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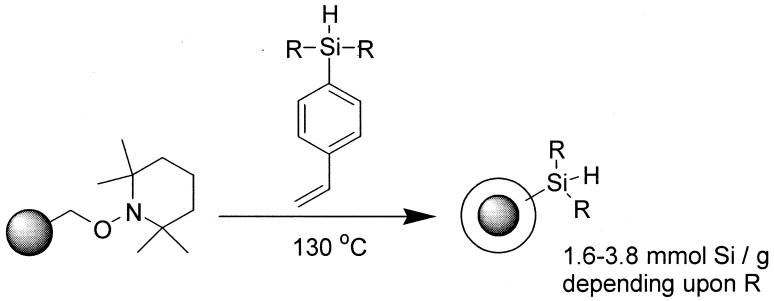

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Rasta Silanes: New Silyl Resins with Novel Macromolecular Architecture via Living Free Radical Polymerization

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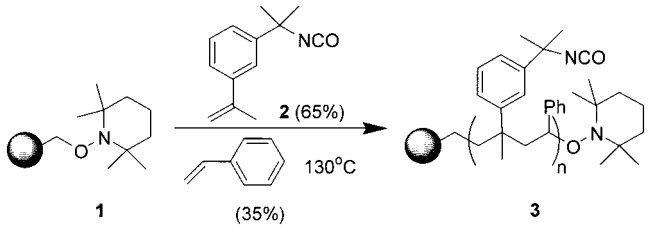
Heating TEMPO-methyl resin with dialkylsilane styrenes affords larger resin beads via living free radical polymerization. The new silyl resins prepared by this solvent-free suspension polymerization protocol have been coined "Rasta silanes". Rasta silanes have a novel macromolecular architecture typified by long straight chain polymers bearing the silanes which emanate from the phenyl rings of a cross-linked polystyrene core. By careful selection of comonomers during the polymerization step, loading capacity, silane spacing, and the relative distance of the silane moieties from the resin core can be controlled. The consistently high-loading Rasta silane resins produced can be easily converted into either a reactive silyl chloride or triflate to subsequently anchor alcohols and phenols to the solid phase. Cleavage from the resin can be mediated by treatment with HF·pyridine, TFA solutions, or TBAF.

Introduction

The solid-phase synthesis of small organic molecules has achieved great success in recent years, and the most critical component for a fruitful sequence is the appropriate choice of resin matrix and linker(s).[1] The majority of solid-supported syntheses have been performed on 1−2% DVB cross-linked polystyrene which requires a nonpolar solvent to swell the resin. This allows reagents to penetrate into the core of the resin bead where the vast majority of the pendant functionalities are located.[2] The second most commonly employed resin matrix is Tentagel, in which poly(ethylene glycol) tentacles emanate from a cross-linked polystyrene core that bears the attachment sites.[3] While Tentagel swells in a wide range of polar and nonpolar solvents, loading capacities are greatly diminished. A third choice is a highly cross-linked macroreticular resin, such as Argopore, which does not require swelling for reagents to enter into the resin cavity wherein lie the pendant functionalities; however, the pores must be "opened" prior to synthesis.[4]

Over the past decade, numerous linkers have been reported that offer selective cleavage of molecules from the solid phase by exposure to acid, base, or light.[1] Unquestionably, silyl linkers have become a popular means of attachment to the solid phase due to their extensive history in natural product synthesis, the ability to vary sterically and stereoelectronically the nature of the groups appended to silicon, and the mild, chemospecific cleavage conditions.[5] To date, the silyl linkers that have been disclosed have been prepared on 1−2% DVB cross-linked polystyrene, a matrix in which greater than 99% of the silyl moieties are contained within the resin matrix leaving less than 1% of the attachment sites outside the resin's hydrophobic core.[1,2] One typical protocol to construct silyl resins involves the direct lithiation of polystyrene followed by trapping with virtually any dialkylchlorosilane; however, this procedure affords resin with variable loading capacities and inconsistent results from lot to lot.[6] Other strategies rely on various hydrosilylation procedures.[7] Of these, Argonaut Technologies has developed a commercially viable route to access large quantities of a TES congener on polystyrene, PS-DES (0.6−1.6 mmol/g). To arrive at a more robust diisopropylsilyl derivative or a simple dimethyl derivative, additional steps and an expensive platinum catalyst are required to ultimately afford resin with low loading capacity (∼0.5−0.7 mmol/g).[7b]

Scheme 1. High-Loading Rasta-NCO Resins



Solid-supported polymerization strategies have recently provided access to alternative polymer architectures which may provide enhanced chemical environments for solid-phase reaction sequences and reagent scavenging as well as the need for achieving greater loading capacities.[8] Of the strategies for creating unique polymer architectures, living free radical polymerization, initiated thermally by nitroxides such as 1-phenethyl-TEMPO, has garnered a great deal of attention.[9] In a recent report from these laboratories, living free radical polymerization was employed to access large, high-loading isocyanate resins for scavenging amines (Scheme 1).[10] In the event, TEMPO-methyl resin **1** is heated at 130 °C in a capped tube with 65% **2** and 35% styrene to afford resin **3** with a loading level of ∼2.5 mmol NCO/g. The term "Rasta resin" was coined to describe this new type of resin

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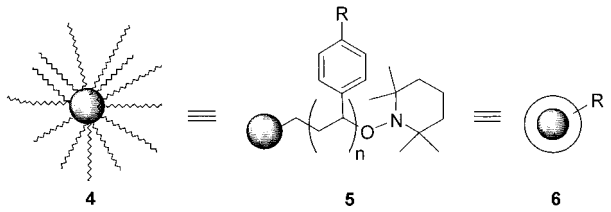
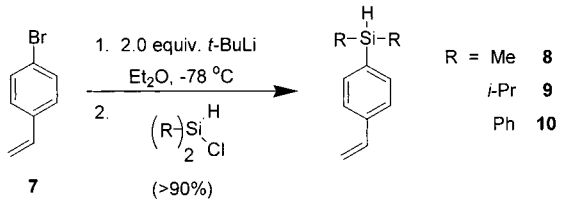


Figure 1. Rasta resin cartoon architecture and shorthand representation.

Scheme 2. Synthesis of Silyl Styrene Monomers



bead in which linear polymers bearing the isocyanate moiety emanate from the phenyl groups of a core, cross-linked polystyrene bead.

Rasta resins offer a novel macromolecular architecture where pendant functionalities, and hence the supported reactions themselves, are not located in cross-linked regions of the polymer matrix as is the case with traditional 1−2% DVB cross-linked polystyrene. Additionally, high loading capacities can be realized. In Figure 1, the architecture of a generic Rasta resin **5** can be depicted by a cartoon structure **4** in which hair-like appendages represent new polymer growth from the original cross-linked bead (shaded circle). An alternative and perhaps more realistic representation of **4** is illustrated by **6** in which the shaded inner circle again signifies the original cross-linked bead while the white outer circle represents the new linear polymer. The new polymer represents the majority of the mass of the bead (typically around 80%), so it is likely that much of this linear polymer extends beyond the original bounds of the bead. Studies to understand the precise physical location of functional groups in Rasta resin beads are in progress in our labs and will be reported in due course.

