

Large Scale Preparation of Silicon-Functionalized SynPhase Polystyrene Lanterns for Solid-Phase Synthesis

Troy D. Ryba,[†] Kristopher M. Depew,[‡] and Lisa A. Marcaurelle^{*,†}

Chemical Biology Platform, The Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, Massachusetts 02142

Received June 10, 2008

The two-step functionalization of 30 000 SynPhase Polystyrene (PS) Lanterns in a 30-L glass process reactor is described. The first step involves bromination of the polystyrene backbone to afford an aryl bromide handle. Subsequent Suzuki cross coupling with the trialkylborane generated in situ from the reaction of allyldiisopropyl(4-methoxyphenyl)silane and 9-BBN provided an alkylsilyl linker ready for loading of various alcohols for solid-phase synthesis applications.

Introduction

In our efforts to synthesize a collection of small molecules using diversity-oriented synthesis (DOS),¹ we chose to employ SynPhase Polystyrene (PS) Lanterns for our solid-phase synthesis needs. The core technology of SynPhase Lanterns supplied by Mimotopes is the grafting of a polystyrene mobile surface onto a rigid polypropylene base polymer (Figure 1a).² We found Lanterns to be a practical alternative to conventional polystyrene resins because they offer the advantage of easy handling and simple washing. Lanterns are available in three different sizes, L-series, D-series, and A-series, and have loading levels of 15, 35, and 75 μmol , respectively (Figure 1b). Lanterns are fully compatible with common laboratory equipment and have the added benefit of using radio frequency (Rf) tags for compound tracking, which eliminates the need for chemical decoding.³ Color-coded Rf tags can also be used for rapid identification of quality control (QC) Lanterns at any synthesis step.

Although Lanterns are commercially available with a variety of acid-labile linkers for the immobilization of carboxylic acids, amines, and phenols, (e.g., Rink Amide, HMP, etc.) our DOS platform required the use of an *n*-alkylsilyl linker **1**⁴ (Scheme 1) for loading library scaffolds (**2**) onto a solid support via a primary alcohol. Following the desired scaffold modification (**3** \rightarrow **4**), cleavage of the silyl ether linker can be achieved under mild conditions using HF-pyridine to produce compounds (**5**) suitable for screening. The primary alcohol serves as a common handle for affinity chromatography, small-molecule microarrays, and the attachment of biasing elements (**6a–c**).⁵ The functionalization of macrobeads with the *n*-alkylsilyl linker has previously been reported for the immobilization of alcohol-containing

substrates, albeit on nanomolar scale.^{4,6} Herein, we describe an adaptation of this methodology to the large-scale functionalization of SynPhase PS Lanterns for the synthesis of diverse compound libraries yielding an average of 15 μmol of compound per Lantern.

Results and Discussion

Reactor System Setup/Component Selection. Lantern functionalization was performed in an unjacketed 30-L Chemglass process reactor⁷ placed within a walk-in fume hood (Figure 2). While the use of similarly sized round-bottom flasks could have been adapted for this purpose, a process reactor had several advantages. First, integration of the overhead mechanical stirrer, heating mantle, and temperature controller into the reactor frame provided a compact footprint. Second, a controlled solvent reflux could be sustained by using an external recirculating chiller to cool the condensers, while the reactor could be maintained under an inert environment by sparging with argon through a fritted-tip glass rod inserted into a 45/50 reducing adaptor. Most importantly, upon reaction or wash cycle completion, waste could easily and safely be drained through a bottom drain valve into waste carboys without exposure to the atmosphere.

Lantern Bromination. The first step in the Lantern functionalization protocol involves the incorporation of bromine into the polystyrene backbone. The strategy we

