2 as the reaction solvent solved these problems. Although the exact reason is unclear for this remarkable change in reactivity, one possible explanation might be increased penetration of the thallium reagent into large polystyrene beads when dissolved in CH_2Cl_2. Under these optimized conditions, the exact level of bromine incorporation was readily modulated by the amount of thallium catalyst and bromine used, always resulting in ≥95% yield of bromine addition with *per bead* levels much greater than our 50 nmol threshold limit (Table 1). Also significant is the uniform appearance of the functionalized beads, off-white with little physical damage to their spherical geometry.[23] More recently, a commercial supplier has made available large (410−500 and 500−600 μm) 1% DVB cross-linked *p*-bromostyrene/styrene copolymerized resins at the 1.0 and 2.0 mequiv of Br per gram loading levels, which have also been used in all of the subsequent experiments (vide infra).[24,25]

Scheme 1[a]



[a] (a) 4-Lithioanisole, THF, −78 °C. (b) Trichloroisocyanuric acid, CH_2Cl_2, 0 °C. (c) Allylmagnesium chloride, THF, 0 °C. (d) 9-BBN, THF, room temperature, 3 h.

Table 2. Solid Phase Suzuki Coupling Optimization[a]



entry	base	$Pd(PPh_3)_4$ yield, % (Si linker/bead, nmol)	$Pd(dppf)_2$ yield, % (Si linker/bead, nmol)
1	Na_2CO_3	88 (112)	77 (98)
2	K_2CO_3	91 (116)	46 (58)
3	NaOH	98 (124)	80 (102)
4	NaOMe	83 (105)	76 (97)
5	K_3PO_4	98 (124)	51 (65)
6[b]	NaOH	98 (204)	

[a] Entries 1−5 were run on 500−560 μm PS beads with 127 nmol of Br/bead initial loading. [b] Entry 6 represents the commercially available 500−600 μm beads initially loaded at 208 mequiv of Br per gram as determined by elemental analysis.

(b) Synthesis of Silicon-Functionalized Alkyl Borane. With access to bromine-functionalized resin as one-half of the Suzuki coupling partners, the synthesis of allyl silane **6** was readily accomplished in three steps from commercially available starting materials (Scheme 1). Diisopropylchlorosilane (**3**) was added to a THF solution of (4-methoxyphenyl)lithium at −78 °C and allowed to come to 23 °C overnight. Aqueous work up and filtration through silica gel produced silane **4** in 94% yield. Treatment of **4** with trichloroisocyanuric acid in CH_2Cl_2 followed by filtration under an inert atmosphere provided a quantitative yield of silyl chloride **5**. Allylmagnesium bromide was then added to **5**, delivering allylsilane **6** in 92% overall yield after vacuum distillation.[26] The Suzuki coupling substrate, alkylborane **7**, was realized by treating a THF solution of trialkylallyl silane **6** with a nearly equimolar amount of solid 9-BBN.[27] This reagent is used without further purification or isolation.

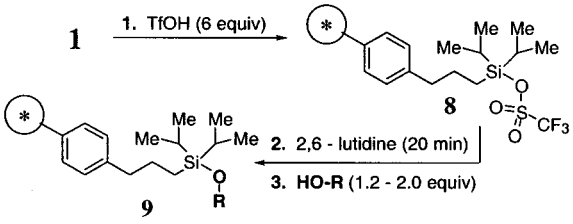
(c) Solid-Phase Suzuki Coupling Optimization. Several reaction conditions were screened to produce the most efficient and reproducible Suzuki coupling on the 500−560 μm polystyrene beads (Table 2). Two catalysts, $Pd(PPh_3)_4$ and $Pd(dppf)_2Cl_2$, were tested in the presence of several commonly used bases. Entry 3 describes the optimal reaction conditions. Interestingly, these conditions were identical to those originally reported by Suzuki (using NaOH as base and $Pd(PPh_3)_4$ as catalyst); none of the standard perturbations offered any improvement.[28,29] A representative procedure is as follows (Table 2, entry 6): To a 0.17 M THF solution of alkylborane **7** (1 equiv) was added 500−600 μm 1% DVB cross-linked brominated polystyrene (0.6 equiv of resin functionalized at 2.0 mequiv of Br per gram), which was allowed to fully swell in the THF/borane solution (45 min). The flask was then fitted with a condenser, and $Pd(PPh_3)_4$ (2.5 mol %) and NaOH (2 equiv of 2 M solution) were added. The reaction mixture was then gently refluxed for 24 h, at which time additional palladium (2.5 mol %) was added. The reaction was then continued at reflux for a total reaction time of 40 h. Subsequent experiments proved the necessity of the additional palladium catalyst.[30] The extent of silicon incorporation was confirmed by elemental analysis, typically delivering nearly quantitative yield under the optimized conditions.[21,31] After Suzuki coupling, the 500−600 μm beads (entry 6) possess ∼200 nmol of Si linker/bead, well above the threshold lower limit of 50 nmol/bead.

