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Synthesis and applications of *tert*-alkoxysiloxane linkers in solid-phase chemistry

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Abstract—Straightforward syntheses of two *tert*-alkoxysilyl chloride functionalised resins **3** and **31** that allow facile attachment of 1°, 2°, 3° alcohols and phenols to the solid-phase have been achieved. Resin **3** displayed useful loading levels (0.7 mmol/g), and it was stable to storage in activated form. Siloxanes from reaction of **3** with alcohols and phenols were compatible with a variety of reaction conditions commonly used in solid-phase synthesis.

1. Introduction

In view of the importance of silicon protecting groups in organic chemistry,[1] the development of related silyl linkers for solid-phase synthesis constitutes an important objective.[2,3] Indeed, silicon-containing linkers have proved to be extremely valuable for the attachment of oxygen, carbon and nitrogen functionalities to solid supports. Some relevant applications of silylether linkers include the synthesis of pheramones,[4] oligosaccharides,[5] glycopeptides,[6] prostaglandins,[7] polyketides,[8] carpanone-like molecules[9] and vitamin D_3 analogues.[10] Traceless cleavage strategies that rely on protodesilylation of silicon–carbon bonds have been utilised for the release of unsaturated small molecules and cyclopeptides.[11,12] Other silicon-containing linkers that can be cleaved to afford amines and carboxylic acids have also been devised.[13,14]

Various strategies have been described to achieve the attachment of alcohols to a solid-support through a silicon–oxygen linkage. Early reports described the synthesis of silyl chloride resins by metallation of polystyrene followed by trapping with dichlorosilanes.[4,15,16] Polymer supported silyl chlorides have also been prepared by co-polymerisation of silyl-containing monomers,[17] or transition metal catalysed hydrosilylation of resin-bound alkenes.[18] In some cases the resulting silyl resins require additional activating steps to generate a reactive silylating agent.[17–20] Alternative routes required more elaborate silylether–substrate conjugates to be prepared in solution prior to coupling with the solid-phase through suitable functional groups.[6,11a–b,12,14a–b]

Siloxane linkers offer an attractive alternative to silylethers because they can be synthesised directly from the reaction of inexpensive commercially available dichlorosilanes with alcohols. Indeed, the virtues of the di-*iso*-propylsiloxane linkage have been highlighted within the solid-phase syntheses of carbohydrates, glycopeptides, oligonucleotides and polyketides.[21] In these syntheses the siloxane linkage was formed by first reacting the alcohol with dichlorosilane (or bis-triflate) in solution prior to attachment of the resultant product to a resin-bound alcohol.

The stability of siloxane protecting groups towards acid, base and fluoride has been investigated by Gillard et al.[22] They showed that the *tert*-butoxydiphenylsilyl (DPTBOS) group was suitable for protection of 1°, 2° and 3° alcohols, giving siloxanes that exhibited improved acid stability over the corresponding *tert*-butyldimethylsilyl (TBS) ethers (Fig. 1). In addition, the *tert*-butyldiphenylsiloxane linkage was shown to offer useful stability under basic conditions, whilst undergoing rapid cleavage with fluoride.

The reactivity profile of *tert*-butoxydiphenylsiloxanes described above prompted us to consider the use of related

Figure 1. Structure of the *tert*-butoxydiphenylsilyl (DPTBOS) protecting group and proposed siloxane linker.

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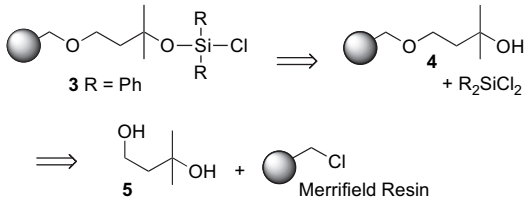
supported analogues as linkers for solid-phase synthesis (Scheme 1).[23] Moreover, these resins should be easy to access from commercially available starting materials using operationally simple chemistry. Herein, we describe a convenient synthesis of diphenyl and dimethylchlorosiloxane resins that are useful for the immobilisation of 1°, 2° and 3° alcohols, and discuss some applications of these siloxane linkers in solid-phase synthesis.

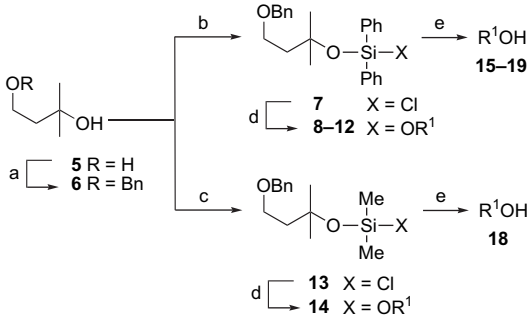


Scheme 1. Proposed synthesis of diphenylchlorosiloxane resin.

2. Results and discussion

The objective of this research was to establish a solid-supported analogue of the DPTBOS protecting group for use as a linker in solid-phase synthesis. It was important that the resin should have a useful loading of chlorosiloxane groups and be easy to prepare. The resin should ideally possess sufficient reactivity for the facile attachment of a range of alcohols of different steric bulk, whilst possessing sufficient stability to allow its storage. Furthermore, the resulting siloxanes should be stable to a range of conditions that are commonly encountered in solid-phase synthesis. With the above requirements in mind, we envisaged a simple route to an alkoxydiphenyl chlorosiloxane resin **3** starting from Merrifield resin, a commercially available diol linking group **5** and dichlorodiphenylsilane (Scheme 1).

The reaction of dichlorodiphenylsilane with *tert*-butanol has been reported to give the mono-adduct selectively in CH_2Cl_2 containing Et_3N,[22] so we were, therefore, confident that the corresponding reaction of a resin-bound 3° alcohol would provide chlorosiloxane resin **3** without significant cross-linking of the hindered 3° hydroxyl groups. In order to corroborate this prediction the synthesis of a solution model chlorosiloxane **7** was undertaken (Scheme 2).



Scheme 2. (a) NaH, DMF, BnCl, 0 °C to rt; (b) Ph_2SiCl_2, Et_3N, DMAP, rt; (c) Me_2SiCl_2, Et_3N, DMAP, CH_2Cl_2, rt; (d) R^1OH, Et_3N, DMAP, rt; (e) TBAF, THF, rt.

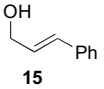
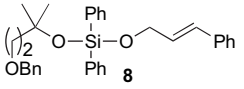
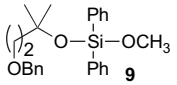
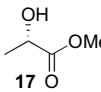
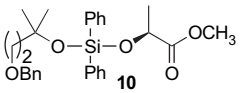
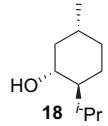
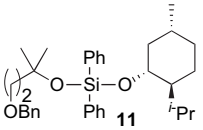
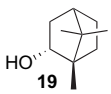
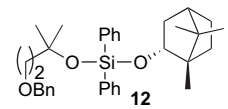
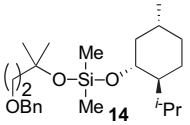
The reaction of dichlorodiphenylsilane and the mono-benzyl ether **6** of diol **5** proceeded slowly in CH_2Cl_2 using Et_3N as the base. Gratifyingly, the rate of reaction was greatly accelerated by the addition of DMAP, providing near quantitative formation of the desired chlorosiloxane **7** in less than 2 h at rt. Critically, even in the presence of DMAP further reaction between the chlorosiloxane **7** and the 3° alcohol **6** was not evident, suggesting that significant cross-linking between 3° alcohols should not be an issue of concern in the solid-phase chemistry.

A spot believed to correspond to the chlorosiloxane model compound **7** was visible by TLC analysis of the reaction mixture,[24] and the chlorosiloxane **7** could be isolated after an aqueous work-up. However, **7** proved too sensitive to permit purification by chromatography on SiO_2. Therefore, in order to establish the reactivity profile for **7**, the crude reaction mixture was directly exposed to a variety of 1° and 2° alcohols **15–19** to afford siloxanes **8–12** in excellent overall yields.

In contrast to the results reported for *tert*-butoxydiphenylsilyl chloride,[22a] we were not able to efficiently couple 3° alcohols with **7**. Consequently, the less hindered dimethylsilyl analogue **13** was prepared and found to react effectively with menthol to give stable siloxane products (Scheme 2). A small amount of double addition of **6** was observed during the formation of chlorosiloxane **13**, indicating that the corresponding resin would be reactive towards 3° alcohols, but might also undergo some cross-linking.