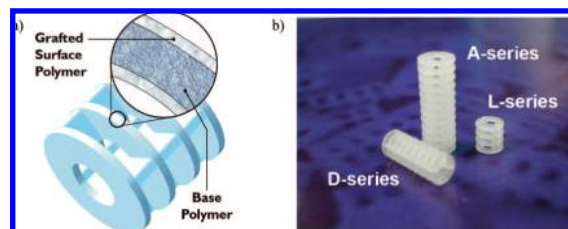


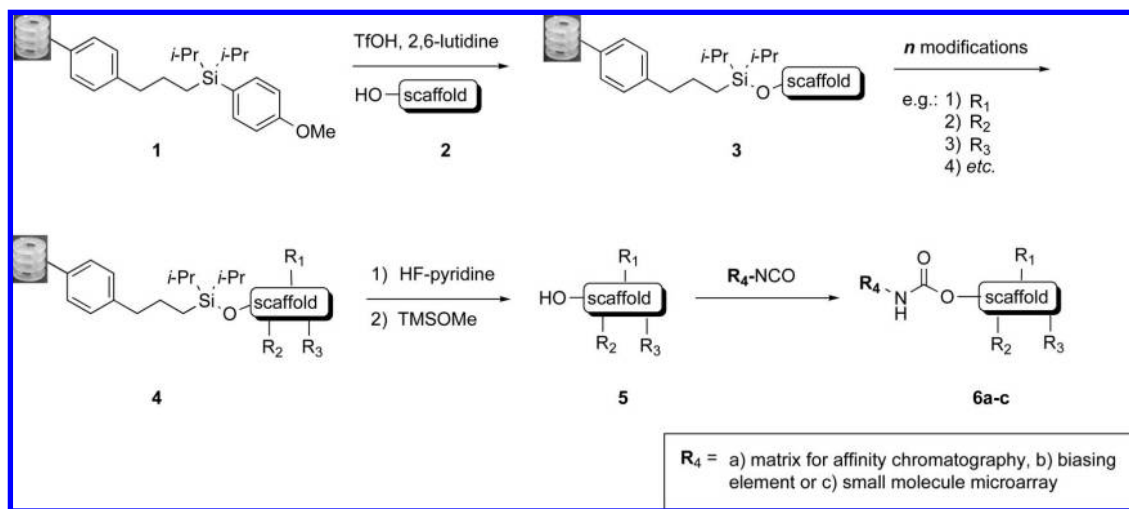
Figure 1. (a) Composition of SynPhase Polystyrene Lanterns. (b) Lanterns are available in three sizes to accommodate different loading needs. A-series: 75 μmol /Lantern. D-series: 35 μmol /Lantern. L-series: 15 μmol /Lantern.

* To whom correspondence should be addressed. E-mail: lisa@broad.mit.edu.

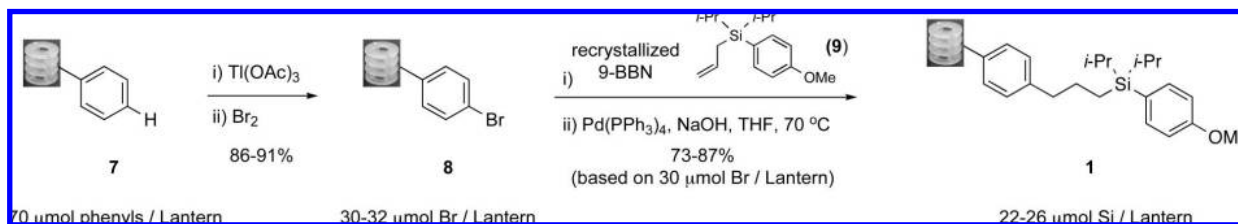
[†] Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, MA 02142.

[‡] Infinity Pharmaceuticals, Inc., 780 Memorial Drive, Cambridge, MA, 02139.

Scheme 1



Scheme 2



employed for the regioselective bromination reaction was based on the original work of Taylor⁸ that was adapted for polystyrene by Fréchet⁹ and then by Tallarico for macrobeads.⁶ The thallium-catalyzed Lantern bromination was straightforward. To begin, Lanterns (7, Scheme 2) were poured into the nondry reactor, suspended in anhydrous, inhibited CH_2Cl_2 and stirred at ambient temperature for 30 min. Thallium (III) acetate¹⁰ was weighed quickly on a top-

loading balance and transferred to the reactor through the 80 mm glass capped port and stirred in the dark for one hour.¹¹ Because of its extreme toxicity and because it was found that thallium (III) acetate could become a dust when transferred, the use of a respirator during this transfer is highly recommended. The dropwise addition of the $\text{Br}_2/\text{CH}_2\text{Cl}_2$ solution afforded an orange suspension that was stirred for an additional three hours at ambient temperature

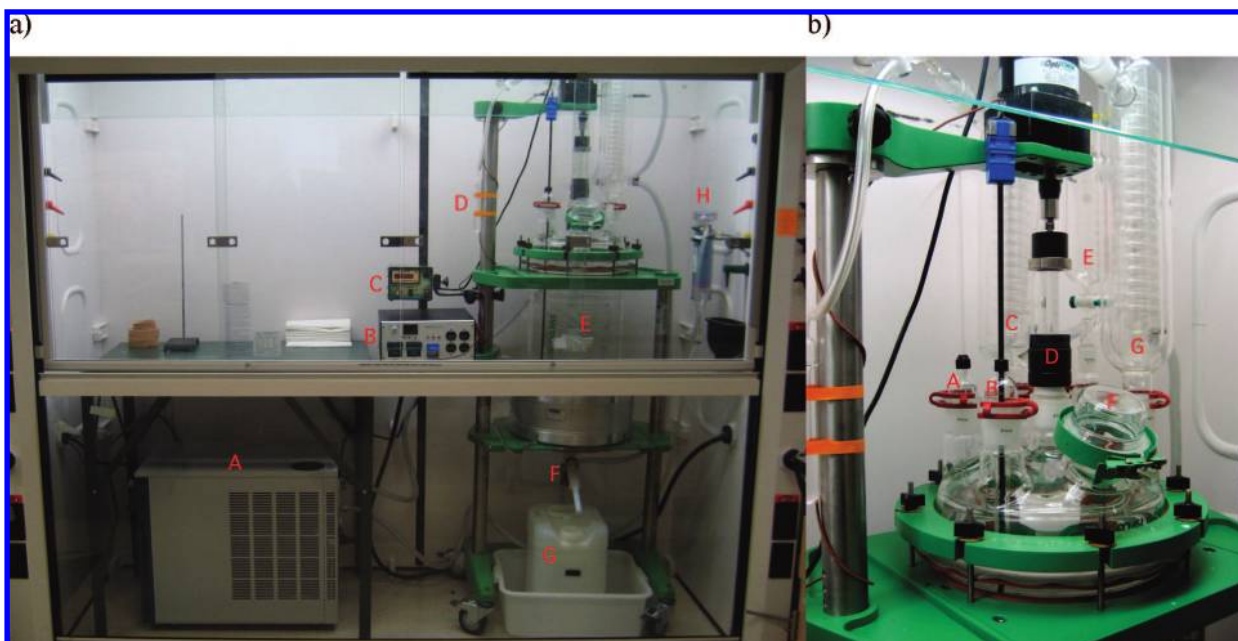
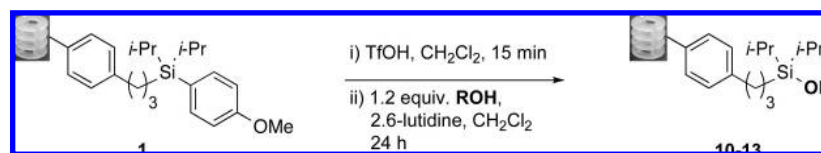


