Novel Polymer-Supported Trialkylsilanes and Their Use in Solid-Phase Organic Synthesis

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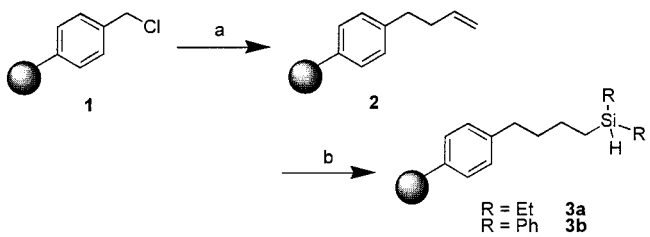
Silyl derivatives are widely used in synthetic organic chemistry as protecting groups for alcohols, phenols, carboxylic acids, amines, acetylenes, and aromatic compounds.[1,2] Silyl groups are inert to a wide range of synthetic transformations but may be easily removed under selective conditions (e.g., HF/pyridine, fluoride ion). To complement existing solution-phase silyl protecting groups, several resin-bound silicon linkers have been developed to enable attachment of alcohols and other functionality to solid supports. Lithiation of polystyrene, followed by trapping of aryllithium intermediates with dialkyldichlorosilanes, has been used for preparation of silyl chloride resins where the silicon is directly attached to the polymer backbone (arylsilane).[3] Suspension polymerization of functional styrene monomers containing a pendant arylsilane has also been employed to prepare polymeric silylating reagents which may be activated by protodesilylation.[4] Several investigators have also reported the preparation of arylsilane linkers for "traceless" attachment/detachment of aromatic compounds.[5] Recent emphasis has been placed on the preparation of silicon linker systems which are devoid of amide bonds or heteroatom attachment to the solid support. For example, Chenera and co-workers prepared "all carbon" dimethylarylsilane derivatives via hydrosilylation of a resin-bound olefin.[6] Recently, Stranix et al. prepared a silicon linker for alcohols on (vinyl)-polystyrene by hydrosilylation of a resin-bound olefin with dialkylchlorosilane derivatives.[7] Ellman and co-workers recently developed a linkage strategy for aromatic derivatives in which the arylsilane group is attached to the support through a stable aliphatic tether.[8] In this work, an unstable silyl chloride resin was masked as an electron-rich arylsilane to avoid prolonged storage of this intermediate.

Scheme 1



(a) allylmagnesium chloride (2.5 equiv), toluene, 60 °C; (b) R_2SiH_2 (2 equiv.) toluene, $RhCl(PPh_3)_3$ (0.4 mol%).

The objective of the present study was to prepare a shelf-stable silicon linker for solid-phase synthesis which could be used for direct attachment of both oxygen- and carbon-based functional groups. Polymer-supported trialkylsilanes with a pendant Si−H functionality appeared to meet these criteria.[9] Silane functional resins offer a number of unique applications and advantages including (a) stability to moisture providing shelf-storable silane resins, (b) potential for direct attachment of various functional groups (e.g., alcohol,[10,11] carbonyl,[12] aromatic, or unsaturated derivatives) without prior transformation to activated silylating agents (e.g., silyl chloride), (c) optional transformation into a reactive silyl chloride derivative if necessary, and (d) the ability to monitor reaction progress using IR spectroscopy by examination of the distinctive Si−H stretch (2000−2200 cm^{-1}).

Our synthetic approach to trialkylsilane linker systems was based on the hydrosilylation of resin-bound olefins with disubsituted silanes (Scheme 1).[13] Olefin **2** was obtained by displacement of Merrifield resin **1** (1% cross-linked, 100−200 mesh) with allylmagnesium chloride.[6,14] Completion of the allylation reaction was determined by residual chlorine elemental analysis and IR analysis of the product (disappearance of C−Cl stretch at 1265