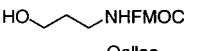
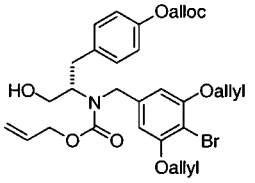
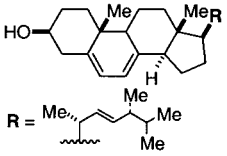
Linker Activation, Substrate Loading, and Compound Release. (a) Silicon Activation. Because diversity-oriented synthesis strives to deliver not only structurally complex but also structurally diverse molecules in a single library, the ability to load several structurally *different* substrates possessing functional groups of *nearly identical* reactivity onto the resin under a common set of reaction conditions to a similar loading level is crucial to success.[4] We chose to activate the linker as trialkylsilyl triflate **8** (see Table 3) as a way to minimize the variability in loading levels between different substrates.[32,33] The specific protocol was adopted directly from the work of Smith[34] and Porco;[35] treatment of trialkylarylsilane-functionalized resin **1** with excess trifluoromethanesulfonic acid for 30 min produced **8**. Washing twice with CH_2Cl_2 removed excess acid. Complete formation of **8** was readily confirmed by MAS ^{29}Si NMR (single peak at ⟨44.0 ppm⟩ relative to tetramethylsilane internal standard at 0 ppm in C_6D_6). Because of the reactive nature of this species, it is recommended that the silyl triflate be used immediately after being formed.

(b) Substrate Loading. To load the alcohols shown in Table 3, the following general protocol was developed: an amount of 8 equiv of 2,6-lutidine (relative to silyl triflate) was added to washed resin **8** followed 15 min later by 2 equiv of the substrate alcohol dissolved in benzene.[36] This mixture is then gently agitated for 10 h, followed by thorough washing.[37] Vacuum drying of the resin overnight delivered substrate-functionalized resin **9**. Significantly, even sterically demanding alcohols were loaded in good yield as witnessed by entries 3 and 4.

(c) Small-Molecule Cleavage. The central feature of this silicon linker is the ease at which it undergoes Si−O bond cleavage under the influence of a 5% solution of HF/pyridine in THF.[38] Although this reagent is corrosive and toxic, it is a relatively mild reagent for silyl ether fluorodolysis and is dispensable by an automated liquid handler, making it particularly useful for large numbers of 384-well microplates in which synthesis beads will be spatially arrayed in a one bead−one well format.[39] We have found that 2.5 h was

Table 3. Small-Molecule Loadings



Entry	Substrate (equiv used)	Recovered (*per bead*)[a]
(1)[b]	 (1.5)	90% (114 nmol)
(2)[c]	 (1.2)	73% (146 nmol)
(3)	 (2.0)	76% (152 nmol)
(4)[d]	*trans*-2-phenyl-1-cyclohexanol (2.0)	69% (137 nmol)
(5)[d]	4-bromo-3,5-dimethylphenol (2.0)	79% (158 nmol)

[a] Material recovered is an indirect determination of the efficiency of substrate loading. All material recovered was >95% pure as determined by HPLC analysis using a photodiode array detector. [b] Entry 1 was run on 500−560 μm beads, and loading was determined by standard Fmoc cleavage analysis. [c] Loading was run on ~6 g of resin in a single experiment. [d] These loadings were confirmed by HPLC analysis and recovered material.

sufficient time for cleavage. Once complete, excess HF was quenched with methoxytrimethylsilane resulting only in volatile byproducts that were readily removed under vacuum and that do no harm to the released small molecules.[40] The purity of compounds cleaved by this method was very high (Table 3).[41]