In principle, R can be almost any desired functionality on the new Rasta resin. Moreover, by careful selection of comonomers in the polymerization step, control can be exercised in regard to the spacing between R groups and the location of the R groups with respect to the original core bead.[10,11] This is in sharp contrast to the uncontrolled spacing and location of R groups that is possible by chemical modification of an existing polymer bead.[1,2] Therefore, we sought to develop a high-loading silyl congener of our Rasta resin in an effort to introduce an alternative chemical environment, fundamentally different from that of 1−2% DVB cross-linked polystyrene, Tentagel, and macroporous supports for those engaged in solid-phase organic synthesis. With this goal in mind, we now add the following results to the increasing literature on solid-supported living free radical polymerization.

Results and Discussion

As shown in Scheme 2, the required silyl substituted styrene monomers for the solid-supported living free radical polymerization protocol with **1** were readily synthesized by lithium−halogen exchange employing *p*-bromostyrene **7** and subsequent quenching with the appropriate dialkylchlorosilane. For the present study, we generated the dimethyl (**8**), diisopropyl (**9**), and diphenyl (**10**) congeners in excellent isolated yields (>90%) as stable water-white oils. Surprisingly, only **8** and **10** were previously described in the literature.[12] All attempts to synthesize the di-*tert*-butyl derivative failed, and the required diethylchlorosilane for a diethyl congener was no longer commercially available.

Scheme 3. High-Loading Rasta Silane Resins

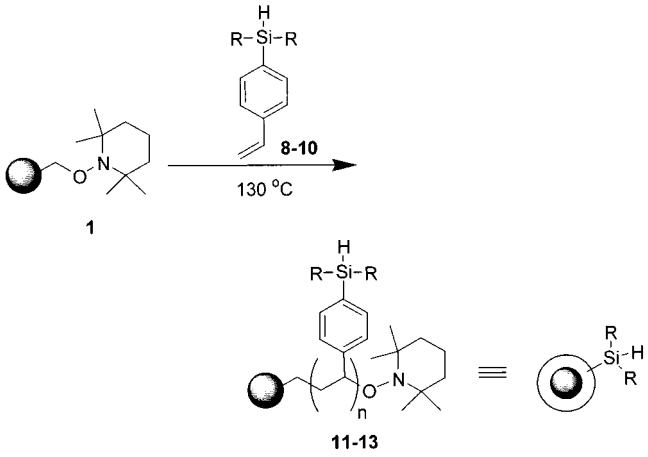


Table 1. Rasta Silanes

Rasta resin	R	styrene molar (xs)	time (h)	P/I[a]	IR (cm^{-1})	Si loading (mmol/g) calcd	Si loading (mmol/g) obs
11	Me	45	20	5.6	2116	5.0	3.8
12	*i*-Pr	45	20	5.0	2102	3.7	2.3
12	*i*-Pr	92	20	4.0	2099	3.4	1.6
13	Ph	45	2.5	4.8	2121	2.9	1.9

[a] P/I = weight of product beads/weight of initator beads.

Living free radical polymerization was initiated (Scheme 3) by heating TEMPO-methyl resin **1** with the silyl styrenes **8**−**10** under solvent free conditions at 130 °C which led to complete solidification of the monomers and the formation of Rasta silanes **11**−**13** (Table 1). After cooling, DCM was added, the polymeric mass was filtered, and the precipitate was subjected to alternating wash cycles of DCM and MeOH, providing free-flowing resin beads noticeably larger than the starting (75−150 μM) 100−200 mesh **1**. After drying to constant weight under reduced pressure, **11**−**13** were found to have undergone significant mass increases (∼5-fold) while the beads still remained spherical in shape.[13] Figure 2 shows photographs of **1** and **12** at equal magnification. Silicon analysis provides experimental evidence for loading levels that range from 1.6 to 3.8 mmol/g. This is less than the calculated loading based upon the observed mass increase. The discrepancy between predicted silicon content based upon observed mass increase and observed silicon content is poorly understood at present and is the subject of additional ongoing studies. All of the resins in Table 1 displayed a strong Si−H stretch in the their respective IR spectrum at ∼2100 cm^{-1}. Notably, the Rasta silanes **11**−**13** do not stick to the walls of glass vessels as do PS and TG resins, and they are very difficult to grind in a mortar and pestel as

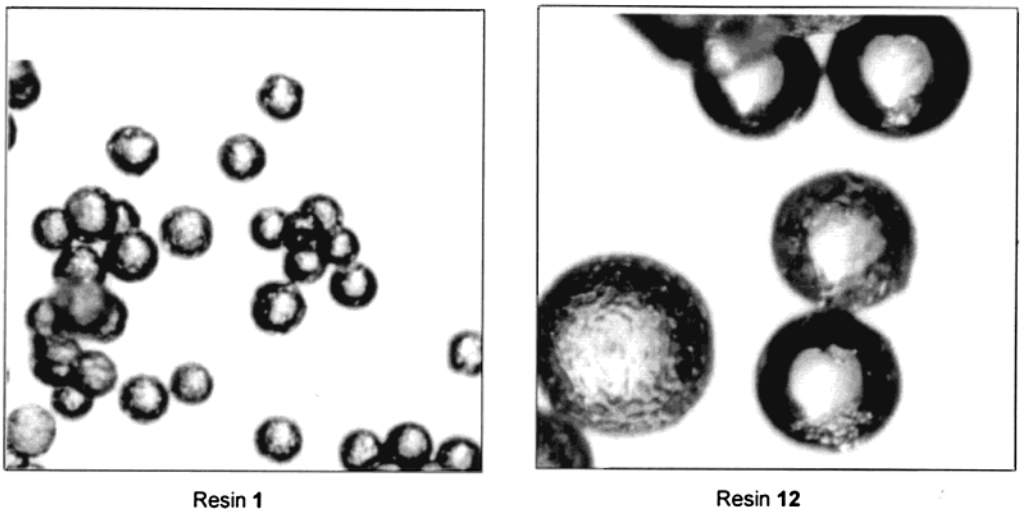


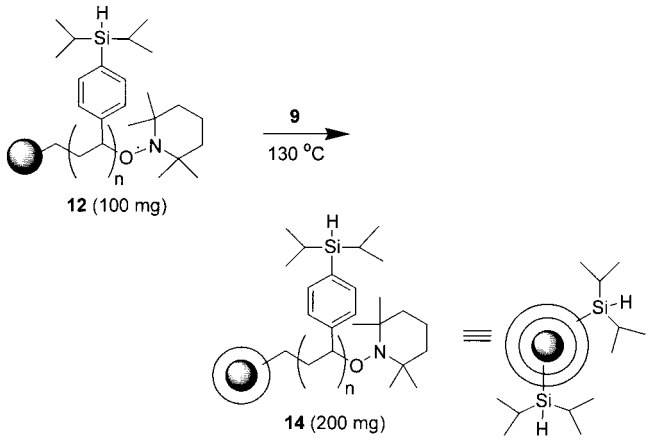
Figure 2. Resin photographs (equal magnification).

compared to **1** which readily grinds to a powder. Qualitative observation shows that the Rasta silanes swell in DCM, THF, DMF, and NMP while shrinking in MeOH and water.