As expected, exposure of the diphenyl- and dimethylsiloxanes **8–12** and **14** to fluoride resulted in a rapid and complete cleavage of the siloxane moiety (Table 1).[22] For example,

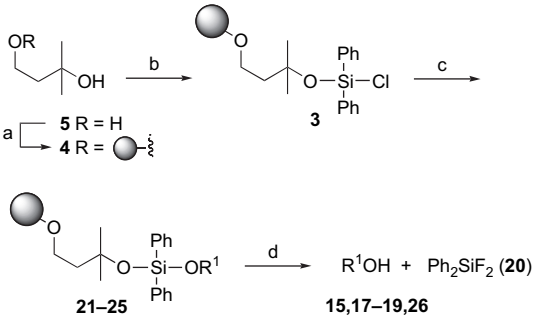
Table 1. Synthesis of siloxane model compounds

Entry	*tert*-BuOSiR$_2$Cl	R^1OH	Siloxane	Yield (%)[a,b]
1	**7**	 **15**	 **8**	98
2	**7**	CH_3OH **16**	 **9**	90
3	**7**	 **17**	 **10**	93
4	**7**	 **18**	 **11**	90
5	**7**	 **19**	 **12**	94
6	**13**	**18**	 **14**	90

[a] All yields refer to the isolated, purified compound.
[b] Overall yield starting from alcohol **6**.

action of TBAF on **8** afforded alcohol **5**, along with Ph_2SiF_2 (**20**) and *trans*-cinnamyl alcohol (**15**) in quantitative yield.

After the excellent results obtained in solution, attention turned to the solid-phase synthesis (Scheme 3). Attachment of diol **5** on Merrifield resin (1% cross-linked, 1.6 mmol/g) was achieved in THF using *tert*-BuOK as the base in the presence of a phase-transfer catalyst, leading to the successful formation of a 3° alcohol resin **4**.[25,26] Alternatively, the resin **4** could be prepared with a slightly improved loading using microwave irradiation at a temperature of 120 °C with reaction time of just 5–10 min. Subsequent exposure of the 3° alcohol resin **4** to Ph_2SiCl_2 and Et_3N afforded chlorosiloxane resin **3** (Scheme 3).



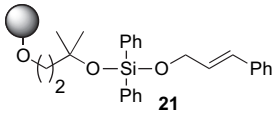
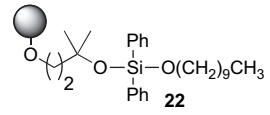
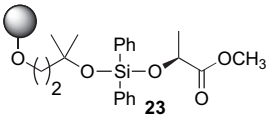
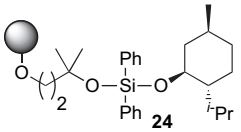
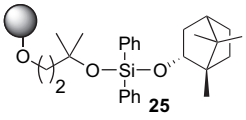
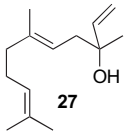
Scheme 3. (a) *tert*-BuOK, THF, 18-crown-6, Merrifield resin, microwave 120 °C, 10 min; (b) Ph_2SiCl_2, Et_3N, DMAP, CH_2Cl_2, rt; (c) R^1OH, Et_3N, DMAP, CH_2Cl_2, rt; (d) TBAF, THF, rt.

Gratifyingly, both 1° and 2° alcohols reacted with resin **3** (Scheme 3 and Table 2) in less than 1 h, in the presence of Et_3N and DMAP. Successful couplings were confirmed by gel phase ^{13}C NMR and by cleavage of the starting alcohols back from the siloxane resins. The loading of **3** (0.65–0.70 mmol/g) was estimated by GC quantification of cleaved *trans*-cinnamyl alcohol from **21**, and this value was used as a basis to calculate the loading efficiencies for other alcohols.

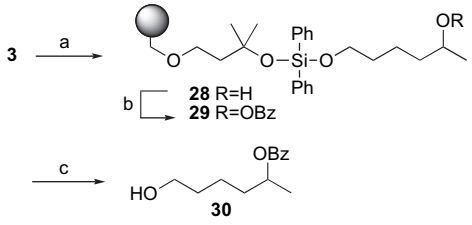
The chlorosiloxane resin **3** was suitable for the selective protection of 1° alcohols in the presence of 2° alcohols when DMAP was omitted from the coupling reaction mixture (Scheme 4).[22a] For example, 1,5-hexanediol was reacted with resin **3** to give alcohol resin **28**. Benzoylation of the 2° alcohol followed by HF mediated cleavage gave exclusively the mono-benzoate ester **30** in good yield. 1,2-Diols also underwent selective protection, although the results were less clear-cut due to some trans-esterification observed under the cleavage conditions.

A limitation of the resin **3** was its low reactivity towards 3° alcohols, even after prolonged reaction times or by employing DMF as solvent (entry 6, Table 2). To overcome this problem, the less bulky dimethylchlorosiloxane resin **31** was obtained from **4** (Scheme 5), and found to react effectively with 3° alcohols (entry 3, Table 3) as well as with less hindered ones. An advantage of the dimethylsiloxane linker over diphenylsiloxane linker is that the silyl by-product Me_2SiF_2, generated upon deprotection, is volatile and is readily removed from the cleaved product. The loading estimated for resin **31** (0.32 mmol of Si–Cl/g) was found to be lower than that of resin **3**. It is possible that the lower loading is due to cross-linking

Table 2. Attachment and cleavage of alcohols from resin **3**

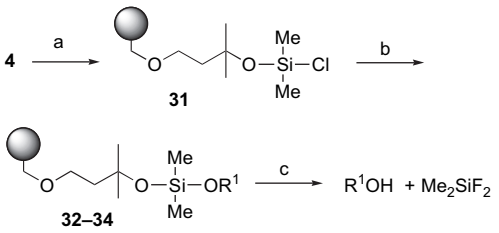
Entry	R^1OH	Siloxane resin	Yield of ROH after cleavage (%)[a]
1	**15**	 **21**	100[b]
2	$CH_3(CH_2)_9OH$ **26**	 **22**	70
3	**17**	 **23**	94
4	**18**	 **24**	96
5	**19**	 **25**	95
6	 **27**	Not observed	0

[a] Based on the loading of resin **3**.
[b] Based on the assumption that quantitative yields were obtained to the attachment of cinnamyl alcohol to resin **3**, and for the cleavage of cinnamyl alcohol from resin **21**.



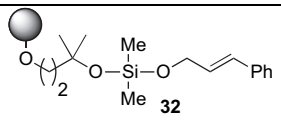
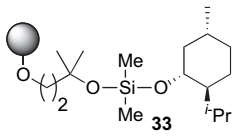
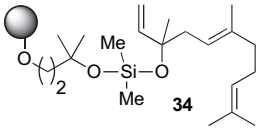
Scheme 4. (a) 1,5-Hexanediol, Et_3N, CH_2Cl_2, rt; (b) BzCl, pyridine, CH_2Cl_2, rt; (c) HF·Py, rt.

between the resin-bound 3° alcohol groups, although we did not observe any evidence for this on the basis of ^{29}Si NMR analysis of resin **33**. No further investigations of the dimethylsiloxane linker have been carried out at this time, but it is likely to be a useful linker for 3° alcohols in solid-phase synthesis.



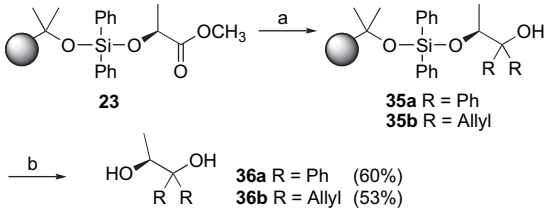
Scheme 5. (a) Me_2SiCl_2, Et_3N, DMAP, rt; (b) R^1OH, Et_3N, DMAP, rt; (c) TBAF, THF, rt.

Table 3. Attachment and cleavage of 1°, 2° and 3° alcohols from resin **31**

Entry	Alcohol	Siloxane	Yield (%)[a,b]
1	**15**	 **32**	100[b]
2	**18**	 **33**	96
3	**27**	 **34**	95

[a] Based on the loading of resin **31**.
[b] Based on the assumption that attachment and cleavage steps for cinnamyl alcohol were quantitative.

Evaluation of the stability of the diphenylsiloxane resin as a linker for alcohols in SPOS was investigated. The comparative stability of *tert*-butoxydiphenylsilyl and *tert*-butyldimethylsilyl (TBS) ethers had been studied by Gillard et al., who concluded that the former displayed greater stability under acidic conditions but was more prone to nucleophilic attack.[22a] We found that siloxane resin **21** was resistant to strong hindered bases such as *tert*-BuOK and LDA (2.5 equiv at 0 °C for 3 h). The addition of phenyl and allyl magnesium reagents to an immobilised ester proceeded in reasonable yields without significant cleavage of the linker at rt (Scheme 6).

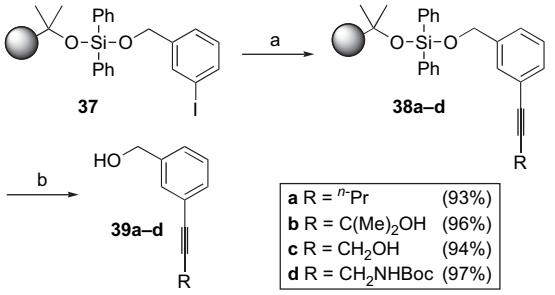


Scheme 6. (a) RMgBr, THF, −5 °C to rt; (b) TBAF, THF, rt.