Figure 2. (a) Photograph illustrating the complete setup of the reactor instrumentation: (A) recirculating chiller, (B) thermocouple module, (C) stirring module, (D) bubbler connected to the reactor, (E) glass reactor, (F) drain valve, (G) waste carboy, and (H) Drierite desiccant chamber. (b) Close-up photograph of reactor lid ports: (A) sparging glass rod, (B) thermocouple probe, (C and G) dual reflux condensers, (D) mechanical stirring shaft, (E) dropwise addition funnel, and (F) glass capped port for addition of solids and Lanterns.

Table 1



Entry	Substrate (ROH)	Substrate Loading ($\mu\text{mol/Lantern}$) ^{a,b}	Fmoc cleavage analysis ($\mu\text{mol/Lantern}$) ^c
1)	(10)	19.6 ± 0.7	18.8
2)	(11)	14.0 ± 0.3	14.3
3)	(12)	15.2 ± 0.1	NA
4)	(13)	15.4 ± 0.3	14.9

^a Loading was determined by measuring the mass of material recovered from cleaving ten Lanterns. ^b All recovered material was >95% pure by UPLC analysis monitoring at 210 nm wavelength. ^c Loading estimated based on standard Fmoc cleavage analysis per Gude, M.; Ryf, J.; White, P. D. J. *Prot. Sci.* 2002, 9, 203–206 and www.novabiochem.com.

to give a rusty, slightly off-white suspension. During the bromination sequence, an internal temperature probe indicated a constant temperature throughout. It was found that the addition of methanol at the end of the reaction to the off-white suspension provided more consistent bromination results.¹² After the mixture was stirred for one hour, the reagents were drained, and the brominated Lanterns were subjected to a standard set of washes.¹³ Elemental analysis¹⁴ of the bromine content was determined to be 5.93–6.36%, which converts to 30.4–32.6 $\mu\text{mol/Lantern}$. The target bromination level of 35 $\mu\text{mol/Lantern}$ for the L-series Lanterns comprise one-half of the maximum theoretical number of phenyl rings (70 $\mu\text{mol/Lantern}$) present in the polystyrene copolymer.¹⁵

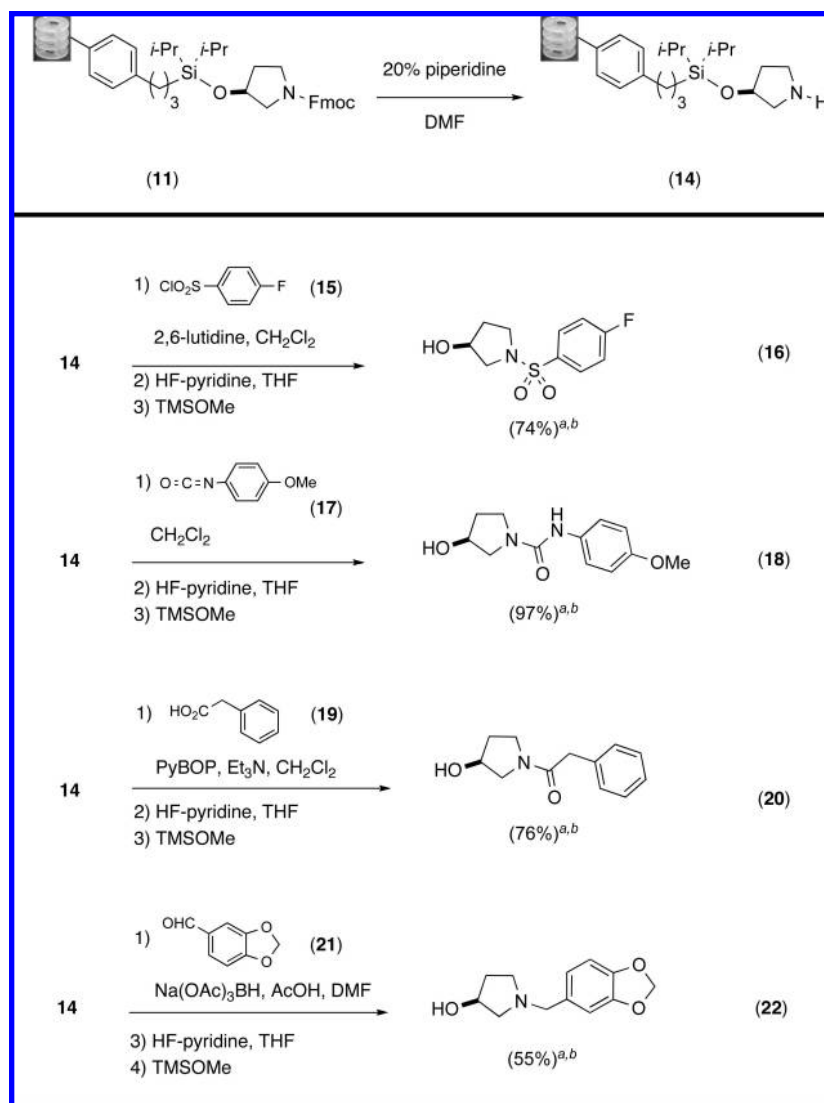
Suzuki Coupling. After achieving sufficient bromination of the polystyrene copolymer backbone, attention was turned to incorporation of the silicon-based linker. The requisite allyldiisopropyl(4-methoxyphenyl)silane was purchased from Maybridge Chemicals,¹⁶ although its three-step synthesis has also been reported.¹⁷ The reactor was prepared for the Suzuki coupling only by rinsing with anhydrous THF and draining the residual solvent. After the viscous but air-stable allylsilane was weighed on a top-loading balance open to the atmosphere, it was poured into the reactor. This was followed by the addition of anhydrous inhibitor-free THF. After the colorless solution was sparged with argon for 30 min, in situ hydroboration was initiated with the addition of freshly recrystallized 9-BBN in one portion. The often slightly discolored commercially available 9-BBN could be used with success, but for safety reasons, 9-BBN recrystallized by the method of Brown and Soderquist¹⁸ was utilized because it provided a nonpyrophoric and moderately air-stable white crystalline solid.¹⁹ A subtle change in solution color from