For the remainder of this study, our efforts focused on "Rasta-DIPPS" **12** and related polymers. These derivatives were chosen due to the robust nature of the diisopropylphenylsilyl moiety, as a TIPS congener, and its previous success and stability to a wide-range of organic reagents in SPOS.[5a,5b,14] Consistently, a 5-fold mass increase was observed from lot to lot of **12**. For example, living free radical polymerization of **1** (100 mg, 0.1 mmol, 1.0 mmol/g) with **9** (1.00 g, 4.5 mmol, 45 molar excess) in three side-by-side trials at 130 °C for 20 h produced resin beads that weighed 505 mg, 500 mg, and 505 mg with loading levels of 2.3, 2.0, and 2.1 mmol/g, respectively (IR: strong Si−H at ∼2100 cm^{-1}). The loading levels were determined by silicon analysis (6.5%, 5.6%, 5.8%, respectively). Larger quantities of **12** could be produced with a consistent 5-fold mass increase as well. In this case, exposure of **1** (500 mg, 0.5 mmol, 1.0 mmol/g) to **9** (4.9 g, 22.5 mmol, 45 molar excess) at 130 °C for 20 h provided 2.51 g of resin with a loading level of 2.35 mmol/g (IR: strong Si−H at 2101 cm^{-1}).

The loading capacity of Rasta-DIPPS **12** could not be increased beyond 2.3 mmol/g (5-fold increase in mass) by simply doubling the amount of **9** (2.00 g, 9.0 mmol, 90 molar excess) in the polymerization step. This was due to the propensity of **9** to undergo self-polymerization as a result of poor dispersion of **1** in the large excess volume of **9** at the temperature required for living free radical polymerization. In fact, utilizing a 90 molar excess of monomer resulted unexpectedly in a diminished loading capacity of 1.58 mmol/g (4.44% Si) with only a 4-fold increase in resin mass. Fortunately, the loading capacity of **12** (100 mg, 0.23 mmol, 2.3 mmol/g) could be increased above 2.3 mmol/g by reexposure to **9** (1.00 g, 4.5 mmol, 20 molar excess) for a second round of living free radical polymerization (Scheme 4). After 48 h at 130 °C, Rasta resin **14** was produced that had undergone a 2-fold increase in mass with a loading capacity (8.49% Si) of 3.0 mmol/g (IR: strong Si−H at 2099 cm^{-1}). A shorthand description is illustrated in which the two colorless bands indicate two rounds of living free radical

Scheme 4. Increased Loading



polymerization. The high-loading Rasta resin **14** produced remained spherical in shape (Figure 3). Moreover, beads of **12** and **14** grown from 75 to 150 μM TEMPO resin (**1**) are larger than commercially available 200−250 μM Tentagel beads (Figure 3, far right).

By addition of α-methylstyrene as a comonomer, the living free radical polymerization process offers the ability to increase the spacing between silane moieties and to attenuate the loading capacity.[10,11] Therefore, when **1** (200 mg, 1 mmol/g, 0.2 mmol) is heated with a 45 molar excess of monomers as a mixture of **9** (698 mg, 3.2 mmol, 35 mol %) and α-methylstyrene (684 mg, 5.8 mmol, 65 mol %), Rasta resin **15** results. The product resin beads had a 4.1-fold mass increase over the starting beads (825 mg grew from 200 mg). Based upon analogy to the literature describing the copolymerization of 35 mol % styrene and 65 mol % 3-isopropenyl-α,α-dimethylbenzyl isocyanate (TMI),[11] the new polymer growth should at first approximation be alternating methylstyrene and **9** as shown in Scheme 5. However, as is seen with the resins in Table 1, the loading of **15** based upon silicon analysis (0.8 mmol/g) is less than what would be predicted from mass gain (2.3 mmol/g), assuming equal incorporation of comonomers. Since α-methylstyrene does not polymerize onto **1** in the absence of a comonomer, it is unlikely that the low silicon content is attributable to preferential incorporation of α-methylstyrene from the

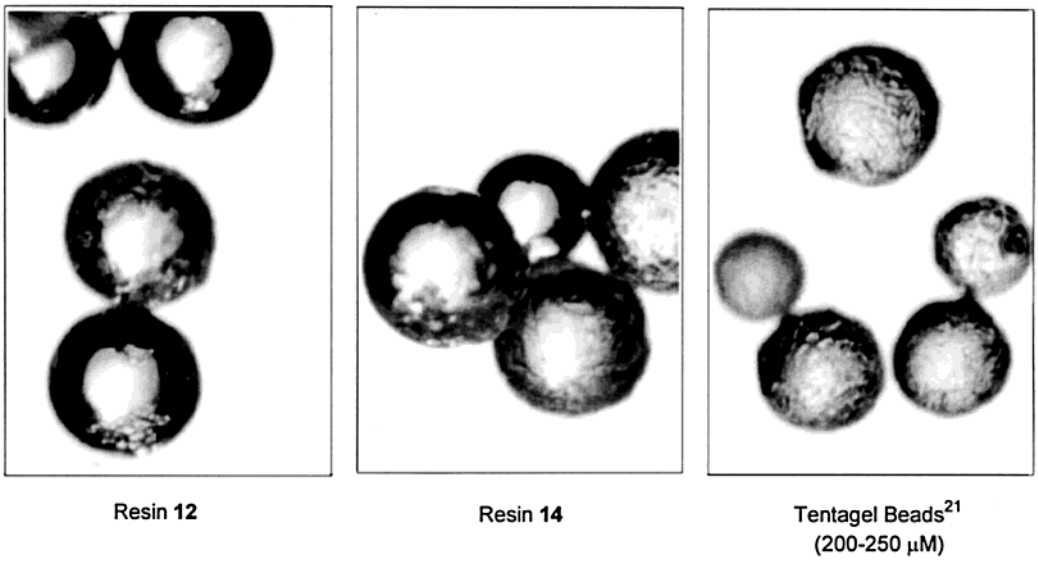
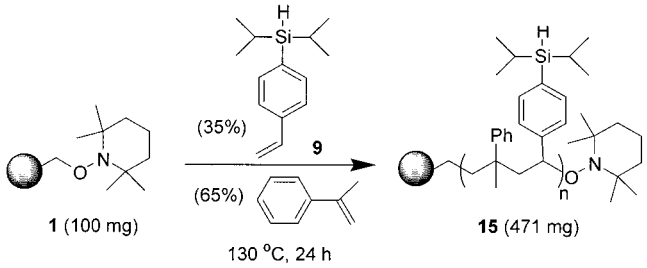
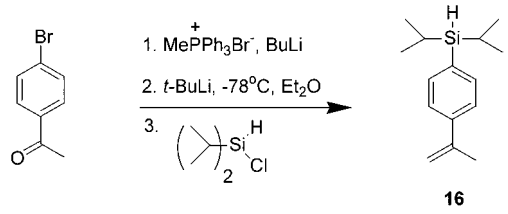


Figure 3. Resin photographs (equal magnification).

Scheme 5. Controlled Spacing



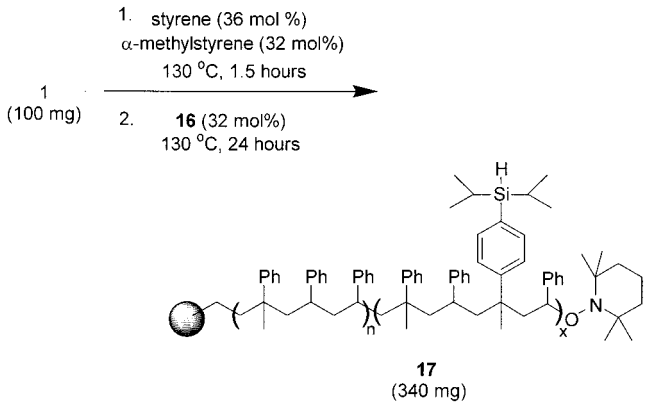
Scheme 6. Synthesis of *p*-Diisopropylsilyl-α-methylstyrene



comonomer mixture. Thus, although the exact architecture of the side chains cannot be precisely described from the data herein, there is a low probability that two adjacent monomer units would contain a silane moiety.