Resin **21** was found to be quite stable to mild acidic conditions ($AcOH/CH_2Cl_2$), but could be cleaved rapidly with stronger acids such as TFA even in low concentrations (1% in CH_2Cl_2). In this case 53% (GC analysis) of the alcohol was detected in solution, after only 2 min.

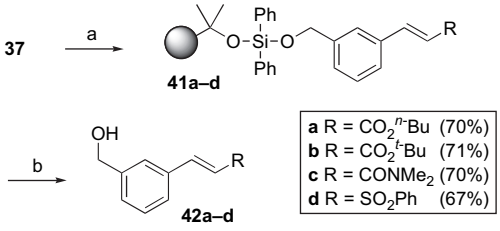
One initial objective was to develop a silyl chloride resin that would be suitable for storage, so the loading of a batch of resin **3** was evaluated over time using the cinnamyl alcohol attachment-cleavage procedure described above. It was found that no observable decrease in the loading of the chlorosiloxane resin **3** was observed when it was stored in a screw-capped bottle for a period of up to 1 year.

Further studies aimed to establish compatibility of the diphenylsiloxane linker with synthetic transformations that are widely used in solid-phase synthesis, such as palladium mediated C–C bond formation,[27] reductive amination[28] and peptide coupling reactions.[29] Thus, 3-iodobenzyl alcohol was reacted with the resin **3**, and Sonogashira couplings of the resulting resin-bound aryl iodide **37** were performed with different terminal alkynes **40a–d** (Scheme 7). Exposure of the product resins **38a–d** to TBAF and purification afforded compounds **39a–d** in excellent isolated yields (>90%) over the three steps from resin **3**.

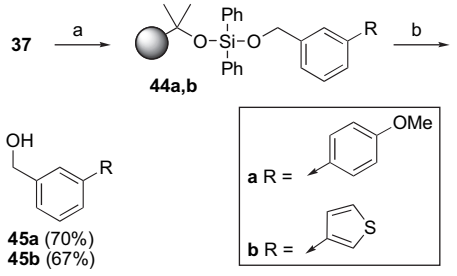


Scheme 7. (a) RCCH (**40a–d**), *trans*-$Pd(PPh_3)_2Cl_2$, dioxane/Et_3N (3:1), rt; (b) TBAF, THF, rt.

Heck and Suzuki cross-coupling reactions were carried out on resin **37** at 100 °C (Schemes 8 and 9), and a number of products were obtained in good yields. The *tert*-alkoxydiphenylsilane linker displayed excellent stability under the Suzuki reaction conditions, and even after 15 h no cleavage was observed. However, small quantities of the products were observed in solution under the Heck coupling conditions employed.



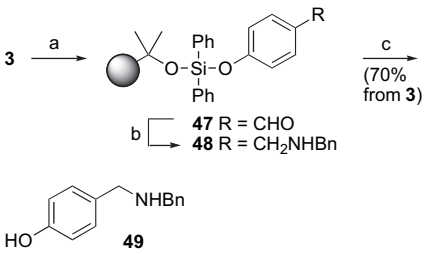
Scheme 8. (a) RCH=CH_2 (**43a–d**), $Pd(OAc)_2$, Bu_4NCl, NaOAc, DMA, 100 °C; (b) TBAF, THF, rt.



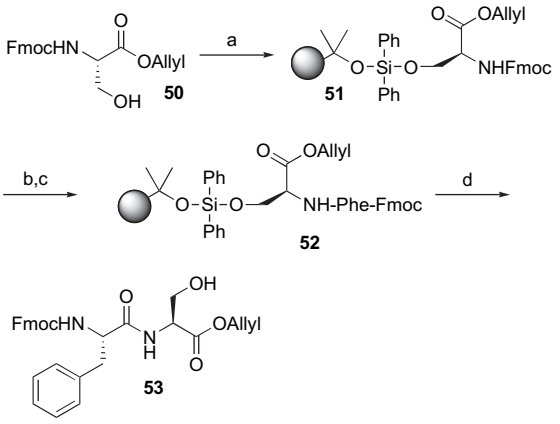
Scheme 9. (a) $RB(OH)_2$ (**46a**,**b**), K_2CO_3 (satd aq), $Pd(OAc)_2$, dioxane, 100 °C; (b) TBAF, THF, rt.

Reductive amination of immobilised 4-hydroxybenzaldehyde was also carried out using the diphenylsiloxane linker, affording the benzylamino derivative **49** in 70% yield (Scheme 10).[28,30]

To further demonstrate the potential of the diphenylsiloxane linker, it was used as a supported side chain-protecting group in SPPS (Scheme 11). Related side-chain linker strategies



Scheme 10. (a) 4-Hydroxybenzaldehyde, Et_3N, DMAP, CH_2Cl_2, rt; (b) $BnNH_2$, $(CH_3O)_3CH$, rt; then $Me_4NBH(OAc)_3$, $AcOH/CH_2Cl_2$ (1:99), rt; (d) TBAF, THF, rt.



Scheme 11. (a) **3**, Et_3N, DMAP, CH_2Cl_2, rt; (b) 20% piperidine/DMF; (c) Fmoc-L-PheOH, DIC, HOBt, CH_2Cl_2/DMF (9:1), rt; (d) 30% TFA in CH_2Cl_2, rt.

have been utilised for the synthesis of glycopeptides[6] and for on-resin macrocyclisation of cyclic peptides.[12] Attachment of *N*-Fmoc-L-Ser(OH)-(*O*-All) (**50**) to **3** afforded the resin-bound protected amino acid **51**, as shown by FTIR and ^{13}C NMR analyses. Nitrogen deblocking with piperidine in DMF and coupling with Fmoc-L-PheOH in the presence of DIC and HOBt afforded resin **52**, which when treated with TFA, released the protected dipeptide **53** in 90% overall yield over four steps based on the loading of **3**. A protected heptapeptide **54** was also synthesised using the side-chain linker strategy in an overall yield of 60% (Fig. 2).

In conclusion, we have described a simple synthesis of a *tert*-alkoxydiphenylsilyl chloride resin **3** that is suitable for the direct immobilisation of 1° and 2° alcohols and phenols. The resulting resin-bound siloxanes display good levels of stability towards a variety of reaction conditions commonly encountered in solid-phase synthesis. An analogous *tert*-alkoxydimethylsilyl chloride resin was also prepared and found to allow the facile attachment of 3° alcohols to the solid-phase.

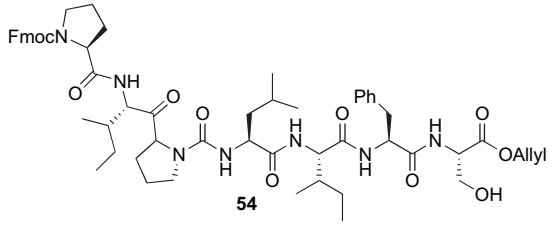


Figure 2. Structure of heptapeptide prepared using the side-chain siloxane linker.

3. Experimental

3.1. General

Melting points were measured with a Gallenkamp apparatus in open capillary tubes and are uncorrected. NMR spectra were recorded using a Bruker AC 300 or DPX 400 FTNMR spectrometer. Unless stated otherwise, signal assignments are in parts per million referenced to TMS as external standard. ^{29}Si NMR spectra were recorded using hexamethyldisilane as external standard. Gel phase ^{29}Si NMR analyses were performed at the University of Durham. Infrared spectra were carried out with the following instruments: Nicolet Impact 400 spectrometer (Spectra Tech Thunderdome accessory; Satellite Thermo Mattson (golden gate screw adaptor); Bio-Rad FTS 135 spectrometer (golden gate screw adaptor); Perkin Elmer Autoimage FTIR spectrometer equipped with an electronic microscope. Spectral assignments were recorded in wavenumbers (cm^{-1}) using the following abbreviations: s, strong; w, weak; m, medium; br, broad. UV measurements were performed with a Hewlett Packard 8452A diode array spectrophotometer. GC measurements were recorded using a Varian 3800 instrument fitted with a 30 m×0.25 mm DB120 fused silica column. HPLC analyses were performed with a Hewlett Packard 1100 system equipped with a Phenomenex Prodigy reverse phase column (150×4.6 mm i.d.). LRMS data were recorded using either a Fisons VG platform single quadrupole mass spectrometer for ESMS, or a ThermoQuest Trace single quadrupole GC mass spectrometer for EIMS and CIMS. HRMS data were recorded with the following instruments: a Bruker Apex III for ESMS, or a VG Analytical 70-250-SE for EIMS and CIMS. Elemental analyses were obtained from University College, London or MEDAC Ltd, Egham, UK. Microwave-assisted chemistry was carried out using a Personal Chemistry (now part of Biotage AB) Smith-Synthesizer™, which produced controlled irradiation at 2450 MHz with a power of 0–300 W.