light yellow to clear was observed with 9-BBN dissolution along with a concomitant 3–5 °C endotherm. Gentle sparging was continued throughout the course of the reaction to promote an inert atmosphere. The progress of the hydroboration was monitored upon removal of a small (2 mL) aliquot of the THF reaction solution from the drain valve (F, Figure 2) and visualization of this nondeuterated solution using No-D NMR.²⁰ After 3 h, nearly all of the alkene had been consumed.²¹

With vigorous sparging, the 80 mm cap was removed and the bromine-functionalized Lanterns were poured into the reactor followed by the subsequent addition of Pd(PPh₃)₄ and aqueous 2 M NaOH. The canary yellow suspension was carefully heated to a gentle reflux (~64–65 °C, internal probe temperature) for 48 h with stirring and slow sparging. After approximately 30 min, the yellow suspension became a dark green color that persisted throughout the course of the reaction. The dark green/black suspension was cooled overnight and the waste then drained into a carboy. The Lanterns were subjected to a standard set of washes,¹³ while the gray-black color from the palladium embedded on the silicon functionalized Lanterns was removed through an additional aqueous NaCN washing sequence. Elemental analysis²² of the silicon content was determined to be 1.45–1.67%, which converts to 22.5–26.1 $\mu\text{mol/Lantern}$.

Substrate Loading Studies. Although elemental analysis indicated that ~22–26 μmol of silicon had been incorporated in the Lanterns, loading studies with a variety of alcohols were carried out to provide a functional measure of linker incorporation. The small molecules chosen for this purpose vary in their level of steric hindrance; they include primary (10) and secondary (11) alcohols, as well as benzylic (12) and phenolic (13) substrates (Table 1). Activation of the

Scheme 3



(a) Yields determined for steps from compound **14**. (b) All material was >95% pure by monitoring UPLC analysis at 210 nm.

Lanterns as the trialkylsilyltriflate was achieved by treatment with excess trifluoromethanesulfonic acid in CH_2Cl_2 for 15 min. The trifluoromethanesulfonic acid solution was removed via canula, and neat 2,6-lutidine was added to the Lanterns prior to the addition of the alcohol in CH_2Cl_2 . The activated Lanterns should be used immediately because they are not stable to prolonged storage. The Lanterns were gently agitated for 24 h at room temperature and then washed thoroughly using a standard set of washes, including CH_2Cl_2 , DMF, and THF. As confirmed by cleavage with 15% HF-pyridine in THF, all substrates tested in this study provided loading levels of >14 μmol using only a slight excess of material (1.2 equiv). As anticipated, the unhindered primary alcohol yielded the highest loading levels (19.6 μmol), while the less reactive substrates were closer to 15 μmol . Interestingly, no noticeable increase in loading was observed when a greater excess of alcohol was used (2.0–5.0 equiv), suggesting that a large excess substrate is not needed to achieve good loading. Unreacted substrates can generally be recovered intact prior to the first CH_2Cl_2 wash. In addition,

extended loading times (>48 h) can be used for more hindered alcohols or substrates with limited solubility in CH_2Cl_2 .