A strategy to confine the silane moiety to the distal region of the new polymer growth employs the previously unknown *p*-diisopropylsilyl-α-methylstyrene **16** which was prepared in a straightforward manner (Scheme 6) in two operations in 80% overall yield. Thus TEMPO-methyl resin **1** (150 mg, 1 mmol/g, 0.15 mmol) was first heated with a mixture of styrene (253 mg, 2.43 mmol, 36 mol %) and α-methylstyrene (309 mg, 2.16 mmol, 32 mol %) for 1.5 h. Then **16** (502 mg, 2.16 mmol, 32 mol %) was added to the monomer feed, and heating continued for 20 h to afford 340 mg of Rasta silane **17** (Scheme 7). The resulting large resin beads underwent a 2.3-fold mass increase, and the Si−H stretch was again observed at 2100 cm^{-1} in the IR spectrum. This protocol grows two blocks of new polymer on the bead with the silane containing monomer confined to the outer block, at the tips of the new polymer growth. Resin **17** has a loading capacity of 0.38 mmol/g (1.07% Si).

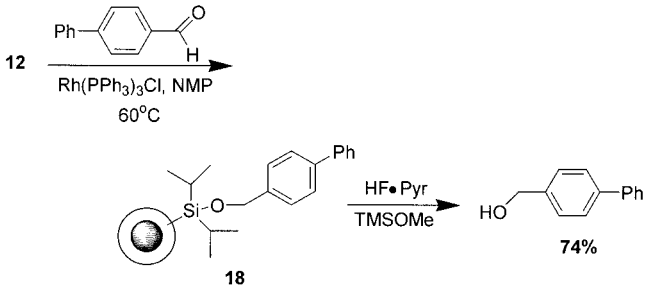
Scheme 7. Tip Functionalization via Late Addition of Functional Monomer



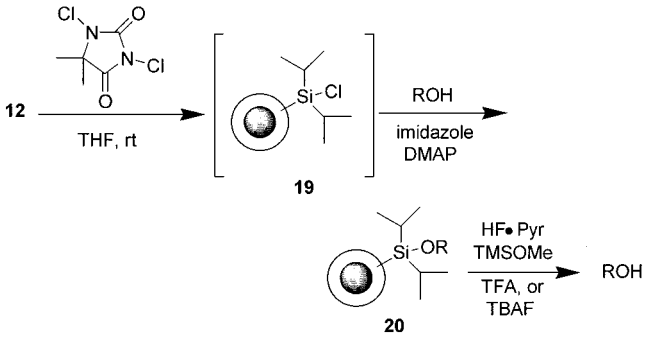
The methods of the preceding two paragraphs illustrate significant opportunities to control the loading, spacing, and location of the silane moiety along the linear polymeric chain. This provides a rational approach to aid in solving the problem of intrabead site−site interactions by custom design of the polymer for any given reaction sequence.[15] Prior to this, the only tools at the chemist's disposal utilizing preformed solid supports were empirical in nature and relied on two observations regardless as to the nature of the resin matrix. First, intrabead interactions could be diminished by lowering the loading level of the resin, and second, linker architecture was shown to exert a strong influence.[16] However, neither tool, alone or in combination, can completely prevent intrabead site−site interactions.

As described elsewhere in the literature, the shelf-stable silane moiety offers numerous opportunities for the attachment of a myriad of functional monomers to the solid phase: Rh(I) catalyzed hydrosilylation/alcoholysis of carbonyl compounds/alcohols, respectively,[17] and conversion to either a reactive silyl chloride[4,7b] or triflate[18] for loading alcohols, phenols, aromatics, and acetylenes. As depicted in Scheme 8, Rasta-DIPPS **12** facilitated the loading of a carbonyl compound by the hydrosilylation of *p*-phenylbenzaldehyde, employing Wilkinson's catalyst, to produce resin **18**. Due to the increased steric bulk of the DIPPS moiety, a

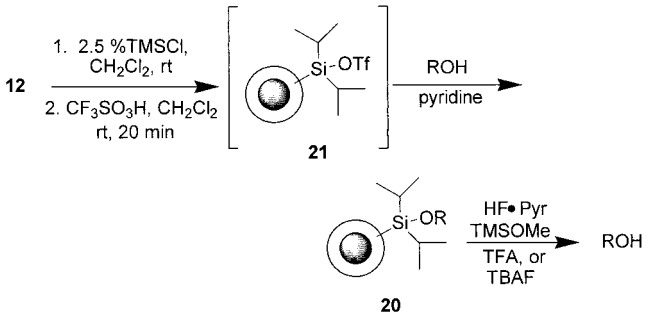
Scheme 8. Hydrosilylation with Rasta-DIPPS



Scheme 9. Conversion of Rasta-DIPPS to Rasta-DIPPSCI

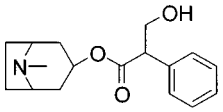
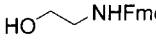
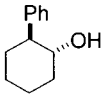
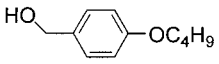
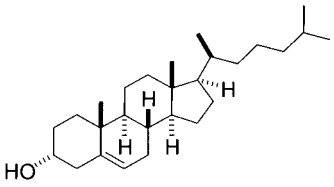
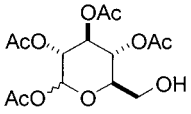
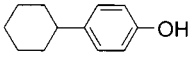


Scheme 10. Conversion of Rasta-DIPPS to Rasta-DIPPSOTf



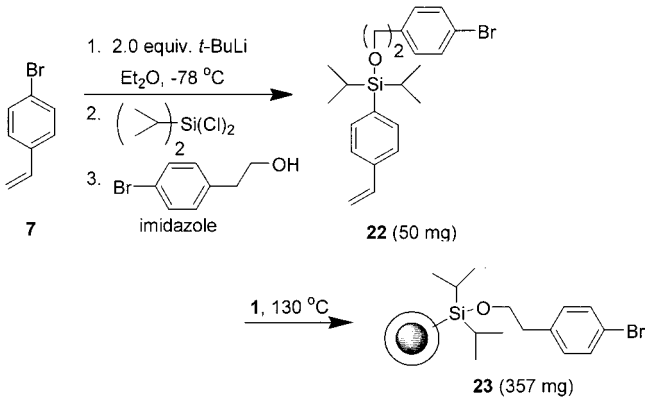
longer reaction time was called for than in the case of PS-DES.[17] Exposure of resin **18** to HF·pyridine/THF followed by TMSOMe as an HF scavenger produced *p*-phenylbenzyl alcohol in 74% yield for the three-step sequence. For a more general synthetic application, Rasta-DIPPS **12** could be smoothly converted into the reactive silyl chloride **19** by treatment with 1,3-dichloro-5,5-dimethylhydantoin in DCM according to a modified protocol of Porco et al.,[4,7b] followed by exposure to an alcohol in the presence of imidazole/DMAP to afford resin **20** (Scheme 9). Again following a protocol set forth by Porco et al.,[18] **12** could also be converted into the very reactive silyl triflate **21** upon exposure to trifluoromethane sulfonic acid (Scheme 10) which afforded yields similar to those achieved with **19**, but with abbreviated reaction times (3 h versus 24 h). Cleavage was affected by exposure to HF·pyridine utilizing TMSOMe as a scavenger, 20% TFA/DCM solutions, or TBAF; as expected, excellent isolated yields (63−88%) were achieved for the three-step activation/loading/cleavage sequence. As seen in Table 2, functionalized primary (entries 1, 2, 4) and secondary alcohols (entries 3, 5), carbohydrates (entry 6), and phenols (entry 7) participate. No evidence of TEMPO cleavage was observed by NMR of the crude cleavage products, and the