THF was distilled from sodium/benzophenone under N_2; Et_3N, Pyridine and CH_2Cl_2 were distilled from CaH_2 prior to use. Other anhydrous solvents were obtained from commercial suppliers and used without any further purification. Thin layer chromatography was carried out using Macherey Nagel plates (model: ALUGRAM® SIL G/UV254 λ=254 nm). Spots were visualised by UV and/or developed with $KMnO_4$ (1.50 g in 150 mL of water), phosphomolybdic acid (12.00 g in 250 mL of ethanol) or ninhydrin (0.50 g in 250 mL of ethanol). Flash column chromatography was performed using Merck 60 mesh silica. Merrifield resin (100–200 mesh, loading 1.6 mmol/g) was purchased from Novabiochem. Unless stated otherwise, reactions were conducted in oven-dried glassware under N_2 atmosphere.

3.1.1. 4-(Benzyloxy)-2-methyl-2-butanol (6). To a rapidly stirred solution of 3-methyl-1,3-butanediol **5** (5.33 mL, 0.05 mol) in dry DMF (25 mL) at 0 °C, NaH (2.00 g, 0.05 mol, 60% dispersion in mineral oil) was added

portionwise [CAUTION: evolution of H_2 gas]. After 10 min benzyl chloride (6.32 g, 0.05 mol) was added and the resulting solution was gradually warmed to rt. After 6 h, crushed ice was added to the mixture followed by extraction with Et_2O (3×100 mL). The combined organic layers were washed with water (3×200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow liquid. Purification was achieved by distillation (87–90 °C at 0.02 mmHg) or by chromatography (hexane/EtOAc, 3:1) to afford **6** (7.10 g, 36.50 mmol, 73%) as a colourless liquid. ^{1}H NMR and bp data were consistent with the literature.[31] R_f: 0.43 (hexane/EtOAc, 3:1); FTIR (neat) ν_{max}: 3417 (br, O–H), 2969 (m), 2934 (m), 1453 (m), 1364 (s), 1152 (s, C–O), 1095 (s, C–OH), 736 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.20 (m, 5H), 4.50 (s, 2H), 3.69 (t, J=6.0 Hz, 2H), 3.44 (br s, 1H), 1.79 (t, J=6.0 Hz, 2H), 1.23 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.5 (s), 128.1 (d), 127.4 (d), 127.3 (d), 72.9 (t), 70.0 (s), 67.3 (t), 41.3 (t), 29.0 (q).

3.1.2. [3-(Benzyloxy)-1,1-dimethylpropoxy](chloro)-diphenylsilane (7). To a rapidly stirred solution of 3° alcohol **6** (710 mg, 3.65 mmol) in CH_2Cl_2 (15 mL) at 0 °C, Et_3N (1.52 mL, 10.96 mmol) was added, followed by dichlorodiphenylsilane (0.77 mL, 3.66 mmol) and DMAP (447 mg, 3.66 mmol). After the complete disappearance of the starting material by TLC (5 min required, R_f: 0.65, hexane/EtOAc, 3:1) the chlorosiloxane formed was used in situ for further transformations.

3.1.3. General method for the formation of siloxanes 8–12: [3-(benzyloxy)-1,1-dimethylpropoxy]diphenyl-{[(*E*)-3-phenyl-2-propenyl]oxy}silane (8). To a rapidly stirred solution of **7** (3.65 mmol, theoretical) in CH_2Cl_2 (15 mL) prepared using the above procedure, further Et_3N (1.52 mL, 10.96 mmol) was added followed by *trans*-cinnamyl alcohol (**15**, 490 mg, 3.66 mmol) and DMAP (446 mg, 3.65 mmol) under N_2. After 20 min, the reaction mixture was partitioned between water (100 mL) and Et_2O (150 mL). The organic phase was then washed with 10% aqueous $KHSO_4$ (2× 100 mL), saturated Na_2CO_3 (2×100 mL) and brine (100 mL). Evaporation of the solvent under reduced pressure and chromatography on silica afforded siloxane **8** as a clear oil (1.80 g, 3.57 mmol, 98%). R_f: 0.76 (hexane/EtOAc, 3:1); FTIR (neat) ν_{max}: 3049 (w), 2978 (w), 1943 (w), 1450 (w), 1427 (w), 1365 (w), 1110 (s), 1058 (s), 963 (s), 736 (s,), 712 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.70 (dt, J=5.8, 1.4 Hz, 4H), 7.40–7.10 (m, 16H), 6.54 (dt, J=15.4, 1.5 Hz, 1H), 6.20 (dt, J=15.4, 5.1 Hz, 1H), 4.40 (s, 2H), 4.34 (dd, J=5.1, 1.5 Hz, 2H), 3.62 (t, J=7.2 Hz, 2H), 1.86 (t, J=7.2 Hz, 2H), 1.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s), 137.0 (s), 135.0 (s), 134.7 (d), 130.0 (d), 129.9 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.7 (d), 127.6 (d), 127.5 (d), 127.4 (d), 126.4 (d), 75.0 (s), 73.3 (t), 67.1 (t), 63.6 (t), 44.0 (t), 30.7 (q, CH_3); ^{29}Si NMR (80 MHz, $CDCl_3$) δ: –45.9; CIMS *m/z*: 315 [Ph_2Si=OCH_2CH=$CHPh$]$^+$ (2%), 177 [$BnOCH_2CH_2(CH_3)_2C$]$^+$ (36%), 117 [$PhCH$=CH–CH_2]$^+$ (28%), 91 [$C_6H_5CH_2$]$^+$ (100%). Anal. Calcd for $C_{33}H_{36}O_3Si$: C 77.91, H 7.13; found: C 77.72, H 7.16.

3.1.4. (3-Benzyloxy-1,1-dimethylpropoxy)methoxydiphenylsilane (9). Following the general method described for siloxane **8**, compound **9** was obtained as a colourless oil (1.33 g, 3.28 mmol, 90%) by the reaction between silyl chloride **7** and MeOH. R_f: 0.44 (hexane/CH_2Cl_2, 1:1); FTIR (neat) ν_{max}: 3068 (w), 2971 (w), 2937 (w), 1429 (m), 1366 (m), 1113 (s), 1078 (s), 1025 (s), 738 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70–7.50 (m, 4H), 7.45–7.20 (m, 11H), 4.46 (s, 2H), 3.67 (t, J=7.3 Hz, 2H), 3.51 (s, 3H), 1.89 (t, J=7.3 Hz, 2H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s), 134.8 (d), 134.6 (s), 129.8 (d), 128.2 (d), 127.6 (d), 127.5 (d), 127.4 (d), 74.8 (s), 72.9 (t), 67.0 (t), 50.0 (q), 43.9 (t), 30.2 (q); ESMS: *m/z*: 429 [M+Na]$^+$; HR ESMS exact mass calculated for $C_{25}H_{30}O_3SiNa$ [M+Na]: 429.1856; found 429.1851.

3.1.5. (2*S*)-[(3-Benzyloxy-1,1-dimethylpropoxy)dimethylsilanoxy]propionic acid methyl ester (10). Following the general method described for siloxane **8**, compound **10** was obtained as a colourless oil (1.62 g, 3.39 mmol, 93%) by the reaction between silyl chloride **7** and *S*-(−)-methyl lactate (**17**). R_f: 0.50 (hexane/EtOAc, 5:1); $[\alpha]_D$: −1.84 (*c* 5.2, EtOAc); FTIR (neat) ν_{max}: 3068 (w), 3035 (w), 2983 (w), 1748 (s), 1360 (w), 1124 (s), 1062 (s), 854 (s), 850 (s), 741 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (m, 4H), 7.25–7.50 (m, 11H), 4.46 (s, 2H), 4.44 (q, J=6.6 Hz, 1H), 3.66 (t, J=7.3 Hz, 2H), 3.59 (s, 3H), 1.88 (t, J=7.3 Hz, 2H), 1.37 (d, J=6.6 Hz, 3H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.0 (s), 138.5 (s), 135.1 (d), 134.3 (d), 134.1 (d), 130.0 (d), 128.3 (d), 127.6 (d), 127.5 (s), 75.2 (s), 72.9 (t), 68.2 (d), 67.0 (t), 51.7 (q), 43.8 (t), 30.2 (q), 21.2 (q); ^{29}Si NMR (80 MHz, $CDCl_3$) δ: −56.4; CIMS *m/z*: 285 [Ph_2Si=O–$CH(CH_3)$(C=O)OMe]$^+$ (50%), 177 [$BnOCH_2CH_2(CH_3)_2C$]$^+$ (36%), 91 [$C_6H_5CH_2$]$^+$ (100%); HR ESMS exact mass calculated for $C_{28}H_{34}O_5SiNa$ [M+Na]: 501.2068; found 501.2080. Anal. Calcd for $C_{28}H_{34}O_5Si$: C, 70.26 H, 7.16; found: C 70.30, H 7.07.