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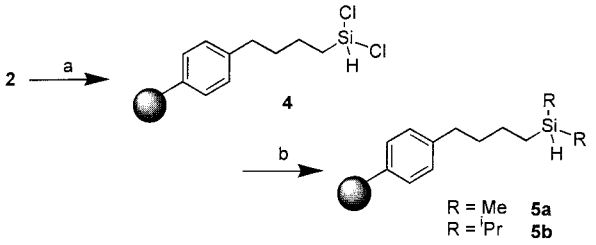
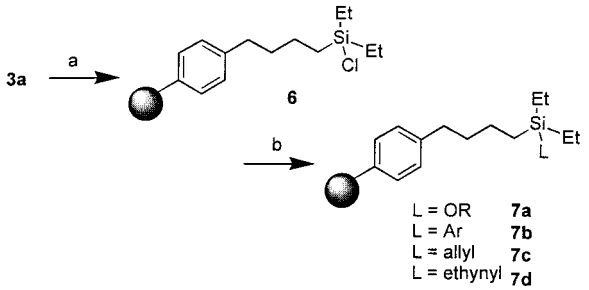
Scheme 2



(a) H_2SiCl_2 (2.5 equiv.), toluene, H_2PtCl_6 (0.5 mol%); (b) RMgBr or RLi (3 equiv.), THF.

Scheme 3



(a) 1,3-dichloro-5,5-dimethylhydantoin (3 equiv.), CH_2Cl_2, 1.5 h; (b) **7a**, ROH (3 equiv.), imidazole (3.5 equiv.), CH_2Cl_2 (L = ROH), 4 h; **7b**, ArLi (5 equiv.), THF (L = Ar), −78−0 °C; **7c**/**d**, allylmagnesium chloride or ethynyl magnesium bromide (5 equiv.), THF (L = allyl), −78−0 °C.

cm^{-1}). Hydrosilylation of olefin **2** with excess diethylsilane or diphenylsilane (0.4 mol % of $Rh(PPh_3)_3Cl$, toluene, 25 °C, 2 h) afforded trialkylsilane resins **3a** and **3b**.[15] In this case, complete hydrosilylation was verified by monitoring the disappearance of the olefin C═C IR stretch (1639 cm^{-1}) and the appearance of the Si−H stretch at 2100−2200 cm^{-1}. Silane (Si−H) loading was determined by GC quantification of triphenylmethane byproduct generated by hydrogen−bromine interchange of compound **3a** with trityl bromide.[16]

A more general route for the preparation of a wide range of silicon alkyl substitutions employing a dichlorosilane intermediate was also investigated (Scheme 2).[17] Hydrosilylation of resin-bound olefin **2** with dichlorosilane (0.5 mol % of chloroplatinic acid, toluene, 25 °C, 12 h) afforded resin-bound dichlorosilane **4**. After being washed with anhydrous THF, this intermediate was treated with an appropriate Grignard or alkyllithium reagent to produce trialkylsilane resins **5a**,**b** which vary in steric bulk around silicon.[18] Resin **5b**, an analogue of the well-known diisopropylmethylsilyl protecting group,[19] may be useful in applications where a bulkier silane linker is required.

Compound **3a** was also converted to an activated silyl chloride resin **6** just prior to use, thus avoiding storage of this highly reactive, moisture-sensitive intermediate (Scheme 3). Chlorination was most efficiently accomplished by treatment of **3a** with 1,3-dichloro-5,5-dimethylhydantoin (CH_2Cl_2, 25 °C, 1.5 h).[20] In this case, examination of the Si−H stretch (IR: 2100 cm^{-1}) was used to monitor the progress of the chlorination. Freshly prepared silyl chloride resin **6** was reacted with alcohols using imidazole as a base. Aromatic, allylic, or alkynyl compounds **7b**−**d** were also attached by treatment of the silyl chloride with the corresponding Grignard or alkyllithium reagents. Cleavage of silyl ethers **7a** was achieved using HF/pyridine (0.4 M HF/pyridine, THF, 2 h). Alternatively, noninvasive cleavage of silyl ethers derived from primary alcohols was accomplished using conditions analogous to those reported for the cleavage of triethylsilyl (TES) ethers in solution (6:6:1 AcOH/THF/H_2O, 50 °C, 4−8 h).[1] Silyl ethers of secondary alcohols required longer treatment (60−80 °C, 8−12 h). Aromatic silane derivatives were cleaved using TFA/DCM (1:1) for electron-rich aromatic derivatives and tetrabutylammonium fluoride (TBAF) for electron-deficient aromatics. Electron-deficient aromatic derivatives attached to the linker thus behave similarly to the traceless linker system recently reported by Ellman in terms of conditions required for cleavage.[8] Representative loading/cleavage results utilizing the derived Si−Cl resin **6** are provided (Tables 1 and 2). Table 1 shows that a variety of primary (entries 1, 2, and 3) and secondary alcohols (entries 4, 5, and 6) have been evaluated for the efficacy of loading/cleavage using trialkylsilane **3a**. In the case of entries 1, 3, and 6, IR of the polymer-supported silyl ethers clearly showed the appearance of a carbonyl stretch from the substrates. Table 2 also shows representative "traceless" attachment/cleavage of electron-rich (entry 1), neutral (entry 2), and electron-deficient (entry 3) aromatic derivatives.