Table 2. Loading and Cleavage of Alcohols with Rasta-DIPPS

Entry	Substrate	Yield [1] (via **19**)	Yield [1] (via **21**)
1		77%[c]	NA
2		85%[a]	NA
3		88%[b]	84%[b]
4		83%[a]	80%[a]
5		63%[a]	70%[a]
6		72%[a]	NA
7		80%[a]	NA

[1] Yield for the two-step sequence of loading/cleavage and based on the initial loading of Rasta-DIPPS. a: cleavage with HF·pyr. b: cleavage with 20% TFA/DCM. c: cleavage with TBAF. NA: not attempted. All compounds were fully characterized and identical to authentic samples.

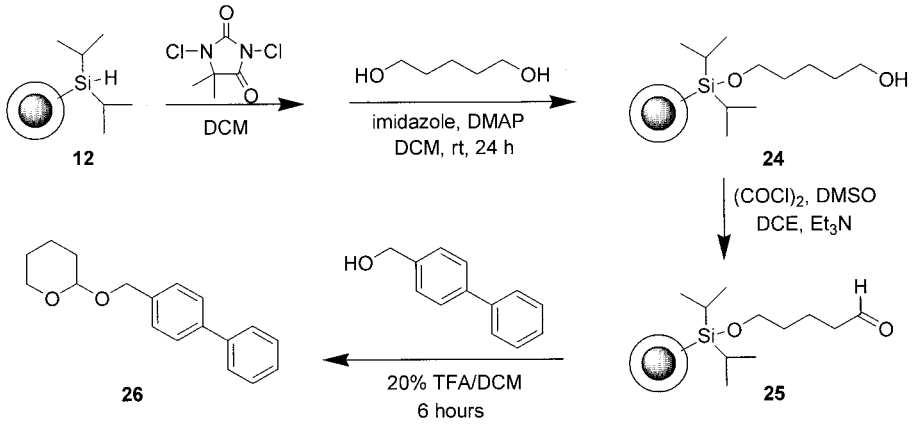
Scheme 11. Alternative Polymerization Strategy



isolated yields correlate well with loading capacities derived from silicon analysis.

The solid-phase loading step can be avoided altogether by preloading the desired monomer in solution, and then initiating living free radical polymerization (Scheme 11). In this instance, *p*-bromostyrene is again subjected to Li−Br exchange and quenched, via reverse addition, with a slight excess of dichlorodiisopropylsilane. To this solution is then

Scheme 12. Synthetic Sequence with Rasta-DIPPS



added *p*-bromophenethyl alcohol and imidazole producing, after isolation, styrene **22** in a modest 45% yield. Heating **1** (50 mg, 0.05 mmol, 1.0 mmol/g) with **22** (938 mg, 2.25 mmol, 45 molar excess) at 130 °C for 20 h led to complete solidification of the monomer and the formation of **23**. After cooling, DCM was added, and the polymeric mass was filtered and then subjected to alternating wash cycles of DCM and MeOH, providing free-flowing resin beads noticeably larger than the starting 100−200 mesh **1**. After being dried under reduced pressure, **23** was found to have undergone significant mass increase (7-fold) and bromine analysis (16.07% Br) corresponding to a loading of 2.0 mmol/g. Cleavage from the resin under standard HF·pyridine conditions afforded an 83% yield of *p*-bromophenethyl alcohol.

To further demonstrate the applicability of Rasta-DIPPS **12** for SPOS, a short synthetic sequence was undertaken (Scheme 12). Once again, **12** was converted into the reactive silyl chloride **19** and then treated with an excess of 1,5-pentanediol under otherwise standard conditions to produce **24**. Exposure of the resin bound primary alcohol to Swern oxidation conditions afforded aldehyde **25**. When resin **25** was subjected to our standard 20%TFA/DCM cleavage conditions in the presence of *p*-phenylbenzyl alcohol, the tetrahydropyranyl ether **26** was obtained in 62% overall yield for the four-step sequence. This yield implies an average yield of 88−89% for each step and is consistent with the initial resin loading as determined by silicon analysis. After each step, the resin washes were analyzed for evidence of TEMPO cleavage; fortunately, the TEMPO moiety remained intact over the course of the synthesis and was found to be quite resilient to a number of common organic reagents. Note, when viewed under a microscope, virtually none of the resin beads suffered "breakage" during the overall four-step synthesis from **12**. The low occurrence of bead "breakage" is most likely attributed to a lack of cross-linking in the new polymer growth of the Rasta silanes.[8d]

Summary

In summary, a new class of high-loading silyl resins, Rasta silanes, has been developed. These resins offer unique macromolecular architecture, fundamentally different from polystyrene and Tentagel, derived from living free radical polymerization of TEMPO-methyl resin and silyl styrene monomers under solvent free conditions. Rasta silanes offer several advantages over existing supports: (1) consistent growth and loading, (2) pendant silanes are attached only to the new polymer portion of the bead where there is no cross-linking, (3) linker loading, spacing, and location are easily customized, (4) high loading on large beads permits isolation of significant product from a single bead, and (5) Rasta resins are resistant to breakage. In addition, conversion of Rasta-DIPPS **12** to a reactive silyl chloride or triflate by standard synthetic methods allows the subsequent immobilization of alcohols and phenols for solid-phase synthesis and isolation of product after chemoselective cleavage by fluoride. Moreover, the solid-phase loading sequence can be avoided by appending desired substrates to the silane monomer while in solution, followed by attachment to the solid support via living free radical polymerization. Finally, by virtue of their ease of preparation and higher loading, Rasta silanes should eventually reduce the cost of silyl linker resins per millimole once economies are realized through large scale production of dialkylsilane styrene monomers. Although the experimentally observed silane content is somewhat lower than expected from the mass gained by living free radical polymerization, the Rasta silanes still afford linking capacities (1.6−3.8 mmol/g) that are significantly higher than other silicon-linker resins from current commercial sources (0.5−1.6 mmol/g).