Select Solid-Phase Transformations. To further illustrate the utility of the Lanterns for use in solid-phase synthesis, several common one-step transformations were performed (Scheme 3). First, immobilized hydroxypyrrolidine **11** was exposed to 20% piperidine in DMF for 30 min to afford secondary amine **14**. Coupling of amine **14** to sulfonyl chloride **15** in the presence of 2,6-lutidine readily occurred, and upon cleavage with HF-pyridine, sulfonamide **16** was obtained in 74% yield. Similarly, exposure of **14** to isocyanate **17** provided urea **18** in 97% yield. Amidation of amine **14** with phenylacetic acid (**19**) in the presence of PyBOP proceeded smoothly to afford the corresponding homobenzylic amide **20** (76%). Lastly, reductive alkylation of amine **14** with piperonal (**21**) yielded tertiary amine **22** (55%).

Conclusions

In summary, we have described a safe and efficient process for the large-scale preparation of silicon-functionalized

Lanterns that deliver an average of 15 μmol of compound per Lantern and are suitable for use with DOS libraries. The resulting Lanterns can be stored indefinitely at room temperature and can be used for the loading of a variety of substrates including both primary and secondary alcohols. We have used the Si-functionalized Lanterns to synthesize over 300 000 DOS compounds and have found the linker to be stable to most commonly employed solid-phase reactions conditions, including N-acylations, reductive alkylations, Weinreb amidations, and Suzuki and Sonagashira reactions. Although the use of acids such as TFA, TfOH, and $\text{BF}_3\text{-Et}_2\text{O}$ should be avoided,^{6b} we have found the *n*-alkylsilyl-linker to be stable to most basic conditions.²³ Given the advantages of Lanterns over typical resins, including ease of handling and compound tracking, this two-step functionalization procedure should prove useful for a variety of applications.

Experimental Section

Recrystallization of 9-BBN. The recrystallization of commercially available 9-BBN was performed according to a slightly modified protocol of Brown and Soderquist.¹⁸ A 2-L, 3-neck flask equipped with a large stir bar was flame-dried under vacuum and cooled to room temperature under positive nitrogen gas flow. With vigorous nitrogen gas flow, 9-BBN dimer (200 g, 0.8 moles, Aldrich) was added to the cooled 2-L flask via a powder addition funnel. 1,2-dimethoxyethane (1.3 L) was then measured into a flame-dried graduated cylinder and slowly poured into the 2-L round-bottom flask. The round-bottom flask was immersed into an ice-bath until gas evolution ceased. The central neck was fitted with a reflux condenser connected to a bubbler vent line to monitor gas evolution. The heterogeneous mixture was heated to a gentle reflux until the white solid dissolved. The solution was allowed to slowly cool to room temperature followed by 0 °C overnight. The supernatant was removed by canula under positive nitrogen gas displacement to a dry round-bottom flask and ultimately carefully quenched by the slow addition of MeOH. The resulting white solid was further dried under vacuum at room temperature over 24 h. The crystalline, free flowing white solid was stored at -20 °C (mp = 152–156 °C).

Bromination of PS-grafted Lanterns. For a Target Bromination Level of 35 $\mu\text{mol/Lantern}$. To the nondried 30-L reactor was added 30 000 pearl white Lanterns (70 μmole phenyl rings/Lantern, 2.1 moles, 1 equiv) through the top opening port and the reactor was vigorously flushed with argon for 30 min. Anhydrous CH_2Cl_2 (10.5 L) was poured into the reactor through the top opening port while continuing to flush with argon. Upon complete solvent addition, the solution was sparged with argon while stirring at 160 rpm for 30 min. Thallium (III) acetate (72 g, 0.189 mol, 0.09 equiv) was carefully weighed into a disposable plastic boat open to the atmosphere and quickly added to the reactor in one portion through the top opening port. The outside of the reactor was wrapped in aluminum foil. Lanterns were stirred (160 rpm) for 3 h and the suspension became a creamy yellow color.²⁴ One of the 45/50 ground glass joints on the reactor was equipped with a 24/40 ground glass adaptor fitted

with a 500 mL addition funnel and an argon line to equilibrate the pressure. Bromine was weighed in a hood into a tared 100 mL Erlenmeyer flask (168 g, 1.05 moles, 0.5 equiv) and then quickly transferred to the 500 mL addition funnel. The residual bromine in the Erlenmeyer flask was rinsed with CH_2Cl_2 (2 \times 50 mL) and the bromine/ CH_2Cl_2 solution was combined with the bromine in the addition funnel. The addition of the bromine/ CH_2Cl_2 solution was performed dropwise over 30 min without a concomitant rise in temperature. Upon complete bromine addition, a dark orange-colored solution resulted. The reactor was rewrapped with aluminum foil and stirred for an additional 2 h (160 rpm). At the end of this time, the suspension was an off-white color with a rust tint. Methanol (1.2 L) was added over 10 min using the 500 mL addition funnel, and the solution became slightly yellow-white. After stirring for 30 min, the cloudy solution was drained through the bottom drain valve.²⁵

All solvents used for washing were technical grade. For good mixing in the reactor, 10 L of solvent in the following order were used for each 30 min wash and upon completion were drained into a waste carboy: (1) THF, (2) 3:1 THF/IPA, (3) 3:1 THF/ H_2O , (4) H_2O , (5) 3:1 THF/IPA, (6) THF, (7) THF, (8) CH_2Cl_2 . After the final CH_2Cl_2 wash, the drain assembly on the bottom of the reactor was removed and the Lanterns were pushed with vigorous argon flow into a receiving bin below the reactor. The slightly yellow Lanterns were divided into three 3-L round-bottom flasks and lyophilized for 48 h, with venting every 12 h. Elemental analysis of the Lanterns indicated an average of 31 μmol bromine/Lantern.