Conclusion

In summary, we have disclosed a route for the synthesis of an alkyl tethered diisopropylarylsilane linker on large polystyrene beads. These beads are suitable for diversity-oriented split-pool synthesis and are capable of delivering ≥50 nmol of small molecule *per bead*. Because this bead/linker system represents one of our central enabling technologies for the practice of chemical genetics, it was important to develop a system that can be synthesized in large scale (>100 g), stored indefinitely, and used in a "right-off-the-shelf" fashion. To date, our results have been very encouraging as we move forward in our efforts to bring the full power of modern organic synthesis to bear on the process of dissecting cellular circuitry.

Experimental Section

General Methods. Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following: methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), and diethyl ether (Et_2O) were passed through two activated alumina columns to remove impurities prior to use (as described in *Organometallics* **1996**, *15*, 1518−1520). 2,6-Lutidine was distilled from CaH_2 under Ar atmosphere. Unfunctionalized polystyrene (400−450 and 500−560 μm 1% DVB cross-linked) was purchased from Rapp Polymere GmbH and used without further purification. Brominated polystyrene (500−600 μm of 1% DVB cross-linked PS−Br, 2.0 mequiv/g and 1.0 mequiv/g) was purchased from Polymer Labs (1462−9999) and used without further purification.

Polystyrene Bromination Procedure (Polystyrene → 2). The 500−560 μm polystyrene beads were weighed out into a 2 L flask containing a stir bar and subsequently sealed under inert atmosphere and purged using a balloon. The 80 g of beads were then swollen in CH_2Cl_2 (1.2 L, ~1 g of resin/15 mL of solvent) for 1 h. To this solution was added 9.4 g of thallic acetate (24.6 mmol). This was allowed to stir gently for 1 h. The solution turned orange with a small amount of white precipitate on the bottom of the flask. To this mixture was added 7.0 mL of bromine (21.6 g/135 mmol) via syringe over a 15 min period. After each portion of Br_2 was added, the solution would turn orange for a few seconds and then lose color. Only near the end of the addition did the color remain for longer than a few minutes. The mixture was then stirred at room temperature for 1 h, at which time most of the color (but not all) had dissipated. The reaction was quenched by slow addition of 10 mL of MeOH; it was then allowed to stir for 10 min. The whole slurry was then filtered directly into a waste flask to remove solvent and dissolved catalyst. The beads on filter are then washed liberally with CH_2Cl_2. The beads were resuspended in a second liter of CH_2Cl_2 and gently agitated for 20 min. This was repeated a second time. The wash procedure was completed as follows: after the two CH_2Cl_2 washes, the beads were washed with THF (1 L × 20 min), THF/IPA (3:1; 1 L × 20 min), THF/H_2O (3:1; 1 L × 20 min × 2), DMF (1 L × 20 min), THF/IPA (3:1; 1 L × 20 min), THF (1 L × 20 min), CH_2Cl_2 (1 L × 20 min). After the wash protocol was finished, the beads were air-dried for 3 h and then placed under vacuum to remove trace solvent and water. *This experiment resulted in resin that possessed 1.43 mequiv of Br per gram of functionalized resin as determined by elemental analysis.*

Diisopropyl(4-methoxyphenyl)silane (4). A solution of *p*-bromoanisole (28.6 mL, 228 mmol, 1 equiv) in THF (550 mL) was chilled to −78 °C (CO_2(s), acetone). *n*-BuLi (91.2 mL, 228 mmol, 2.5 M in hexanes, 1 equiv) was added via cannula over a 5 min period. After 5 min a white precipitate began to form. The mixture was stirred for 30 min at −78 °C, after which chlorodiisopropylsilane (34.6 g, 228 mmol, 1 equiv) was slowly added via syringe. After 1 h the ice bath was removed and the solution was allowed to come to 23 °C with stirring overnight. The reaction was quenched with $NH_4Cl_{sat'd}$ (50 mL) and extracted with ether (3 × 500 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a light-yellow oil. Filtration through SiO_2 (gradient: 3−5% EtOAc/hexanes) yielded 47.7 g (94%) of a colorless oil. This