Table 1. Alcohol Loading and Cleavage Using Trialkylsilane 3a

entry	L = OR	overall yield[a]
1	1-(2-methoxybenzoyl)-2-pyrrolidinemethanol	79%
2	2-(1-naphthyl)ethanol	91%
3	*N*-Fmoc-ethanolamine	72%[b]
4	1-(4-methoxyphenoxy)-2-propanol	75%
5	*trans*-2-phenylcyclohexanol	60%
6	epiandrosterone	77%

[a] The overall yield (GC) represents the sequence from **3a** to **6** to **7a** followed by cleavage of the alcohol using 0.4 M HF/pyridine in THF (except entry 3). [b] Yield determined by cleavage of the Fmoc group using 20% piperidine (DMF) followed by UV measurement.

Preliminary results indicate that direct attachment of alcohols to trialkylsilane resin **3a** without prior conversion to active chloride was viable. We were able to successfully attach primary alcohols by using conditions similar to those reported by Doyle.[21] For example, loading of 1-(2-methoxybenzoyl)-2-pyrrolidinemethanol

(13) For hydrosilylation of olefins with disubstituted silanes in solution, see: (a) Lewis, L. N.; Uriarte, R. J. *Organometallics* **1990**, *9*, 621. (b) Onopchenko, A.; Sabourin, E. T. U.S. Patent 4,572,791, 1986. (c) Onopchenko, A.; Sabourin, E. T.; Beach, D. L. *J. Org. Chem.* **1984**, *49*, 3389.

(14) Kaeriyama, K.; Shimura, Y. *Makromol. Chem.* **1979**, *180*, 2499.

(15) Compound **3a** (PS-DES resin) is commercially available from Argonaut Technologies.

(16) For examples of trityl halide−silane interchange, see: Corey, J. Y.; West, R. *J. Am. Chem. Soc.* **1962**, *94*, 2430.

(17) For hydrosilylation of olefins with dichlorosilane in solution, see: (a) Out, G. J. J.; Klok, H.; Schwegler, L.; Frey, H.; Moller, M. *Macromol. Chem. Phys.* **1995**, *196*, 185. (b) Koga, I.; Terui, Y.; Ohgushi, M.; Kitahara, T. U.S. Patent 4,297,499, 1981.

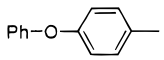
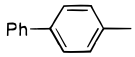
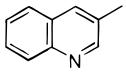
(18) The Si−H IR stretch was found to shift from 2200 cm^{-1} for compound **7** (dichlorosilane) to 2130 cm^{-1} for compound **5** (dialkylsilane) and could be used for evaluation of reaction progress.

(19) For a recent review of silyl ether protecting groups, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

(20) Other chlorinating reagents include trichloroisocyanuric acid, *N*-chlorosuccinimide, and trityl chloride. These chlorination methods were found to be inferior to 1,3-dichloro-5,5-dimethylhydantoin either because of the formation of insoluble byproducts or requirement for longer reaction times.