Suzuki Coupling to Aryl Bromide. For a Target Silicon Incorporation Level of 30 $\mu\text{mol/Lantern}$. To the nondried 30-L reactor was added anhydrous THF (10.7 L) through the top opening port while flushing with argon. Allylsilane (385 g, 1.4 moles, 1.5 equiv, 95%, Maybridge), a viscous yellow oil, was weighed into a dried, tared flask and then poured into the reactor with complete transfer ensured by washing with THF (2 \times 50 mL). The solution was sparged with argon and stirred (160 rpm) for 30 min. Recrystallized, white 9-BBN (164 g, 1.3 moles, 1.42 equiv) was weighed open to the atmosphere and added to the slightly yellow solution of allylsilane through the top port. A slight *endotherm* resulted (ca., 3–5 °C). The reaction became homogeneous and lighter in color after ~30 min. After 3 h an aliquot (1 mL) of the reaction mixture was removed from the bottom drain valve and analyzed by No-D ^1H NMR. At this time the hydroboration had proceeded to nearly full conversion as determined by the decrease in sp^2 proton resonances. Next, with vigorous argon sparging, 30 000 slightly yellow Lanterns (31 μmol of bromine incorporation/Lantern, 0.93 mol, 1 equiv) were added through the top port. The solution was sparged for 30 additional min. $\text{Pd}(\text{PPh}_3)_4$, a canary yellow solid (60 g, 0.052 mol, 0.056 equiv., Strem) was added in one portion, followed by NaOH (930 mL of 2 M aqueous solution, 1.9 mol, 2 equiv). The initial canary yellow solution was heated to an internal temperature of 64–65 °C with the aid of a bottom heating mantle and stirred (160 rpm) for 48 h. Notably, after 1 h,

the solution color changed from canary yellow to a very dark green that persisted for the duration of the reaction. A black solid on the reactor glass walls, assumed to be palladium metal, was observed at small but noticeable levels after 10 h. After 48 h, heating was discontinued and the reaction cooled to room temperature (22 °C) overnight. The dark green reaction solution was drained through the bottom drain valve, leaving the dark gray/black Lanterns in the reactor.

For good mixing in the reactor, 10 L of solvent in the following order was used for each 30 min wash and upon completion, was drained into a waste carboy: (1) THF, (2) 3:1 THF/IPA, (3) 3:1 THF/1 M NaCN, ²⁶ (4) H₂O, (5) H₂O, 3:1 THF/H₂O, (6) 3:1 THF/IPA, (7) THF, (8) CH₂Cl₂. After it was washed with CH₂Cl₂, the drain assembly on the bottom of the reactor was removed and the Lanterns were pushed with vigorous argon flow into a receiving bin below the reactor. The slightly off-white Lanterns were divided into three 3-L round-bottom flasks and lyophilized for 48 h, with venting every 12 h. Elemental analysis of the Lanterns indicated an average of 23 μmol silicon/Lantern.²²

Loading Protocol. To a 20-mL vial containing ten Lanterns (based on 18 μmol Si/Lantern) was added a freshly prepared solution of TfOH in CH₂Cl₂ (3.16 mL, 3% by volume, 6 equiv. relative to Si) via syringe. The 3% TfOH solution was prepared by adding a 5 g ampule of TfOH to a 100 mL bottle of anhydrous CH₂Cl₂. The Lanterns turned bright orange upon treatment with TfOH. After gentle shaking for 15 min, the TfOH solution was removed via syringe and anhydrous 2,6-lutidine (182 μL, 9 equiv. relative to Si) was added. Once the Lantern color had changed from orange to white, the alcohol (1.2 equiv. relative to Si) was added as a CH₂Cl₂ solution (300 μL/Lantern). After gentle shaking at room temperature for 24 h, the loading mixture was removed via syringe and the Lanterns were washed for 10 min each as follows: (1) CH₂Cl₂, (2) DMF, (3) 3:1 THF/H₂O, (4) 3:1 THF/IPA, (5) THF, (6) CH₂Cl₂. The Lanterns were dried on a manifold overnight to remove excess CH₂Cl₂ (Note: Stabilized THF should be used for washing substrates that may be prone to oxidation).

Representative Procedures for Solid-Phase Transformations. Fmoc Removal. To Lanterns was added 20% piperidine in DMF (~800 uL/Lantern), and the mixture was shaken at room temperature for 30 min. The piperidine solution was then removed, and the Lanterns were washed (~800 uL/Lantern) as follows: (1) DMF (2×), (2) THF/H₂O (3:1), (3) THF/IPA (3:1), (4) THF, (5) CH₂Cl₂. Lanterns were dried under lyophilization or high vacuum overnight (or for 1–2 h when using <10 Lanterns).