3.1.6. (1*R*,2*S*,5*R*)-(3-Benzyloxy-1,1-dimethylpropoxy)-(2-isopropyl-4-methylcyclohexyloxy)diphenylsilane (11). Following the general method described for siloxane **8**, compound **11** was obtained as a colourless oil (1.74 g, 3.28 mmol, 90%) by the reaction between silyl chloride **7** and (1*R*,2*S*,5*R*)-(−)-menthol (**18**). R_f: 0.57 (hexane/CH_2Cl_2, 1:1); $[\alpha]_D$: −0.25 (*c* 1, EtOAc); FTIR (neat) ν_{max}: 3067 (w), 2953 (w), 2921 (w), 1156 (m), 1111 (s), 1049 (s), 740 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70–7.60 (m, 4H), 7.45–7.25 (m, 11H), 4.46 (s, 2H), 3.68 (t, J=7.0 Hz, 2H), 3.49 (td, J=10.0, 4.0 Hz, 1H), 2.32 (m, 1H), 1.95 (m, 1H), 1.86 (t, J=7.0 Hz, 2H), 1.47–1.60 (m, 2H), 1.35–1.00 (m, 9H), 0.86 (d, J=7.3 Hz, 3H), 0.81 (d, J=6.0 Hz, 3H, overlapped with 2H, m), 0.49 (d, J=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.6 (s), 136.0 (s), 135.5 (d), 135.1 (d), 129.6 (d), 128.3 (d), 127.6 (d), 127.4 (d), 74.7 (s), 73.5 (d), 72.9 (t), 67.2 (t), 50.2 (d), 45.4 (t), 43.9 (t), 34.4 (t), 31.5 (d), 30.3 (q), 25.2 (d), 22.6 (t), 22.3 (q), 21.3 (q), 15.6 (q); ^{29}Si NMR (80 MHz, $CDCl_3$) δ: −49.3; EIMS *m/z*: 395 [$(CH_3)_2C$=$OSiPh_2OMenthyl$]$^+$ (8%), 337 [Ph_2Si=$OMenthyl$]$^+$ (10%), 199 [Ph_2Si=OH]$^+$ (89%), 91 [$C_6H_5CH_2$]$^+$ (100%); HR ESMS exact mass calculated for $C_{34}H_{46}O_3SiNa$ [M+Na]: 553.3108; found: 553.3104.

3.1.7. (1*S*,2*R*)-(3-Benzyloxy-1,1-dimethylpropoxy)-diphenyl-(1,1,7-trimethylbicyclo[2.2.1]hept-2-yloxy)silane (12). Following the general method described for siloxane **8**,

compound **12** was obtained as a colourless oil (1.81 g, 3.43 mmol, 94%) by the reaction between silyl chloride **7** and *endo*-(1*S*)-(−)-borneol (**19**). R_f: 0.57 (hexane/CH_2Cl_2, 1:1); $[\alpha]_D$: −0.18 (*c* 5.5, EtOAc); FTIR (neat) ν_{max}: 3067 (s), 2948 (m), 2871 (w), 1163 (m), 1113 (s), 1064 (s), 1037 (s), 739 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (t, *J*=5.8 Hz, 4H), 7.45–7.22 (m, 11H), 4.45 (s, 2H), 4.12 (ddd, *J*=9.5, 2.9, 1.4 Hz, 1H), 3.67 (t, *J*=7.0 Hz, 2H), 2.21 (m, 1H), 1.88 (t, *J*=7.0 Hz, 2H), 1.67 (m, 1H), 1.51 (m, 1H), 1.35–1.14 (m, 9H), 0.99 (dd, *J*=13.2, 3.7 Hz, 1H), 0.79 (s, 3H), 0.71 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s), 135.8 (s), 135.6 (s), 135.0 (d), 129.6 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 78.0 (d), 74.6 (s), 72.9 (t), 67.2 (t), 50.0 (s), 47.2 (s), 45.1 (d), 44.0 (t), 39.0 (t), 30.0 (s), 28.3 (t), 26.5 (t), 20.2 (q), 18.7 (q), 13.7 (q); ESMS *m*/*z*: 551 $[M+Na]^+$; HR ESMS exact mass calculated for $C_{34}H_{44}O_3SiNa$ [M+Na]: 551.2952; found: 551.2953.

3.1.8. (3-Benzyloxy-1,1-dimethylpropoxy)chlorodimethylsilane (13). To a rapidly stirred solution of dichlorodimethylsilane (90 μL, 0.73 mmol) in CH_2Cl_2 (15 mL), Et_3N (153 μL, 1.10 mmol) was added, followed by 3° alcohol **6** (142 mg, 0.73 mmol) and DMAP (90 mg, 0.73 mmol). After the complete disappearance of the starting material (5 min, TLC hexane/EtOAc, 3:1) the solution containing (3-benzyloxy-1,1-dimethylpropoxy)chlorodimethylsilane (**13**) was used directly for further transformations.

3.1.9. (1*R*,2*S*,5*R*)-(3-Benzyloxy-1,1-dimethylpropoxy)-(2-isopropyl-4-methylcyclohexyloxy)dimethylsilane (14). To a solution containing the dimethylsiloxane **13** (0.73 mmol, theoretical) in CH_2Cl_2 (15 mL) prepared following the above procedure, Et_3N (153 μL, 1.10 mmol) was added followed by (1*R*,2*S*,5*R*)-(−)-menthol (**18**, 103 mg, 0.66 mmol) and DMAP (90 mg, 0.73 mmol). After the complete disappearance of **13** that was observed by TLC (hexane/EtOAc, 6:1) the reaction mixture was partitioned between water and Et_2O (100 mL of each). The aqueous phase was extracted with Et_2O (2×100 mL) and the combined organics were washed with 10% $KHSO_4$ (100 mL), brine (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica (hexane/EtOAc, 6:1) afforded pure **14** (268 mg, 0.66 mmol, 100% based on menthol) as a colourless oil. R_f: 0.70 (hexane/EtOAc, 6:1); FTIR (neat) ν_{max}: 2950 (w), 2916 (w), 1252 (m), 1110 (s), 1062 (s), 1048 (s), 788 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.22 (m, 5H), 4.48 (s, 2H), 3.60 (t, *J*=7.3 Hz, 2H), 3.50 (td, *J*=10.3, 4.4 Hz, 1H), 2.17 (m, 1H), 1.98–1.87 (m, 1H), 1.83 (t, *J*=7.3 Hz, 2H), 1.70–1.50 (m, 2H), 1.45–1.22 (m, 1H, overlapped with a singlet at 1.27, 6H), 1.18–0.90 (m, 3H), 0.87 (d, *J*=7.3 Hz, 6H), 0.83–0.76 (m, 1H), 0.72 (d, *J*=6.6 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s), 128.3 (d), 127.5 (d), 127.4 (d), 73.1 (s), 72.9 (t), 72.2 (d), 67.2 (t), 49.8 (d), 45.3 (t), 43.9 (t), 34.5 (t), 31.6 (d), 30.2 (q), 25.2 (d), 22.8 (t), 22.3 (q), 21.2 (q), 15.9 (q), 1.0 (q), 0.7 (q); ^{29}Si NMR (80 MHz, $CDCl_3$) δ: −15.9; CIMS *m*/*z*: 271 $[Me_2C{=}OSiMe_2{-}OMenthyl]^+$ (37%), 251 $[BnOC_2H_4C(CH_3)_2O{=}SiMe_2]^+$ (80%), 91 $[C_6H_5CH_2]^+$, (100%), 75 $[Me_2Si{=}OH]^+$ (34%). Elemental analysis: anal. calcd for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41; found: C, 70.45, H, 10.81.

3.1.10. 4-(Polystryloxy)-2-methyl-2-butanol (4).