(21) Doyle, M. P.; Shanklin, M. S. *Organometallics* **1994**, *13*, 1081.

Table 2. Loading/Cleavage of Aromatics Using Trialkylsilane 3a

entry	L = Ar	Cleavage solution	Overall Yield[a]
1		TFA/DCM (1:1)	80%
2		TFA/DCM (1:1)	70%
3		TBAF/THF (1.0 M)	58%

[a] The overall yield (GC) represents the sequence from **3a** to **6** to **7b** followed by cleavage of the aromatic compound using the indicated cleavage solution.

using 1 mol % of rhodium(II) perfluorobutyrate ($Rh_2(pfb)_4$) in CH_2Cl_2 was successful as indicated by IR spectroscopy. Cleavage of this silyl ether resin (HF/pyridine/THF) afforded alcohol in 99% yield (GC, anthracene as internal standard).

In conclusion, a method for the preparation of stable trialkylsilane linkers for use in solid-phase organic synthesis has been developed which is based on the hydrosilylation of resin-bound olefins with disubstituted silanes. These linkers contain a stable Si−H functional group which can be used for the loading of alcohols, aromatics, allyl, or alkynyl compounds. Further studies on the direct loading of alcohols and unsaturated compounds and other solid-phase synthesis applications are underway and will be reported in due course.

Experimental Section

Standard reagents were obtained from commercial suppliers and used without further purification. Gel-phase ^{13}C NMR spectra were obtained on a Varian 300 spectrometer and are reported in ppm (δ). Infrared spectra were recorded on a Nicolet Impact 410 spectrometer equipped with an InspectIR microscope on a random sampling of single beads and are reported in cm^{-1}. Elemental analysis was performed at Galbraith Laboratories, Inc., Knoxville, TN.

Gel-Type Polystyrene Olefin Resin 2. A dry 1-L, three-necked flask was fitted with a mechanical stirring paddle, temperature controller thermocouple, and nitrogen/vacuum inlet. Care was taken to ensure that the stirring paddle did not touch the bottom of the flask. This reaction setup was charged with 50 g of Merrifield resin **1** (100−200 mesh, Novabiochem, Lot A16510, 0.85 mmol/g, 42.5 mmol) and purged with argon for 20 min. The reactor was then charged with 400 mL of anhydrous toluene and agitated for 5 min to swell the resin. Allylmagnesium chloride (55 mL, 2.0 M in THF, 110 mmol) was then added slowly to the reactor with a syringe, and the reaction mixture was agitated at room temperature for 30 min. The suspension was then heated to 60 °C for 12 h, and the mixture was allowed to cool to room temperature. The agitation was stopped, and the liquid removed via a vacuum filter tube. The reactor was charged with 400 mL of THF, agitated for 30 min, and the liquid was removed via a vacuum filter tube. The reactor was charged with 400 mL of THF/1 N HCl (3:1) and heated to 45 °C for 12 h. The liquid was removed via vacuum filter tube, and the reaction mixture was washed with 2 × THF and 2 × MeOH. The product was collected with a glass funnel and suction dried for 15 min. The product was transferred to a glass tray and dried in a vacuum oven at 65 °C for 12 h to give resin **2**. IR (cm^{-1}): 1639 (C═C), the C−Cl stretch at 1265 cm^{-1} from starting Merrifield resin was absent. Anal. Found: C, 90.81; H, 7.98. Olefin loading was determined to be 0.79 mmol/g (bromination of the olefin followed by elemental analysis, Br 11.22).[14]