Experimental Section

General. TEMPO-methyl resin, **1**, was prepared as previously described starting from Merrifield resin purchased from Novabiochem (product number 01-64-0070, 100−200 mesh, 1% cross-linking, 1.2 mmol of Cl per gram of resin).[10] Polymerization reactions were carried out under N_2 atmosphere in capped tubes. Heating was provided by an aluminum well dry bath (Barnstead Thermolyne model DB28215) with temperature monitored by a thermometer inserted into the reaction block. Gentle agitation was achieved by shaking the dry bath on an orbital stirrer. Drying of resin was accomplished by heating at 50 °C in a vacuum (10−12 mmHg) to constant weight (overnight). Chlorination and triflation reactions of the Rasta silanes were carried out in oven-dried solid-phase peptide synthesis vessels purchased from ChemGlass (CG-1866-04) with agitiation provided by a LabLine 3D rotator. 1,3-Dichloro-5,5-dimethylhydantoin (98% Cl) and the dialkylchlorosilanes were purchased from

Fluka. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus instrument (400 MHz/100 MHz). IR spectra were obtained by pulverizing the resin beads and fixing the powder into a KBr pellet. IR absorptions are reported in cm^{-1}. Elemental analyses were performed by Quantitative Technologies Inc.[19]

TEMPO-Methyl Resin (1). A solution of sodium ascorbate (12 g, 60 mmol) in water (150 mL) was shaken with a solution of TEMPO$^\bullet$ in Et_2O (125 mL) until the deep red burgundy color faded to a pale orange. The Et_2O layer was separated and dried over $MgSO_4$ and concentrated in vacuo to afford an orange oil. The oil was then dissolved in dry DMF (50 mL) and added dropwise over 10 min to a stirred, septum-capped flask of NaH (1.5 g, 37.5 mmol, 60% mineral oil dispersion) and DMF (50 mL) under an N_2 atmosphere. After 30 min, Merrifield resin (5.0 g, 6.0 mmol) was quickly added, and the septum immediately replaced. Stirring was continued for 16 h at 22 °C. The reaction flask was then cooled in an ice water bath and quenched carefully with cold water while stirring the contents of the flask. The pale yellow resin was collected by filtration and washed successively with 35−40 mL portions of DMF, H_2O, MeOH, H_2O (×2), MeOH (×2), DCM then MeOH (×3), DCM (×2), and hexanes. The resin was then dried overnight at 0.5 mmHg, 25 °C to afford 5.6 g of **1**. Found: C, 87.87; N, 1.39; Cl, 0.12; indicates ∼1.0 mmol TEMPO-methyl residues per gram based upon N content.

General Procedure for Preparing *p*-Dialkylsilane Styrenes 8,[12] 9−10. To an oven-dried 250 mL round-bottom flask, equipped with stir bar and cooled/purged under a stream of N_2 gas, was placed dry Et_2O (150 mL, 0.2 M) and cooled to −78 °C. *tert*-Butyllithium (39 mL, 1.7 M in pentane, 66 mmol) was added via syringe, followed by the dropwise syringe addition of *p*-bromostyrene (4.33 mL, 33 mmol). The solution rapidly changed from bright red to a deep orange hue. After 20 min at −78 °C, a dialkylchlorosilane (33 mmol) was added dropwise via syringe. The bath was removed, and the reaction was allowed to slowly warm to room temperature. The color lightened to a pale yellow, and the salts precipitated out after 2 h. The reaction was then quenched with water, extracted into hexanes, and washed with brine. Concentration in vacuo and column chromatography [hexanes doped with 2% Et_3N] and/or distillation afforded (>90%) of a water-white oil.

***p*-Diisopropylsilane Styrene (9).** Yield: 6.6 g (92%) of a water-white oil. TLC [hexanes] $R_f = 0.85$. IR (thin film) cm^{-1}: 3064, 3012, 2943(s), 2685(s), 2101(s, Si−H), 1462. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, $J = 8$ Hz, 2H), 7.37 (d, $J = 8$ Hz, 2H), 6.69 (dd, $J = 10.9$, 17.5 Hz, 1H), 5.77 (d, $J = 17.5$ Hz, 1H), 5.24 (d, $J = 17.5$ Hz, 1H), 3.91 (m, 1H), 1.2 (m, 2H), 1.04 (d, $J = 7.3$ Hz, 6H), 0.97 (d, $J = 7.3$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 137, 136, 134, 125.7, 114.3, 18.8, 18.7, 11. Calcd for $C_{14}H_{22}Si$: C, 76.99; H, 10.15; Si, 12.86. Found C, 76.79; H, 10.25; Si, 12.96.

***p*-Diphenylsilane Styrene (10).** Yield: 6.7 g (92%) of a water-white oil. TLC [hexanes] $R_f = 0.80$. IR (thin film) cm^{-1}: 3067, 3011, 2121 (s, Si−H), 1428, 1111, 799. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 6H), 7.37 (m, 8H), 6.7 (dd, $J = 11$, 17.5 Hz, 1H), 5.8 (d, $J = 17.5$ Hz, 1H), 5.44 (s, 1H), 5.27 (d, $J = 17.5$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139, 136.9, 136.3, 136, 133.5, 133, 130, 128.4, 128.3, 126, 125, 115. Calcd for $C_{20}H_{18}Si$: C, 83.86; H, 6.33; Si, 9.80. Found: C, 84.00; H, 6.40; Si, 9.70.

Rasta-DMPS (11). A suspension of TEMPO-methyl resin, **1** (56 mg, 1.0 mmol/g, 0.056 mmol), in **8** (408 mg, 2.5 mmol, 45 molar excess) was heated at 130 °C for 20 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded, on average, 316 mg of **11** (a 5.6-fold mass increase) as large, white beads. IR cm^{-1}: 2101(s, Si−H). Found: Si, 10.8%, which correlates to a loading of 3.8 mmol/g.

Rasta-DIPPS (12). A suspension of TEMPO-methyl resin, **1** (100 mg, 1.0 mmol/g, 0.10 mmol), in **9** (1.0 g, 4.5 mmol, 45 molar excess) was heated at 130 °C for 20 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded, on average, 500 mg of **12** (a 5-fold mass increase) as large, white beads. IR (KBr pellet) cm^{-1}: 2101-(s, Si−H). Found: Si, 6.5%, which correlates to a loading of 2.3 mmol/g.

Rasta-TPS (13). I. Long Reaction Time (20 h). A suspension of TEMPO-methyl resin, **1** (100 mg, 1.0 mmol/g, 0.10 mmol), in **10** (1.28 g, 4.5 mmol, 45 molar excess) was heated at 130 °C for 20 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM and the resin collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded, on average, 450 mg of **13** (a 4.5-fold mass increase) as large, white globular aggregates. IR (KBr pellet) cm^{-1}: 2101(s, Si−H). Found: Si, 7.6%, which correlates to a loading of 2.7 mmol/g.

II. Abbreviated Reaction Time (2.5 h). A suspension of TEMPO-methyl resin, **1** (56 mg, 1.0 mmol/g, 0.056 mmol), in **10** (720 mg, 2.52 mmol, 45 molar excess) was heated at 130 °C for 2.5 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded, on average, 269 mg of **13** (a 4.8-fold mass increase) as large, white resin beads. IR (KBr pellet) cm^{-1}: 2121(s, Si−H). Found: Si, 5.33%, which correlates to a loading of 1.9 mmol/g.

Rasta-DIPPS Resin with Increased Loading Capacity (14). A suspension of Rasta-DIPPS, **12** (100 mg, 2.3 mmol/g, 0.23 mmol), in **9** (1.0 g, 4.5 mmol, 20 molar excess) was heated at 130 °C for 48 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded 200 mg of **14** (a 2-fold mass increase) as large, white beads. IR

(KBr pellet) cm^{-1}: 2099(s, Si−H). Found: Si, 8.49%, which correlates to a loading of 3.0 mmol/g.