Sulfonyl Chloride Capping (16). To Lanterns in a capped vial was added CH₂Cl₂ (~800 uL/Lantern) followed by 2,6-lutidine (25 equiv) and 4-fluorobenzene sulfonyl chloride (20 equiv.). After the Lanterns were shaken at room temperature overnight, the reaction mixture was removed and the Lanterns washed as follows: (1) CH₂Cl₂, (2) THF, (3) THF/IPA (3:1), (4) THF/H₂O (3:1), (5) DMF, (6) DMF (7) THF/H₂O (3:1), (8) THF/IPA (3:1), (9) THF, (10) CH₂Cl₂. ¹H NMR (500 MHz, CDCl₃): δ = 7.86 (m, 2H, aryl), 7.21 (app. t, J = 9.0, 2H, aryl), 4.41 (dddd, J = 4.5, 4.5, 2.0, 2.0 Hz, 1H, C3–H), 3.44 (dd, J = 11.0, 4.5 Hz, 1H C2–H), 3.42 (m,

1H, C5–H), 3.37 (dd, J = 11.0, 4.5 Hz, 1H, C2–H), 2.02–1.95 (nfom, 1H, C4–H), 1.89–1.84 (m, 1H, C4–H). HRMS [M + H] C₁₀H₁₃FNO₃S Calcd: 246.0600. Found: 246.0599.

Isocyanate Capping (18). To Lanterns in a capped vial was added CH₂Cl₂ (~800 uL/Lantern), followed by 4-methoxyphenyl isocyanate (15 equiv). After the Lanterns were shaken at room temperature overnight, the reaction mixture was removed and the Lanterns washed as follows: (1) CH₂Cl₂, (2) THF, (3) THF/IPA (3:1), (4) THF/H₂O (3:1), (5) DMF (2×), (6) THF/H₂O (3:1), (7) THF/IPA (3:1), (8) THF, (9) CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃): δ = 7.28 (d, J = 9 Hz, 2H, aryl), 6.85 (d, J = 9 Hz, 2H, aryl), 6.08 (m, 1H, OH), 4.41 (dddd, J = 4.5, 4.5, 2.3, 2.3 Hz, 1H, C3–H), 3.77 (s, 3H, OMe), 3.56 (m, 4H, C2–H and C5–H), 2.33 (br s, 1H, NH), 2.06 (m, 2H C4–H). HRMS [M + H] C₁₂H₁₇N₂O₃ Calcd: 237.1239. Found: 237.1229.

Amidation (20). To Lanterns in a capped vial was added CH₂Cl₂ (~800 μL/Lantern), followed by the addition of phenylacetic acid (20 equiv.), Et₃N (10 equiv.), and PyBOP (10 equiv.). After the Lanterns were shaken at room temperature overnight, the reaction mixture was removed, and the Lanterns were washed as follows: (1) DMF (2 ×), (2) THF/H₂O (3:1), (3) THF/IPA (3:1), (4) THF, (5) CH₂Cl₂. ¹H NMR (500 MHz, CDCl₃): δ = 7.33–7.22 (m, 5H, aryl), 4.47 (m, 1H, C3–H), 3.67–3.41 (m, 6H, PhCH₂-, C2–H, C2–H, C5–H, C5–H), 2.03–1.87 (m, 2H, C4–H, C4–H), 1.75 (br s, 1H, –OH). HRMS [M + H] C₁₂H₁₆NO₂ Calcd: 206.1181. Found: 206.1177.

Reductive Alkylation (22). To Lanterns in a capped vial was added 2% AcOH in DMF (~800 uL/Lantern), followed by the addition of piperonal (20 equiv.). The reaction mixture was shaken at room temperature for 1 h and then Na(OAc)₃BH (22 equiv.) was added. After the Lanterns were shaken at room temperature for 3 d, the reaction mixture was removed, and the Lanterns were washed as follows: (1) DMF (2×), (2) THF/H₂O (3:1), (3) THF/IPA (3:1), (4) THF, (5) CH₂Cl₂. ¹H NMR (500 MHz, CDCl₃): δ = 6.88 (s, 1H, aryl), 6.78 (d, J = 8.5 Hz, 1H, aryl), 6.76 (d, J = 8.0 Hz, 1H aryl), 5.96 (s, 2H, –OCH₂O–), 4.38 (m, 1H C3–OH), 3.68 (AB, J_{AB} = 13.0 Hz, Δν = 16.5 Hz, 2H, PhCH₂–), 3.00 (dt, J = 9.0, 6.0 Hz, 1H, C5–H), 2.82 (d, J = 11 Hz, 1H, C2–H), 2.68 (dd, J = 10.5, 5.0 Hz, 1H, C2–H), 2.50 (m, 1H, C5–H), 2.24 (br m, 2H, C4–H and –OH), 1.85 (dt, J = 13.5, 6.5 Hz, 1H, C4–H). HRMS [M + H] C₁₂H₁₆NO₃ Calcd: 222.1130. Found: 222.1220.

Cleavage Protocol. The dried Lanterns were placed in a 96-well plate and treated with a solution of 15% HF-pyridine in stabilized THF (350 μL/Lantern) for 2 h. The cleavage solution was quenched with TMSOMe (700 μL), and the solution was transferred to a preweighed 2-mL vial. The Lanterns were washed with an additional 200 μL of stabilized THF (or THF/MeOH), and the solution was transferred to the 2-mL vial. The samples were concentrated on a Genevac solvent evaporation system overnight without heating. Loading masses for each alcohol was determined on a FlexiWeigh system.