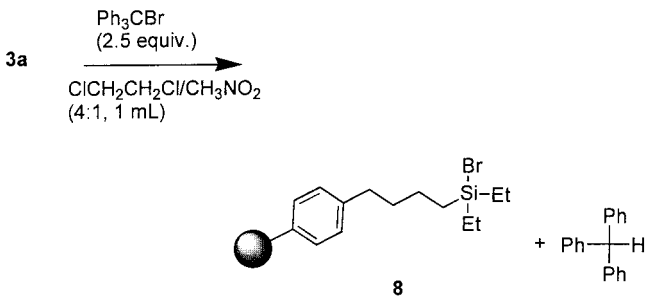
Gel-Type Polystyrene Silane Resin 3a (PS-DES resin). A dry 500-mL, two-necked flask was fitted with a mechanical stirring paddle and a nitrogen/vacuum inlet. Care was taken to ensure that the stirring paddle did not touch the bottom of the flask. This reaction setup was charged with 30 g (0.79 mmol/g, 23.7 mmol) of olefin resin **2**. The vessel was purged with argon for 20 min. Then the reactor was charged with 240 mL of a toluene solution of $RhCl(PPh_3)_3$ (96 mg, 0.1 mmol, 0.4 mol %) and agitated for several minutes to swell the resin. Et_2SiH_2 (6.4 mL, 50.0 mmol) was added dropwise with a syringe at room temperature, and the reaction mixture was agitated for 2 h. The liquid was removed via a vacuum filter tube. The reaction mixture was washed with 3 × toluene and 3 × THF. The product was collected with a glass funnel and suction dried for 15 min. The product was transferred to a glass tray and dried in a vacuum oven at room temperature to give **3a**. ^{13}C NMR (75 MHz, C_6D_6): δ 2.55, 7.96, 10.20, 24.24, 35.07, 40.43 ppm. IR (cm^{-1}), 2100 (Si−H), 1229 (Si−C). Anal. Found: Si, 2.29 (0.81 mmol/g); C, 88.62; H, 8.58. Silane (Si−H) loading was determined by hydrogen−bromine interchange: 0.75 mmol/g.

Gel-Type Polystyrene Silane Resin 3b. Silane resin **3b** was synthesized in a procedure similar to that for **3a**. IR (cm^{-1}): 2121 (Si−H). Anal. Found: Si, 1.59 (0.57 mmol/g).

Gel-Type Polystyrene Dichlorosilane Resin 4. A dry 10-mL flask was charged with 0.5 g (0.79 mmol/g, 0.40 mmol) of olefin resin **2** and purged with argon. The reactor was charged with 3.5 mL of a toluene solution. To this solution was added 0.10 mL of H_2PtCl_6 (0.02 M). H_2SiCl_2 (0.58 mL, 25% in xylene) was added dropwise with a syringe at room temperature, and the reaction mixture was agitated at room temperature for 12 h. The liquid was removed via a vacuum filter tube. The reaction mixture was washed with 4 × toluene and dried in a vacuum at room temperature. IR (cm^{-1}): 2202 (Si−H). Anal. Found: Si, 1.97 (0.70 mmol/g).

Gel-Type Polystyrene Dimethylsilane Resin 5a. To the dichlorosilane resin **4** in diethyl ether (4 mL) under argon at 0 °C was added 3 equiv of methylmagnesium bromide. The mixture was allowed to warm to room temperature. After 2 h of reaction, the mixture was filtered, washed with 3 × THF, 3 × THF/H_2O (1:1), and 3 × THF, and dried in a vacuum at room temperature. IR (cm^{-1}): 2105 (Si−H), 1250.07 (Si−C). Anal. Found: Si, 1.40 (0.50 mmol/g).

Gel-Type Polystyrene Silyl Chloride Resin 6. Chlorination with 1,3-Dichloro-5,5-dimethylhydantoin. To a 5 mL round-bottom flask under argon were added 100 mg (0.075 mmol) of silane resin **3a** and 3 equiv of 1,3-dichloro-5,5-dimethylhydantoin (0.225 mmol) in 0.8 mL DCM, (*Note*: The concentration of the chlorinating agent should be approximately 0.3 M. It is important to use this concentration for the complete chlorination of the silane.) After 1.5 h, the mixture was filtered and washed with DCM (3 × 3 mL) and dry THF (2 × 3 mL). The resin was used for further transformations immediately after washing. The chlorination reaction can be monitored by IR analysis (Figure 1).