Rasta-DIPPS Resin with Controlled Spacing (15). A suspension of TEMPO-methyl resin, **1** (200 mg, 1.0 mmol/g, 0.20 mmol), in a mixture (45 molar excess) of **9** (698 mg, 3.2 mmol, 35 mol %) and α-methylstyrene (684 mg, 5.8 mmol, 65 mol %) was heated at 130 °C for 20 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded 471 mg of **15** (a 4.1-fold mass increase) as large, white beads. IR (KBr pellet) cm^{-1}: 2098(s, Si−H). Found: Si, 2.25%, which correlates to a loading of 0.80 mmol/g.

***p*-Diisopropylsilyl-α-methylstyrene (16).** 4-Bromo-(α-methyl)styrene (5.48 g, 27.82 mmol) was dissolved in 50 mL of diethyl ether and cooled to −78 °C. In another flask, *tert*-butyllithium (32.7 mL of a 1.7 M solution in pentane, 55.64 mmol) was added to 50 mL of ether and cooled to −78 °C. The solution of styrene was slowly cannulated into the lithium solution and stirred for 0.5 h. Diisopropylchlorosilane (4.4 g, 29.21 mmol) in 30 mL of ether was cooled to −78 °C and added slowly to the metal anion solution and then allowed to warm to room temperature over 1 h. The reaction was carefully quenched with water (50 mL), and then the ether portion was separated, washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo. Distillation (85 °C, 0.150 mmHg) gave 2.98 g (92%) of the title compound as a clear colorless oil. TLC [hexanes] $R_f = 0.70$. IR (thin film) cm^{-1}: 3068, 3016, 2943(s), 2685(s), 2101(s, Si−H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49 (d, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 7.6$ Hz, 2H), 5.45 (s, 1H), 5.11 (s, 1H), 3.90 (m, 1H, Si−H), 2.09 (s, 3H), 1.21 (m, 2H), 0.99 (m, 6H), 0.93 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 143.0, 141.8, 135.9, 132.9, 125.4, 113.7, 21.9, 19.2, 19.0, 10.7. Calcd for $C_{15}H_{24}Si$: C, 77.51; H, 10.41. Found C, 77.70; H, 10.50.

Low Loading Rasta-DIPPS Resin with Functionalization on Distal Regions of New Polymer Growth (17). A suspension of TEMPO-methyl resin, **1** (150 mg, 1.0 mmol/g, 0.15 mmol), in a mixture of α-methylstyrene (309 mg, 2.16 mmol, 32 mol %) and styrene (253 mg, 2.43 mmol, 36 mol %) was heated at 130 °C for 1.5 h in a capped vial under an atmosphere of N_2. After this time, **16** (509 mg, 2.16 mmol, 32 mol %) was added, and the reaction was again heated for 20 h. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM/methanol (1:1) (5 cycles) followed by drying in a vacuum oven at 50 °C afforded 340 mg of **17b** (a 2.3-fold mass increase) as large, white beads. IR (KBr pellet) cm^{-1}: 2100(s, Si−H). Found: Si, 1.07%, which correlates to a loading of ∼0.38 mmol/g.

Procedure for Rasta-DIPPS (12) $RhCl(PPh)_3$-Catalyzed Hydrosilylation (18). To a 10 mL oven-dried round-bottom flask cooled/purged under an atmosphere of N_2 was placed Rasta-DIPPS **12** (100 mg, 0.23 mmol, 2.3 mmol/g) *p*-phenylbenzaldehyde (83 mg, 0.46 mmol, 2.0 equiv) and $RhCl(PPh)_3$ (21 mg, 0.023 mmol, 10 mol %). Anhydrous NMP (5 mL) was added, and the reaction vessel was heated to 60 °C for 8 h. (Note, in the Porco et al. procedure, the reaction time was 2 h with PS-DES; in the present case, Rasta-DIPPS, with the bulkier diisopropylsilane moiety, required longer reaction times). After cooling, the resin was filtered and washed with NMP (5 × 5 mL), DCM (5 × 5 mL), MeOH (5 × 5 mL), and finally THF (5 × 5 mL). After drying, the washed resin, **18**, was transferred to a PEG bottle, swollen in THF (4 mL) and HF·pyridine (100 μL) added. After 2 h at room temperature, TMSOMe was added and the suspension agitated for an additional 2 h. The filtrate and THF washings of the resin were concentrated and passed through a small pipet column to provide 32 mg (74%) of *p*-phenylphenethyl alcohol, identical in all respects to an authentic sample.

Representative Procedure for Chlorination of Rasta DIPPS (12), Loading and Cleavage (Table 2, entry 4). To a 50 mL oven-dried solid-phase peptide reaction vessel, cooled and purged under an atmosphere of N_2, was placed Rasta-DIPPS **12** (300 mg, 0.69 mmol, 2.3 mmol/g) and 1,3-dichloro-5,5-dimethylhydantoin (815 mg, 4.14 mmol, 6.0 equiv). Dry DCM (8 mL) was added, and the vessel was placed on an orbital stirrer and agitated at room temperature for 6 h. After this time, the resin was filtered under N_2 and washed with dry THF (3 × 20 mL) and DCM (3 × 20 mL) to remove the excess 1,3-dichloro-5,5-dimethylhydantoin to afford Rasta-DIPPSCl **19**. [The chlorination was monitored by IR, and complete disappearance of the Si−H stretch at ∼2100 cm^{-1} was observed after 6 h.] The resin was then re-swollen in DCM (8 mL), and a DCM solution of 4-butoxybenzyl alcohol (250 mg, 1.38 mmol, 2.0 equiv) and catalytic DMAP (8.4 mg, 0.069 mmol, 0.1 equiv) was added via cannula followed by imidazole (94 mg, 1.38 mmol, 2.0 equiv). The vessel was again placed on an orbital stirrer and allowed to stir for 24 h. After this time, the resin was filtered, washed (×5: DCM, THF, MeOH, hexane), and dried in vacuo. The washed resin was transferred to a PEG bottle and swollen in THF (8 mL), and HF·pyridine (300 μL) was added. After 2 h at room temperature, TMSOMe was added and the suspension agitated for an additional 2 h. The filtrate and THF washings of the resin were concentrated and passed through a small pipet column to provide 103 mg (83%) of 4-butoxybenzyl alcohol.

Representative Procedure for Triflation of Rasta-DIPPS (12), Loading and Cleavage (Table 2, entry 4). To a 50 mL oven-dried solid-phase peptide reaction vessel, cooled and purged under an atmosphere of N_2, was placed Rasta-DIPPS **12** (300 mg, 0.69 mmol, 2.3 mmol/g) and dry DCM (8 mL). TMSCl (17 μL, 1.0 M, 2.5 mol %) was then added, and the contents were agitated to dry the resin and remove all traces of water. The resin was filtered under N_2 and washed with dry DCM (2 × 10 mL). The resin was then re-swollen in DCM (8 mL) and triflic acid (366 μL, 4.4 mmol, 6.0 equiv) was added. The beads changed from colorless to red-orange as the triflate, Rasta-DIPPSOTf **21**, was formed. After 20 min, the resin was filtered and again washed under N_2 with dry DCM (2 × 10 mL). As before, the resin was swollen in DCM (8 mL), and a DCM solution of 4-butoxybenzyl alcohol (250 mg, 1.38 mmol, 2.0 equiv)

and pyridine (109 μL, 1.38 mmol, 2.0 equiv) were added and placed on an orbital stirrer and agitated at room temperature for 3 h. After this time, the red resin beads, corresponding to the triflate **21**, dissipated, and the beads again became translucent. The resin was filtered, washed (×5: DCM, THF, MeOH, hexane), and dried in vacuo. The washed resin was transferred to a PEG bottle and swollen in THF (8 mL), and HF·pyridine (300 μL) was added. After 2 h at room temperature, TMSOMe was added and the suspension agitated for an additional 2 h. The filtrate and THF washings of the resin were concentrated and passed through a small pipet column to provide 99 mg (80%) of 4-butoxybenzyl alcohol.