material could also be purified by distillation; bp = 76−85 °C at 275 mTorr (40 g, 63%). TLC R_f = 0.61 (9:1 hexanes/EtOAc). IR (film): 2393, 1853, 1710, 1691, 1658, 1584, 1482, 1346 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, 2H, J = 8.10, C3−H, C7−H), 6.95 (d, 2H, J = 8.10, C4−H, C6−H), 3.97 (s, 1H, Si−H), 3.85 (s, 3H, C1−H), 1.39 (q, 2H, J = 3.0, C8−H, C11−H), 1.10 (d, 6H, J = 6.5, C9−H, C10−H), 1.03 (d, 6H, J = 7.5, C12−H, C13−H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.13, 113.73, 113.62, 55.18, 18.95, 18.72, 11.08. Anal. Calcd for $C_{13}H_{22}OSi$: C, 70.21; H, 9.97; Si, 12.63. Found: C, 70.43; H, 9.83; Si, 12.39.

Chloro(4-methoxyphenyl)diisopropylsilane (5). Diisopropyl(4-methoxyphenyl)silane (47.7 g, 214 mmol, 1.0 equiv) was taken up in CH_2Cl_2 (700 mL). The solution was cooled to 0 °C and trichloroisocyanuric acid (16.6 g, 71.3 mmol, 0.33 equiv) was carefully added in three equal portions, making sure that each portion had at least 7 min to react before the next was added (caution: adding trichloroisocyanuric acid too rapidly results in a rapid evolution of gas). The mixture was stirred at 0 °C for 40 min, followed by warming to 23 °C with stirring. The solids were filtered under an inert atmosphere and the filtrate concentrated in vacuo to yield 54.8 g (98%) of a cloudy oil. The chlorosilane, which is unstable, was used immediately and without purification in the next step.

Allyl(4-methoxyphenyl)diisopropylsilane (6). To the crude chloro(4-methoxyphenyl)diisopropylsilane (54.8 g, 214 mmol, 1.0 equiv) was added THF (335 mL) via cannula under positive argon pressure. The solution was chilled to 0 °C and treated with allylmagnesium chloride (128 mL, 256 mmol, 2.0 M in THF, 1.2 equiv). After 3 h at 0 °C, the solution was allowed to warm to 23 °C with stirring overnight. The mixture was treated with $NH_4Cl_{sat'd}$ (50 mL) and the aqueous layer extracted with ether (3 × 500 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (3−5% EtOAc/hexanes) to yield 52.86 g (94%) of a slightly cloudy, viscous oil. This reagent is distilled at 130 °C at 500 mTorr as a colorless oil. TLC R_f = 0.40 (9:1 hexanes/EtOAc). IR (film): 2942, 2865, 1630, 1595, 1504, 1463, 1277 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, 2H, J = 6.84, C3−H,C7−H), 6.81 (d, 2H, J = 6.84, C4−H, C6−H), 5.82 (q, 1H, J = 8.5, 8.5, C15−H), 4.88 (d, 1H, J = 17.05, C16−Hb), 4.76 (d, 1H, J = 9.77, C16−Ha), 1.82 (d, 2H, J = 7.32, C14−H), 1.17 (q, 2H, J = 7.3, C8−H, C11−H), 0.94 (d, 6H, J = 7.3, C9−H, C10−H), 0.90 (d, 6H, J = 7.3, C12−H, C13−H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.51, 136.48, 135.70, 125.78, 113.78, 113.62, 55.09, 19.34, 18.22, 18.17, 17.68, 11.30. Anal. Calcd for $C_{16}H_{26}OSi$: C, 73.22; H, 9.98; Si, 10.70. Found: C, 73.25; H, 9.97; Si, 10.77.

Representative Suzuki Coupling Procedure (2 → 1). This procedure is included because commercially available palladium(0) did not perform as well as freshly made material.