3.1.10.1. Method 1. To a solution of 3-methyl-1,3-butanediol (**5**, 512 μL, 4.80 mmol) in dry THF (12 mL) at 0 °C, *tert*-BuOK (4.80 mmol, 1 M solution in THF) was added followed by 18-crown-6 (1.20 g, 4.80 mmol). The reaction was allowed to run for 1 h at 0 °C and for 3 h at rt. The yellow solution was then transferred via cannula to a flask containing Merrifield resin (1.00 g, loading=1.6 mmol/g, pre-swollen in dry THF for 2 h) under N_2, and the resulting suspension was shaken for 3.5 days. The resin was then washed with THF (5×5 mL, 2 min), DMF (5×5 mL, 2 min), 1:1 DMF/H_2O (5×5 mL, 2 min), DMF (5×5 mL, 2 min), THF (5×5 mL, 2 min), CH_2Cl_2 (5×5 mL, 2 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.10.2. Method 2: microwave-assisted formation of resin 4. To a solution of 3-methyl-1,3-butanediol (**5**, 512 μL, 4.80 mmol) in dry THF (12 mL) at 0 °C, *tert*-BuOK (4.80 mmol, 1 M solution in THF) was added followed by 18-crown-6 (1.20 g, 4.80 mmol). The reaction was allowed to run for 1 h at 0 °C and for 3 h at rt. The yellow solution was then transferred via cannula into a capped vial containing Merrifield resin (1.00 g, loading=1.6 mmol/g, pre-swollen in dry THF for 2 h) under N_2. The resulting suspension was then heated in a SmithSynthesizer™ microwave reactor at 120 °C for 10 min; the resin was then washed with THF (5×5 mL, 2 min), DMF (5×5 mL, 2 min), 1:1 DMF/H_2O (5×5 mL, 2 min), DMF (5×5 mL, 2 min), THF (5×5 mL, 2 min), CH_2Cl_2 (5×5 mL, 2 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h. FTIR (on-bead) ν_{max}: 3458 (s), 3059 (s), 2885 (s), 1153 (s), 1093 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 73.0 (t), 70.3 (s), 67.4 (t), 41.4 (t), 29.2 (q).

3.1.11. [3-(Polystyryloxy)-1,1-dimethylpropoxy]-(chloro)-diphenylsilane (3). Resin **4** (200 mg) was briefly rinsed with dry CH_2Cl_2 (10 mL, 3 min). Then freshly dried CH_2Cl_2 (10 mL) was added followed by Et_3N (0.27 mL, 1.92 mmol), diphenyldichlorosilane (0.27 mL, 1.30 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was then sealed and shaken at rt for 1 h. The resin was then drained, rinsed with dry CH_2Cl_2 (3×5 mL, 1 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h. The loading of resin **3** (0.65–0.70 mmol/g) was determined employing the method described below. FTIR (on-bead) ν_{max}: 3058 (s), 2975 (s), 1601 (s), 1154 (s), 744 (s), 700 (s).

3.1.12. Siloxane resin 21. A typical procedure is as follows: resin **3** (200 mg, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (10 mL). Then Et_3N (0.27 mL, 1.92 mmol) was added followed by *trans*-cinnamyl alcohol (**15**, 175 mg, 1.30 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was shaken for 1 h. The resin was then drained and washed with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h. In the same way resins **22**–**25** and **47** were obtained. FTIR (on the bead) ν_{max}: 3026 (s), 2924 (s), 1600 (s), 1156 (s), 740 (s); gel phase ^{13}C NMR (75 MHz, C_6D_6) δ: 75.3 (s), 73.0 (t), 67.8 (t), 44.3 (t), 29.2 (q).

3.1.13. Loading calculation by GC measurement of the cleaved cinnamyl alcohol from resin 21. Resin **21**

(100 mg) was suspended in THF (5 mL), then TBAF (0.16 mmol, 2.5 equiv respect to the loading of the resin **3**) was added and the resulting suspension was vigorously stirred at rt for 2 h. Then, the resin was drained and washed with THF (2×3 mL, 5 min). The original solution and the washings were collected and partitioned between water (10 mL) and Et_2O (15 mL). TLC analysis of the organic phase showed the presence of the *trans*-cinnamyl alcohol (**15**), and its amount was then quantified by GC by comparison with standard solutions.

3.1.14. (3-Polystyryloxy-1,1-dimethylpropoxy)decanoxydiphenylsilane (22). Resin **22** was prepared following the procedure described above for the synthesis of resin **21**. FTIR (on-bead) ν_{max}: 3058 (w), 2918 (w), 1603 (m), 1153 (s), 1118 (s), 1050 (s), 913 (s).

3.1.15. (2*S*)-2-[(3-Polystyryloxy-1,1-dimethylpropoxy)diphenylsilanoxy]propionic acid methyl ester (23). Resin **23** was prepared following the procedure described above for the synthesis of resin **21**. FTIR (on-bead) ν_{max}: 3058 (s), 2852 (s), 1758 (s), 1601 (s), 1125 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8 (s), 75.2 (s), 72.7 (t), 68.1 (d), 51.6 (q), 30.2 (q), 21.1 (q).

3.1.16. (1*R*,2*S*,5*R*)-(3-Polystryloxy-1,1-dimethyl-propoxy)-(2-isopropyl-5-methylcyclohexyloxy)diphenylsilane (24). Resin **24** was prepared following the procedure described above for the synthesis of resin **21**. FTIR (on the bead) ν_{max}: 3060 (s), 2917 (s), 3027 (s), 1600 (s), 1068 (s), 760 (s).

3.1.17. (1*S*,2*R*)-(3-Polystryloxy-1,1-dimethylpropoxy)-diphenyl-(1,1,7-trimethylbicyclo[2.2.1]hept-2-yloxy)silane (25). Resin **25** was prepared following the procedure described above for the synthesis of resin **21**. FTIR (on the bead) ν_{max}: 2926 (s), 1601 (m), 1604 (s), 907 (m), 860 (s).

3.1.18. 6-[(3-Polystyryloxy-1,1-dimethylpropoxy)diphenylsilanoxy]hexan-2-ol (28). Resin **3** (200 mg, 0.65 mmol/g) was suspended in freshly dried CH_2Cl_2 (4 mL) and then dry Et_3N (1.92 mmol) was added followed by 1,5-hexanediol (1.60 mmol). The system was purged with N_2 for 5 min and then sealed. The resulting suspension was shaken at rt for 1.5 h. Then, the resin was drained, rinsed thoroughly with CH_2Cl_2 (5×10 mL) and dried under high vacuum (40 °C at 10 mmHg) for 48 h to afford resin **28**. FTIR (on-bead) ν_{max}: 3392 (s), 3063 (s), 2971 (s), 1601 (s), 1157 (s), 1119 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 74.0 (s), 67.8 (d), 62.7 (t), 38.8 (t), 32.2 (t), 30.3 (s), 23.3 (t), 21.9 (q).

3.1.19. Benzoylation of polymer supported diol 28 to give resin 29. Resin **28** (100 mg) was suspended in dry CH_2Cl_2 (3 mL) under N_2. Then, freshly dried pyridine (1.12 mmol) was added, followed by benzoyl chloride (0.80 mmol). The resulting suspension was then sealed and shaken for 24 h at rt. Then, the resin was drained, washed thoroughly with dry CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 48 h to afford resin **29**. FTIR (on-bead) ν_{max}: 3062 (s), 2974 (s), 1715 (s), 1601 (s), 1275 (s), 1156 (s), 1120 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0 (s), 74.8 (s), 71.5 (d), 62.6 (t), 35.7 (t), 32.1 (t), 30.3 (s), 21.7 (t), 20.0 (q).

3.1.20. 5-Benzyloxy-1-hexanol (30). Resin **29** (100 mg) was suspended in THF (3 mL), then HF·pyridine was added (1.00 mL) and the resulting suspension was vigorously stirred at rt for 1 h. After this period the solution was collected and the resin was washed thoroughly with THF (5×5 mL, 5 min). The washings and the original solution were combined and partitioned between saturated $NaHCO_3$ (30 mL) and Et_2O (30 mL). The aqueous phase was then further extracted with Et_2O (5×10 mL) and the organics were dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **30** as a colourless oil (12 mg, 0.05 mmol, 80% overall yield from the loading of **3**). Spectroscopic data were consistent with the literature.[32] R_f: 0.23 (hexane/EtOAc, 7:3).

3.1.21. (3-Polystyryloxy-1,1-dimethylpropoxy)chlorodimethylsilane (31). Resin **4** (500 mg) was suspended in a mixture of dichlorodimethylsilane (0.97 mL, 8.00 mmol) and Et_3N (1.67 mL, 12.00 mmol) in dry CH_2Cl_2 (10 mL) under N_2. DMAP (0.97 g, 8.00 mmol) was added and the resulting suspension was shaken at rt for 1 h. The resin was then drained under N_2, rinsed with CH_2Cl_2 (2×5 mL, 1 min) and used immediately for the successive transformations. The loading of resin **31** was determined employing the methods described above for resin **21**, and it was found to be 0.37 mmol/g.

3.1.22. [3-(Polystyryloxy)-1,1-dimethylpropoxy]-dimethyl-{[(*E*)-3-phenyl-2-propenyl]oxy}silane (32). Resin **32** was prepared following the procedure described below for the synthesis of resin **33**. FTIR (on-bead) ν_{max}: 3060 (s), 2853 (s), 1601 (s), 1186 (s), 1156 (s), 822 (s).