***p*-[(4-Bromophethyloxy)diisopropylsilyl]styrene (22).** To an oven-dried 250 mL round-bottom flask, equipped with stir bar and cooled/purged under a stream of N_2 gas, was placed dry Et_2O (150 mL, 0.2 M) and cooled to −78 °C. *tert*-Butyllithium (11.7 mL, 1.7 M, 20 mmol) was added via syringe, followed by the dropwise syringe addition of *p*-bromostyrene (1.31 mL, 10 mmol). After 30 min, the styrenyllithium solution was transferred via cannula to an etheral solution of dichlorodiisopropylsilane (4.5 mL, 25 mmol, 2.5 equiv) at −78 °C. The solution was allowed to slowly warm to room temperature at which point *p*-bromophenethyl alcohol (10 g, 50 mmol, 5.0 equiv) was added followed by immidazole (3.4 g, 50 mmol, 5.0 equiv). After stirring at room temperature overnight, the reaction was quenched water and extracted into hexanes. Concentration in vacuo and column chromatography [hexanes doped with 2% Et_3N] afforded 1.9 g (45%) of a water-white oil. TLC [hexanes] $R_f = 0.76$. IR (thin film) cm^{-1}: 3064, 2945, 2866, 1099(s). ^1H NMR (400 MHz, DMSO-d_6): δ 7.43 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.3 (d, $J = 8$ Hz, 2H), 7.18 (d, $J = 8$ Hz, 2H), 6.68 (dd, $J = 10.8$, 17.6 Hz, 1H), 5.82 (d, $J = 17.6$ Hz, 1H), 5.25 (d, $J = 11.2$ Hz, 1H), 3.85 (t, $J = 6.4$ Hz, 2H), 2.78 (t, $J = 6.4$ Hz, 2H), 1.18 (m, 2H), 0.9 (d, $J = 7.2$ Hz, 6H), 0.85 (d, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 139.0, 138.0, 137.0, 132.0, 131.9, 131.5, 125.0, 119.0, 115.0, 64.0, 38.0, 17.9, 17.7, 11.9. Calcd for $C_{22}H_{29}SiOBr$: C, 63.30; H, 7.00; Br, 19.14. Found C, 63.26; H, 7.19; Br, 18.80.

Rasta Resin from Preloaded 22 (23). A suspension of TEMPO-methyl resin, **1** (50 mg, 1.0 mmol/g, 0.05 mol), in **22** (938 mg, 2.25 mmol, 45 molar excess) was heated at 130 °C for 20 h in a capped vial under an atmosphere of N_2. After cooling, the polymeric mass was diluted with DCM, and the resin beads were collected by filtration. Washing with DCM and then methanol (5 cycles) followed by drying in a vacuum oven at 50 °C afforded 357 mg of **23** (7-fold mass increase) as large, white beads. Bromine analysis (16.07% Br) correlates to a loading of 2.0 mmol/g. The washed resin (100 mg, 0.2 mmol) was transferred to a PEG bottle and swollen in THF (4 mL), and HF·pyridine (100 μL) was added. After 2 h at room temperature, TMSOMe was added and the suspension agitated for an additional 2 h. The filtrate and THF washings of the resin were concentrated and passed through a small pipet column to provide 33.6 mg of *p*-bromophenethyl alcohol (83%) identical to an authentic sample.

Conversion of 12 to 24. To a 50 mL oven-dried solid-phase peptide reaction vessel, cooled and purged under an atmosphere of N_2, was placed Rasta-DIPPS **12** (400 mg, 0.94 mmol, 2.35 mmol/g) and 1,3-dichloro-5,5-dimethylhydantoin (1.11 g, 5.64 mmol, 6.0 equiv). Dry DCM (10 mL) was added, and the vessel was placed on an orbital stirrer and agitated at room temperature for 6 h. After this time, the resin was filtered under N_2 and washed with dry THF (3 × 20 mL) and DCM (3 × 20 mL) to remove the excess 1,3-dichloro-5,5-dimethylhydantoin to afford Rasta-DIPPSCl **19**. The resin was then re-swollen in DCM (10 mL), and a DCM solution of 1,5-pentanediol (586 μL, 5.64 mmol, 6.0 equiv) was added, followed by imidazole (128 mg, 1.88 mmol, 2.0 equiv) and DMAP (11.4 mg, 0.094 mmol, 0.1 equiv). The vessel was again placed on an orbital stirrer and allowed to stir for 24 h. After this time, the resin was filtered and washed (×5: DCM, THF, MeOH, hexane) and dried in vacuo.

Swern Oxidation of 24. Rasta Resin (25). To an oven-dried flask, equipped with stir bar and cooled/purged under an atmosphere of N_2, was added dry DCE (8 mL, 0.1 M) and $(COCl)_2$ (341 μL, 3.76 mmol, 4.0 equiv). The reaction vessel was cooled to −78 °C, and dry DMSO (581 μL, 7.52 mmol, 8.0 equiv) was added. The reaction was stirred for 30 min to generate the Swern reagent. Then, the solution was transferred via cannula to a DCE suspension of **24** (400 mg, 0.94 mmol, 2.35 mmol/g) in a 50 mL solid-phase peptide reaction vessel and placed on an orbital stirrer for 3 h. After this time, Et_3N (2.5 mL, 18 mmol, 19.2 equiv) was added, and the reaction was again placed on an orbital stirrer for 2 h. The resin was then filtered, washed (×5) with DCM, THF, H_2O, MeOH and hexanes, and dried in vacuo.

Tetrahydropyranyl-4-phenylbenzyl Ether (26). To a 50 mL oven-dried solid-phase peptide reaction vessel, cooled and purged under an atmosphere of N_2, was placed resin **25** (400 mg, 0.94 mmol, 2.35 mmol/g) and swollen in dry DCM (1 mL). Then, 4-phenylbenzyl alcohol (519 mg, 2.82 mmol, 3.0 equiv) was added, followed by a 20% TFA/DCM solution (5 mL), and the reaction vessel was placed on an orbital stirrer for 6 h. The resin was then filtered and washed with DCM (5 × 10 mL). TLC indicated a new UV spot above that of the starting alcohol which was used in excess. Concentration in vacuo and column chromatography [(20% EtOAc:hexanes) doped with 2% Et_3N] afforded 155 mg (62%) of an orange oil. TLC [20% EtOAc:hexanes] $R_f = 0.68$. IR (thin film) cm^{-1}: 3031, 2942, 2870, 1030(s). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (m, 4H), 7.43 (m, 4H), 7.34 (m, 1H), 4.73 (m, 1H), 4,67 (abquart., $J = 11.9$, 104 Hz, 2H), 3.94 (m, 1H), 3.54 (m, 1H), 1.8−1.5 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 140.0, 137.0, 128.9, 128.5, 127.4, 127.3, 97.0, 68.0, 62.0, 30.0, 25.0, 19.0. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.40; H, 7.58.

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