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GC Quantification of Si−H Loading. To a 5 mL round-bottom flask were added under argon 100 mg of silane resin **3a**, 2.5 equiv of trityl bromide, and $ClCH_2CH_2Cl/CH_3NO_2$ (4:1, 1 mL). After 2 h, the mixture was filtered and washed with DCM (5 × 2 mL). The combined filtrate was mixed with 20 mg of anthracene (internal standard) and 0.5 mL of H_2O. The organic layer was used for GC analysis of the triphenylmethane produced.

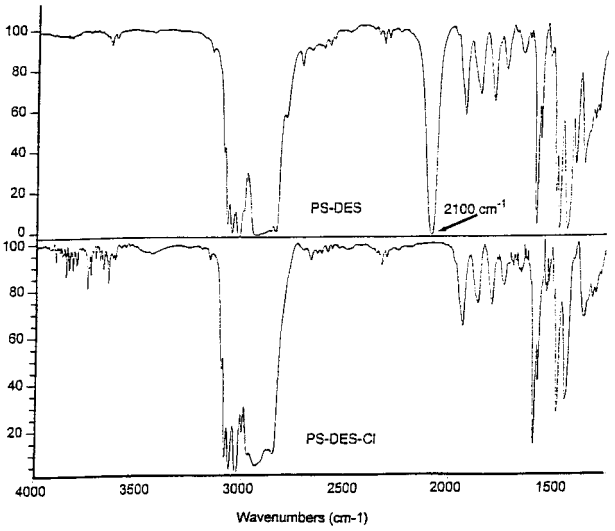
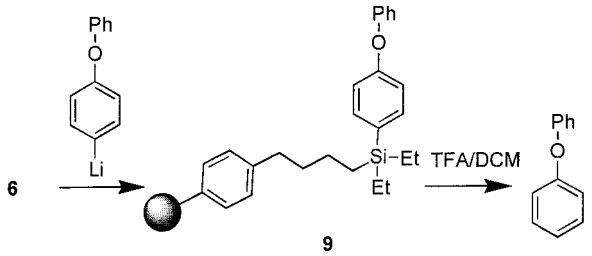
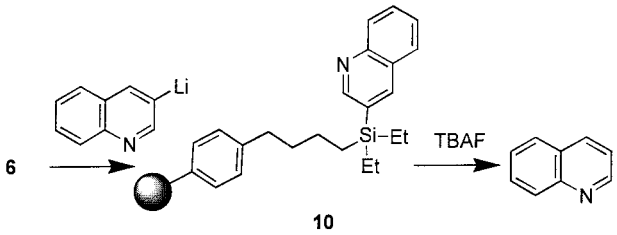


Figure 1. Chlorination of PS-DES resin **3a**: IR Monitoring.

Loading and Cleavage of Alcohols. The alcohols (1-(2-methoxybenzoyl)-2-pyrrolidinemethanol, 2-(1-naphthyl)ethanol, 1-(4-methoxyphenoxy)-2-propanol, and *trans*-2-phenylcyclohexanol, 100 mg) were loaded by treating the Si−Cl resin **6** with a DCM solution of 3 equiv of alcohol and 3.5 equiv of imidazole for 4 h at room temperature under argon. The mixture was then washed with 2 × DMF, 2 × DMF/H_2O (1:1), 2 × THF/H_2O (1:1), and 2 × THF. Cleavage was performed using a 0.4 M HF/pyridine solution in THF for 2 h. The filtrate was treated with a saturated solution (3 mL) of $NaHCO_3$ and an EtOAc solution of anthracene (internal standard). After extraction with EtOAc, the organic layer was used for GC analysis. The yields (GC) calculated for the alcohols are 79%, 91%, 75%, and 60%, respectively. Alcohols (epiandrosterone, *N*-Fmoc-ethanolamine) were loaded to the Si−Cl resin **6** similarly to give **7a**. IR (cm^{-1}): **7a** (L = epiandrosterone), 1742 (C═O), **7a** (L = *N*-Fmoc-ethanolamine), 1726 (C═O). Cleavage of **7a** (L = epiandrosterone) was performed by using AcOH/THF/H_2O (6:6:1) at 80 °C for 4 h to give epiandrosterone in 77% yield. Loading of compound **7a** (L = *N*-Fmoc-ethanolamine) was determined by cleavage of the Fmoc group using 20% piperidine (in DMF) followed by UV measurement.