To a standard Schlenk apparatus was added palladium dichloride (275 mg, 1.55 mmol, 1.0 equiv) and triphenylphosphine (2.04 g, 7.77 mmol, 5.0 equiv) followed by DMSO (20.0 mL). The mixture was heated at 155 °C until total dissolution of solid material occurred. The mixture was then cooled for 2 min. Hydrazine hydrate (303 μL, 6.22 mmol, 4.0 equiv) was added by syringe over a 1 min period, and the solution was immediately cooled in a cold water bath to initiate crystallization. When the first few crystals formed, the flask was removed from the ice bath and covered in foil. Once formed, the crystals were washed sequentially with ethanol (4 × 3 mL) and diethyl ether (2 × 1 mL). The yellow solid was protected from light and dried in vacuo overnight, yielding 1.76 g of bright-yellow crystals (98% yield).[42]

Alkyl borane 7 (6 → 7). Solid 9-BBN dimer (6.29 g, 53.0 mmol, 0.95 equiv) was weighed out in a glovebox and sealed under an argon atmosphere. Freshly distilled THF (365 mL) and allyl(4-methoxyphenyl)diisopropylsilane (**6**, 14.64 g, 55.8 mmol, 1.0 equiv) were added via syringe, and the mixture was allowed to stir for 3 h at 23 °C. The overall concentration of the allyl(4-methoxyphenyl)diisopropylsilane in THF is 0.16 M, which is the appropriate concentration for the subsequent Suzuki coupling. The yield of this reaction is assumed to be nearly quantitative.

Suzuki Coupling To Produce Silicon Functionalized 1. To an alkylborane-containing THF solution (53.0 mmol in 365 mL of THF, 1.74 equiv) was added the brominated polystyrene **2** (15.25 g, 2 mequiv/g, 30.5 mmol of Br, 1.0 equiv). Care was taken to maintain an argon blanket over the solution. Reagent **2** was allowed to swell for 45 min followed by addition of tetrakis(triphenylphosphine)palladium-(0) (880 mg, 0.76 mmol, 0.025 equiv) and $NaOH_{aq}$ (61 mmol, 30.5 mL of a 2 M NaOH solution, 2.0 equiv). The reaction was then heated to mild reflux with gentle stirring for 24 h. An additional amount of Pd(0) (880 mg, 0.76 mmol, 0.025 equiv) was added after the first 24 h and the reaction continued to reflux for another 16 h. Generally, the biphasic reaction mixture turns slightly green from its initial yellow color. Upon completion, the mixture was filtered and the beads washed repeatedly (see procedure below). Large beads (500−600 μm, in this instance) require time to take up the washing solvent. It is unnecessary to agitate the beads during the washing, but it is important to allow the resin enough time to take up the solvent. The wash procedure involved THF (2 × 200 mL × 45 min), 3:1 THF/1 M aqueous NaCN (1 × 200 mL × 1 h or until all dark color is gone), 3:1 THF/H_2O (2 × 200 mL × 45 min), 3:1 THF/IPA (2 × 200 mL × 45 min), THF (2 × 200 mL × 45 min), and DCM (2 × 200 mL × 45 min). The beads were air-dried overnight and then placed on a lyophilizer for 24 h, producing an almost colorless resin (white). ^1H NMR (500 MHz, CD_2Cl_2, nanoprobe): δ 7.34 (C3−H, C7−H), 6.82 (C4−H, C6−H), 5.27 (CH_2Cl_2), 3.69 (C1−H), 1.76 (C14−H), 1.48 (H_2O), 1.22(C15−H, C16−H), 1.16 (C8−H, C11−H), 0.97 (C9−H, C10−H), 0.91 (C12−H, C13−H).[43] Anal. Found: C, 83.54; H, 8.28; Si, 4.35; Br, <0.02; Cl, 0.247. The 2.0 mmol *p*-bromopolystyrene beads, quantitatively loaded with all carbon silicon linker, contain 41 mg of Si per gram of resin or 4.1% Si. Assuming quantitative loading, the mass of 1 g of resin increases to 1.37 g, so linker loading is calculated to be ∼1.45 mequiv/mol. Thus, resin loading is estimated from two elemental analyses parameters, %Si and %Br. The

%Br being less than 0.02 by weight indicates qualitative disappearance of bromine (note that halogens can be confused by elemental analysis, and therefore, it is necessary to perform separate Br and Cl analyses), while percent silicon indicates the loading level. Percent silicon typically ranges from 3.79 to 4.05. The procedure used to calculate percent silicon can overestimate the actual amount of silicon by 0.2−0.3% because these numbers are calculated by weighing ash resulting from sample digestion with acid and residue combustion, which leaves some elements unresolved from silicon. An amount of 4.35% Si is equivalent to 43.5 mg of Si per gram of resin or 1.54 mequiv Si per gram. Actual loading used in subsequent calculations is 1.45 mequiv/g, the theoretical maximum. There are 9350 beads per gram of 500−600 μm copolymerized *p*-bromopolystyrene beads with 2.0 mmol Br per gram loading level. We assume quantitative conversion, justified by the disappearance of bromine and the appearance of the appropriate amount of silicon. The number of polystyrene beads in 1 g of resin is then scaled with 37% mass increase, or about 6800 beads per gram.