3.1.23. (1*R*,2*S*,5*R*)-(3-Polystryloxy-1,1-dimethylpropoxy)-(2-isopropyl-5-methylcyclohexyloxy)dimethylsilane (33). Resin **31** was suspended in dry CH_2Cl_2 (10 mL) and then Et_3N (1.67 mL, 12.00 mmol) was added, followed by (1*R*,2*S*,5*R*)-(−)-menthol (**18**, 1.07 g, 8.00 mmol) and DMAP (0.97 g, 8.00 mmol). The suspension was sealed and shaken at rt for 1 h. The resin was then drained and washed with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h. FTIR (on the bead) ν_{max}: 3083 (s), 3060 (s), 1602 (s), 1161 (s), 1067 (s), 881 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 73.8 (s), 73.4 (t), 72.9 (d), 50.6 (d), 46.0 (t), 44.6 (t), 35.2 (d), 32.3 (d), 30.8 (q), 25.9 (d), 23.6 (t), 22.9 (q), 21.8 (q), 16.6 (q), 1.7 (q), 1.4 (q); gel phase ^{29}Si NMR (60 MHz, $CDCl_3$) δ: −12.7.

3.1.24. Resin 34. Resin **34** was prepared following the procedure described above for the synthesis of resin **33**. FTIR (on-bead) ν_{max}: 3063 (s), 2924 (s), 1158 (s, C–O), 1116 (s, C–O).

3.1.25. General procedure for the reactions of polymer-bound ester (23) with Grignard reagents. Resin **23** (500 mg) was suspended in freshly dried THF (4 mL) under N_2. The resulting suspension was rapidly stirred and cooled to −5 °C. PhMgBr (330 μL, 3 M in THF, 3 equiv based on the loading of **3**) or allyl magnesium bromide (980 μL, 1 M in THF, 3 equiv) was added dropwise. The system was then gradually allowed to return to rt and every 20 min a sample of beads was analysed by FTIR spectroscopy. After the

complete disappearance of the ester band (1 h required), the resin was drained, washed extensively with THF/H_2O/acetone (1:1:1, 5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.26. Resin (35a). Prepared using the general procedure described above. FTIR (on-bead) ν_{max}: 3412 (br), 3026 (s), 2971 (s), 1602 (s), 1154 (s), 1116 (s).

3.1.27. Resin (35b). Prepared using the general procedure described above. FTIR (on-bead) ν_{max}: 3384 (br), 2961 (s), 2874 (m), 1608 (m), 1485 (m), 1116 (s), 1056 (s).

3.1.28. Fluoride-mediated cleavage of diols 36a and 36b from resins 35a and 35b. Resins **35a** and **35b** (110 and 400 mg, respectively) were pre-swollen in THF (3 mL, 20 min). The resins were drained and fresh THF (7 mL) was added, followed by a solution of TBAF in THF (0.18 and 0.65 mmol, respectively, 2.5 equiv with respect to the loading of resin **3**). The resulting suspensions were shaken for 1 h at rt. The solutions were then collected separately and the resins were further washed with THF (3×5 mL, 5 min). The solutions and the washings were combined and Et_2O (25 mL) was added. The organic phases were washed with brine (5×10 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography afforded compounds **36a** and **36b**.

3.1.29. (2*S*)-1,1-Diphenyl-1,2-propanediol (36a). Following the general procedure described above, from resin **35a** (110 mg), compound **36a** was obtained as a white solid (9 mg, 0.04 mmol, 60% overall yield over three steps, based on the loading of **3**). Mp 89–90 °C (lit. 91.5–92 °C).[33]

3.1.30. (2*S*)-3-Allyl-hex-5-ene-2,3-diol (36b). Following the general procedure described above, from resin **35b** (400 mg), compound **36b** was obtained as a colourless oil (21 mg, 0.13 mmol, 53% overall yield based on the loading of **3**). Spectroscopic data were consistent with those previously reported.[34]

3.1.31. (3-Polystyryloxy-1,1-dimethylpropoxy)-(3-iodobenzyloxy)diphenylsilane (37). The silyl chloride resin **3** (1.00 g, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (9 mL). Et_3N (1.33 mL, 9.60 mmol) was added followed by 3-iodobenzyl alcohol (0.80 mL, 6.40 mmol) and DMAP (400 mg, 3.20 mmol). The resulting suspension was shaken at rt for 1 h. The resin **37** was drained, washed with CH_2Cl_2 (10×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.32. General protocol for the Sonogashira coupling between polymer-bound aryl iodide 37 and terminal alkynes.[35] Resin **37** (400 mg) was suspended in a mixture of dry dioxane and Et_3N (3:1) (6 mL) under N_2, then CuI (24 mg, 0.13 mmol) and the appropriate alkyne **40a**, **40b**, **40c** or **40d** (6.60 mmol of each) was added, followed by *trans*-$(PPh_3)_2PdCl_2$ (0.06 mmol). The system was purged with N_2 for 5 min and sealed; the resulting suspension was then wrapped with an aluminium foil and shaken at rt for 24 h. The resin was washed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), water (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.33. Resin 38a. Prepared using the general Sonogashira procedure described above. FTIR (on-bead) ν_{max}: 3027 (m), 2918 (s), 1601 (s), 1015 (s), 753 (s).

3.1.34. Resin 38b. Prepared using the general Sonogashira procedure described above. FTIR (on-bead) ν_{max}: 3414 (s), 3060 (s), 2977 (s), 1602 (s), 1163 (s).

3.1.35. Resin 38c. Prepared using the general Sonogashira procedure described above. FTIR (on-bead) ν_{max}: 3400 (br), 3025 (s), 2924 (s), 1601 (s), 1127 (s).

3.1.36. Resin 38d. Prepared using the general Sonogashira procedure described above. FTIR (on-bead) ν_{max}: 3423 and 3349 (s), 3060 (s), 2975 (s), 1722 (s), 1602 (s), 1247 (s), 1170 (s, C–O).

3.1.37. General protocol for the cleavage of Pd-coupling products from the resin. Resins (300–410 mg) were suspended in THF (5 mL), then TBAF (0.60–0.66 mmol, 2.5 equiv with respect to the loading of silyl chloride resin **3**) was added and the resulting suspension was stirred at rt for 2 h. Then the solution was collected and the resin was washed with THF (5×5 ml, 5 min); the original solution and the washings were collected and partitioned between brine (20 mL) and Et_2O (60 mL). The aqueous phase was extracted again with Et_2O (2×30 mL) and the combined organics were washed further with brine (30 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded the pure products.

3.1.38. (3-Pent-1-ynylphenyl)methanol (39a). Following the general cleavage protocol described above, starting from resin **38a** (371 mg), compound **39a** was obtained as a light yellow oil (39 mg, 0.22 mmol, 93% overall yield based on the loading of silyl chloride resin **3**). R_f: 0.15 (hexane/EtOAc, 6:1); FTIR ($CHCl_3$) ν_{max}: 3324 (br), 2962 (m), 2932 (m), 2871 (m), 1428 (s), 1126 (s), 1042 (s), 788 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60–7.00 (m, 4H), 4.57 (s, 2H), 2.36 (t, J=7.3 Hz, 2H), 2.10 (br s, 1H), 1.60 (sx, J=7.3 Hz, 2H), 1.03 (t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.0 (s), 130.6 (d), 129.9 (d), 128.3 (d), 127.6 (d), 124.1 (s), 90.4 (s), 80.4 (s), 64.7 (t), 22.1 (t), 21.3 (t), 13.5 (q); CIMS *m/z*: 192 $[M+NH_4]^+$ (22%), 174 $[M]^+$ (57%), 145 $[M-C_2H_5]^+$ (64%), 115 (100%), 91 $[C_6H_5CH_2]^+$ (33%); HR CIMS exact mass calculated for $C_{12}H_{14}O$: 174.1045; found: 174.1040.

3.1.39. 4-(3-Hydroxymethylphenyl)-2-methylbut-3-yn-2-ol (39b). Starting from resin **38b** (378 mg), compound **39b** was obtained as a pink oil (45 mg, 0.23 mmol, 96% overall yield from the loading of silyl chloride resin **3**). R_f: 0.23 (hexane/EtOAc, 6:4); FTIR ($CHCl_3$) ν_{max}: 3311 (s, O–H), 2981 (m), 2932 (w), 1362 (m), 1153 (s, C–OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (br s, 1H), 7.36–7.25 (m, 3H), 4.60 (s, 2H), 2.65 (br s, 1H), 2.50 (br s, 1H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.0 (s), 130.7 (d), 130.0 (d), 128.4 (d), 126.7 (d), 122.8 (s), 94.0 (s), 82.0 (s), 65.5 (s), 64.5 (t), 31.4 (q); CIMS *m/z*: 190 $[M]^+$ (7%),

$[M–OH]^+$ (100%), 132 (97%); HR CIMS exact mass calculated for $C_{12}H_{14}O_2$: 190.0994; found: 190.0996.