Loading and Cleavage of 4-Phenoxyphenyl Bromide. To 500 mg of PS-DES resin **3a** (0.75 mmol/g, 0.375 mmol) was added 220 mg of 1,3-dichloro-5,5-dimethylhydantoin (1.12 mmol) in 4 mL of DCM under argon. The mixture was stirred for 1.5 h at room temperature. The resin was washed with DCM (3 × 7 mL) and dry THF (3 × 7 mL) under argon. To the resin was added at −78 °C 5 equiv of 4-phenoxyphenyllithium (generated by treating 4-phenoxyphenyl bromide with 1 equiv of *n*-BuLi at −78 °C for 1 h) in 5 mL of THF. The reaction mixture was allowed to warm to room temperature in 4 h. The resulting mixture was washed with THF (3 × 7 mL), THF/H_2O (1:1) (3 × 7 mL), THF (3 × 7 mL), and DCM (3 × 7 mL) and dried under vacuum for 12 h to give the 4-phenoxyphenyl silyl resin **9**. IR (cm^{-1}): 1240 (Ar−O). To the 4-phenoxyphenyl silyl resin **9** (100 mg) was added TFA/DCM (1:1, 3 mL). The mixture was stirred at 25 °C for 3 h. The resin was filtered and washed with DCM (3 × 2 mL). The combined filtrate was treated with saturated $NaHCO_3$ and analyzed by GC (quantification using anthracene as internal standard). Yield: 80%.



Loading and Cleavage of 3-Bromoquinoline. To a t-BuLi solution in pentane (2 equiv) was added dropwise a THF solution of 3-bromoquinoline (1 equiv) under argon at −78 °C. The mixture was stirred at this temperature for 5 min before being transferred via cannula to freshly prepared PS-DES-Cl resin **6** (100 mg) at −78 °C. The reaction mixture was allowed to warm to room temperature in 4 h. The resin was washed with THF (3 × 7 mL), THF/H_2O (1:1) (3 × 7 mL), THF (3 × 7 mL), and DCM (3 × 7 mL) and dried under vacuum for 12 h to give resin **10**. Treatment of the silylquinoline resin **10** with TBAF (1.0 M in THF, 3 mL) for 12 h followed by extraction of the product into DCM led to the recovery of quinoline in 58% yield (GC quantification using anthracene as internal standard).

Allylsilane Resin 7c. Compound **7c** was synthesized similarly to **9** using allylmagnesium chloride. IR (cm^{-1}): 1629 (C═C).

Ethynylsilane Resin 7d. Compound **7d** was synthesized similarly to **9** using ethynylmagnesium bromide. The alkynylsilane resin was washed with THF/1 N HCl (3:1, 60 °C, 5 h) to remove reagent-based impurities and dried in vacuo. IR (cm^{-1}): 3282 (≡C−H), 2030 (C≡C).

Direct Loading of Primary Alcohols to PS-DES Resin 3a. To a blue DCM solution of 1.7 mg of $Rh_2(pfb)_4$ in a 10 mL round-bottom flask under argon was added 200 mg of silane resin **3a**. Then 66 mg of (*S*)-(−)-1-(2-methoxybenzoyl)-2-pyrrolidinemethanol was added, and the reaction mixture was stirred at room temperature (monitored by IR analysis). After 3 h, the reaction mixture was filtered and washed with 3 × DCM, 2 × toluene, 2 × THF/H_2O (1:1), and 3 × THF. The product was dried under vacuum to give **7a** (L = (*S*)-(−)-1-(2-methoxybenzoyl)-2-pyrrolidinemethanol). This product was then treated with AcOH/THF/H_2O (6:6:1) at 50 °C for 4 h, and the filtrate was concentrated to obtain alcohol in 99.3% yield (GC, anthracene as internal standard).

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