General Experiment for Conversion of Tetralkylsilane 1 to Silyl Triflate Functionalized Resin 8. Silicon-functionalized resin **1** (1.43 mequiv of Si per gram) that had been dried under high vacuum for 12 h was weighed (200 mg, 0.286 mmol, 1 equiv) into a 10 mL polypropylene PD-10 column fitted with a Teflon stopcock and swollen in CH_2Cl_2 (2.0 mL, 10 mL of solvent per gram of resin) under N_2 atmosphere for 30 min. The solvent was then drained under positive N_2 pressure, and 3.8 mL of a 4% tifluoromethanesulfonic acid/CH_2Cl_2 solution (6 equiv of TfOH relative to Si) was added by syringe. The resin turned bright red/orange upon acid treatment and was then gently agitated for 30 min while still under N_2 atmosphere. Once activation was completed, two CH_2Cl_2 washes removed excess acid.

Loading of *trans*-2-Phenyl-1-cyclohexanol onto Resin 8. Treatment of **8** with 2,6-lutidine (0.27 mL, 8 equiv relative to Si) for 15 min followed by addition of 0.5 mL of an azeotropically dried 1.0 M solution of *trans*-2-phenyl-1-cyclohexanol (2 equiv) resulted in a colorless resin. The beads are then gently agitated for an additional 10 h under N_2 atmosphere. The beads were drained, exposed to atmosphere, and subjected to the following wash protocol: CH_2Cl_2 (2 × 3 mL × 45 min), THF (2 × 3 mL × 30 min), THF/IPA (3:1, 2 × 3 mL × 30 min), THF/H_2O (3:1, 2 × 3 mL × 30 min), THF/IPA (3:1, 2 × 3 mL × 30 min), DMF (2 × 3 mL × 30 min), and THF (2 × 3 mL × 30 min). The resin was air-dried for 3 h and then placed under high vacuum for 24 h to remove trace solvent and H_2O. The mass of the loaded and dried resin was 207.0 mg, indicating an apparent loading efficiency of 74% based on weight gain. Single-bead cleavage experiments resulted in an average per bead loading of 137 nmol/bead (69% efficiency; data included in table). See Supporting Information for details. This procedure is applicable for loading all alcohols listed in Table 3.

MAS ^{1}H NMR of *trans*-2-phenyl-1-cyclohexanol (500 MHz, CD_2Cl_2, nanoprobe): δ 7.30−7.20 (5 H), 3.72−3.64 (broad s, 1 H), 2.45−2.40 (broad, 1 H), 2.13−2.10 (broad, 1H), 1.89−1.85 (broad, 1H), 1.79−1.75 (broad, 1H), 1.60−1.32 (complex, 6H).

Cleavage of 8 from Resin. Vacuum-dried resin **8** was weighed (100.0 mg) into a solvent-resistant scintillation vial and allowed to swell in 1.0 mL of THF for 30 min. The THF solution was removed and replaced with a fresh 0.95 mL of THF and 0.05 mL of HF/pyridine solution (7:3 ratio of HF/pyr, available from Aldrich Chemical Co.). The vial was sealed and agitated for 3 h, at which time 0.1 mL of methoxytrimethylsilane was added to quench unreacted HF. (Note: The quenching is mildly exothermic; therefore, use caution.) The beads are further agitated for 30 min to ensure complete quenching. The solution was removed and the beads washed twice with additional 1.0 mL portions of fresh THF. All solvents were combined and concentrated in vacuo, delivering 16.3 mg of *trans*-2-phenyl-1-cyclohexanol as a white solid. On the basis of the assumption that 100% of the material loaded onto the resin is cleaved and recovered, this amount of material represents 71% of the theoretical maximum, or approximately 143 nmol/bead.

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Supporting Information Available. Experimental details regarding equipment, disposables, and representative single-bead cleavage experiments and analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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