Acknowledgment. We would like to thank Anita Vrcic, Michael Lewandowski, and Dr. Stephen Johnston for analytical support, Dr. Jeremy Duvall and Dr. Bhaumik Pandya for assistance monitoring overnight reactions, Dr. Haibo Liu for assistance with initial Lantern loading studies, and Dr. Michael Foley for helpful discussions.

Supporting Information Available. General methods, ^1H NMR spectra, and UPLC chromatograms of unpurified products **16**, **18**, **20**, and **22**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) Nielson, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56.
- (2) <http://www.mimotopes.com> (accessed May 2008).
- (3) Nestler, H. P.; Bartlett, P. A.; Still, W. C. *J. Org. Chem.* **1994**, *59*, 4723–4724.
- (4) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312–318.
- (5) (a) Wang, X.; Imber, B. S.; Schreiber, S. L. *Bioconjugate Chem.* **2008**, *19*, 585–587. (b) Radner, J. E.; McPherson, O. M.; Mazitschek, R.; Barnes-Seeman, D.; Shen, J. P.; Dhaliwal, J.; Stevenson, K. E.; Duffner, J. L.; Park, S. B.; Neuberger, D. S.; Nghiem, P.; Schreiber, S. L.; Koehler, A. N. *Chem. Biol.* **2006**, *13*, 493–504. (c) Wong, J. C.; Hong, R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 5586–5587.
- (6) For the synthesis of additional silicon-based linkers, see: (a) Randolph, J. T.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5712–5719. (b) DiBlasi, C. M.; Macks, D. E.; Tan, D. S. *Org. Lett.* **2005**, *7*, 1777–1780. (c) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518–4521.
- (7) The 30-L Chemglass reactor was modified slightly from the standard configuration. Specifically, the frame was shortened to accommodate the height of our walk-in fume hood and the cooling coil was removed. Both modifications were performed at the Chemglass factory prior to shipping.
- (8) McKillop, A.; Bromley, D.; Taylor, E. C. *J. Org. Chem.* **1972**, *37*, 88–92.
- (9) Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877–3882.
- (10) Handling of this reagent should be performed in a well-ventilated fume hood with the appropriate protective gear. According to the MSDS, thallium (III) acetate is rated as “very toxic by inhalation, in contact with skin and if swallowed. Danger of cumulative effects. Readily absorbed through skin.”
- (11) Light was excluded based on the protocol of Fréchet and co-workers (see ref 9). It has not been determined if the presence of light has a significant impact on Lantern bromination.
- (12) The addition of methanol at the end of the reaction was adapted from observations by Tallarico and co-workers (see ref 4). The benefits are believed to be 2-fold: (1) to quench the reaction and (2) to promote thallium salt particle formation that facilitates Lantern washing.
- (13) Standard wash sequence: 10 L of each solvent for 30 min with stirring. Upon completion of each wash, the solvent was drained into a waste carboy. The solvent order is (1) THF, (2) 3:1 THF/IPA, (3) 3:1 THF/water, (4) H₂O, (5) 3:1 THF/IPA, (6) THF, (7) THF, (8) CH₂Cl₂.
- (14) Bromine elemental analyses were performed by Robertson Microtit Laboratories, Inc., 29 Samson Ave. Madison, NJ 07940.
- (15) Personal communication with Dr. Nicholas Ede (Mimotopes).
- (16) Maybridge U.S.A., 500 American Road, Morris Plains, NJ 07950.
- (17) Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 6102–6103.
- (18) Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 4599–4600.
- (19) In-house experience with commercial 9-BBN has shown that this reagent can and will ignite spontaneously when exposed to the atmosphere. However, 9-BBN recrystallized from diglyme via a slightly modified protocol from Soderquist (see Experimental Section and ref 18) provides a nonpyrophoric 9-BBN crystalline solid that can be weighed open to the atmosphere.
- (20) Hoyer, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. *J. Org. Lett.* **2004**, *6*, 953–956.
- (21) It routinely took approximately 30 min for solution sampling and No-D ^1H NMR analysis of the reaction solution. However, stirring the solution for longer than 3h while under an inert atmosphere does not adversely affect the reaction.
- (22) Elemental Analysis, Incorporated, 2101 Capstone Dr., Suite 110, Lexington, KY 40511.
- (23) In some cases prolonged exposure (> 12 h) to LiOH has led to premature cleavage of compound from the Lantern, thus we usually employ NaOTMS for ester hydrolysis. KOTMS has also been reported for solid-phase ester hydrolysis, see: Mitchell, J. M.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1722–1726.
- (24) The color of the Lantern suspension can vary from a creamy yellow to a faint orange.
- (25) Stirring the solution overnight after the addition of MeOH can also be done without adverse effects.
- (26) Washing the Lanterns with THF/1 M NaCN can be performed overnight if necessary to remove all of the color. Usual times range from 30 min to several hours. If a single wash does not remove the grey-black color, re-exposure to the wash conditions should be done until an off-white or dull grey color is observed.

CC8000986