3.1.40. 3-(3-Hydroxymethylphenyl)propynol (39c). From resin **38c** (392 mg), compound **39c** was obtained as a pink oil (39 mg, 0.24 mmol, 94% overall yield from the loading of silyl chloride resin **3**). R_f: 0.21 (hexane/EtOAc, 6:4); FTIR ($CHCl_3$) ν_{max}: 3305 (br), 2920 (w), 2870 (w), 1429 (m), 1026 (s), 790 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (br s, 1H), 7.37–7.25 (m, 3H), 4.63 (s, 2H), 4.45 (s, 2H), 2.14 (br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.0 (s), 130.8 (d), 130.1 (d), 128.5 (d), 127.0 (d), 122.7 (s), 87.4 (s), 85.4 (s), 64.7 (t), 51.5 (t); CIMS *m/z* (abundance): 180 $[M+NH_4]^+$ (8%), 162 $[M]^+$ (46%), 131 (100%); HR CIMS exact mass calculated for $C_{10}H_{10}O_2$: 162.0681; found: 162.0678.

3.1.41. [3-(3-Hydroxymethylphenyl)prop-2-ynyl]carbamic acid *tert*-butyl ester (39d). Starting from resin **38d** (410 mg), compound **39d** was obtained as a yellow oil (67 mg, 0.25 mmol, 97% overall yield from the loading of silyl chloride resin **3**). R_f: 0.22 (hexane/EtOAc, 6:3); FTIR ($CHCl_3$) ν_{max}: 3398 (s), 3306 (s), 2980 (w), 1685 (s), 1513 (s), 1291 (s), 1158 (s), 1024 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (br s, 1H), 7.35–7.25 (m, 3H), 4.80 (br s, 1H), 4.63 (s, 2H), 4.11 (br d, J=5.0 Hz, 2H), 1.97 (br s), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.3 (s), 141.1 (s), 130.8 (d), 130.1 (d), 128.5 (d), 126.9 (d), 122.8 (s), 85.5 (s), 83.0 (s), 80.0 (s), 64.7 (t), 31.1 (t), 28.4 (q); ESMS *m/z*: 545 $[2M+Na]^+$ (90%); HR ESMS exact mass calculated for $C_{15}H_{19}NO_3Na$ [M+Na]: 284.1257; found: 284.1264.

3.1.42. General protocol for the Heck reaction between polymer-bound aryl iodide 37 and terminal alkenes.[35] To a vigorously stirred suspension of resin **37** (400 mg) in DMA (9 mL), NaOAc (106 mg, 0.78 mmol) was added, followed by Bu_4NCl (144 mg, 0.52 mmol) and the appropriate alkene **43a**, **43b**, **43c** or **43d** (2.73 mmol of each). $Pd(OAc)_2$ (20 mg, 0.08 mmol) was added and the system was purged with N_2 for 10 min; the resulting suspension was stirred and heated at 100 °C for 3 h. Then, the resin was washed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), water (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.43. Resin 41a. Prepared using the general Heck reaction procedure described above. FTIR (on-bead) ν_{max}: 3060 (s), 2970 (s), 1712 (s), 1640 (s), 1601 (s), 1161 (s), 1118 (s), 820 (s).

3.1.44. Resin 41b. Prepared using the general Heck reaction procedure described above. FTIR (on the bead) ν_{max}: 3060 (s), 2973 (s), 1710 (s), 1638 (s), 1602 (s), 1232 (s), 1161 (s).

3.1.45. Resin 41c. Prepared using the general Heck reaction procedure described above. FTIR (on-bead) ν_{max}: 3060 (s), 2972 (s), 1653 (s), 1602 (s), 1115 (s), 821 (s).

3.1.46. Alkene bound resin 41d. Prepared using the general Heck reaction procedure described above. FTIR (on-bead) ν_{max}: 3059 (s), 2923 (s), 1616 (s), 1603 (s), 1309 (s), 1152 (s), 1117 (s), 840 (s).

3.1.47. 3-(3-Hydroxymethylphenyl)acrylic acid butyl ester (42a). From resin **41a** (316 mg), compound **42a** was obtained as a colourless oil (33 mg, 0.14 mmol, 70% overall yield from the loading of silyl chloride resin **3**). R_f: 0.20 (hexane/EtOAc, 6:2); FTIR (neat) ν_{max}: 3420 (br), 2958 (m), 2872 (w), 1707 (s), 1636 (s), 1159 (s), 980 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, J=16.0 Hz, 1H), 7.48 (br s, 1H), 7.43–7.27 (m, 3H), 6.40 (d, J=16.0 Hz, 1H), 4.65 (s, 2H), 4.15 (t, J=6.6 Hz, 2H), 2.56 (br s, 1H), 1.65 (quin, J=8.0 Hz, 2H), 1.40 (sx, J=8.0 Hz, 2H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2 (s), 144.4 (d), 141.7 (s), 134.6 (s), 129.0 (d), 128.7 (d), 127.2 (d), 126.3 (d), 118.3 (d), 64.6 (t), 64.5 (t), 30.7 (t), 19.2 (t), 13.7 (q); CIMS *m/z*: 235 $[M+H]^+$ (16%), 103 $[C_5H_{11}O_2]^+$ (70%), 91 $[C_6H_5CH_2]^+$ (32%); HR CIMS exact mass calculated for $C_{14}H_{18}O_3$: 234.1256; found: 234.1260.

3.1.48. 3-(3-Hydroxymethylphenyl)acrylic acid *tert*-butyl ester (42b). From resin **41b** (355 mg), compound **42b** was obtained as a colourless oil (38 mg, 0.16 mmol, 71% overall yield from the loading of silyl chloride resin **3**). R_f: 0.20 (hexane/EtOAc, 6:2). Spectroscopic data were consistent with the literature.[36]

3.1.49. 3-(3-Hydroxymethylphenyl)-*N*,*N*-dimethylacrylamide (42c). From resin **41c** (312 mg), compound **42c** was obtained as a white solid (29 mg, 0.14 mmol, 70% overall yield from the loading of silyl chloride resin **3**). R_f: 0.13 (CH_2Cl_2/MeOH, 97:3); mp 78–80 °C (hexane/EtOAc); FTIR ($CHCl_3$) ν_{max}: 3254 (s), 2924 (w), 2852 (w), 1648 (s), 1588 (s), 1138 (s), 1054 (s), 786 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, J=15.0 Hz, 1H), 7.48 (br s, 1H), 7.40–7.20 (m, 3H), 6.80 (d, J=15.0 Hz, 1H), 4.66 (s, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 1.89 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8 (s), 142.3 (d), 141.8 (s), 135.4 (s), 128.8 (d), 128.1 (d), 127.1 (d), 125.8 (d), 117.3 (d), 64.7 (t), 37.4 (q), 35.9 (q); ESMS *m/z*: 411 $[2M+H]^+$; HR ESMS exact mass calculated for $C_{24}H_{30}N_2O_4Na$ $[2M+Na]^+$: 433.2098; found: 433.2100.

3.1.50. [3-(2-Benzenesulfonylvinyl)phenyl]methanol (42d). From resin **41d** (327 mg), compound **42d** was obtained as a white solid (39 mg, 0.14 mmol, 67% overall yield from the loading of silyl chloride resin **3**). R_f: 0.21 (CH_2Cl_2/MeOH, 97:3); mp 95–97 °C (hexane/EtOAc); FTIR (neat) ν_{max}: 3336 (br), 3048 (w), 2918 (w), 1618 (m), 1296 (s), 1140 (s), 1083 (s), 757 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J=4.0 Hz, 2H), 7.70–7.30 (m, 8H), 6.83 (d, J=15.0 Hz, 1H), 4.60 (s, 2H), 2.34 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0 (d), 141.9 (s), 140.4 (s), 133.4 (d), 132.4 (s), 129.5 (d), 129.3 (d), 129.1 (d), 127.8 (d), 127.5 (d), 127.2 (d), 126.5 (d), 64.3 (t); ESMS *m/z*: 845 $[3M+Na]^+$; HR ESMS exact mass calculated for $C_{30}H_{28}O_6S_2Na$ $[2M+Na]^+$: 571.1220; found: 571.1224.

3.1.51. General protocol for the Suzuki reaction between polymer-bound aryl iodide 37 and boronic acids.[37] To a vigorously stirred suspension of resin **37** (500 mg) in dry dioxane (7 mL), the boronic acid **46a** or **46b** (1.30 mmol of each) was added, followed by K_2CO_3 (180 mg, 1.30 mmol, previously dissolved in the minimal amount of H_2O). $Pd(OAc)_2$ (10 mg, 0.03 mmol) was then added and the resulting suspension was rapidly stirred at 100 °C for

15 h. The resin was then drained and rinsed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), THF/water 1:1 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.52. Resin 44a. Prepared using the general Suzuki reaction procedure described above. FTIR (on the bead) ν_{max}: 3026 (s), 2972 (s), 1602 (s), 1156 (s), 1060 (s), 830 (s).

3.1.53. Resin 44b. Prepared using the general Suzuki reaction procedure described above. FTIR (on the bead) ν_{max}: 3026 (s), 2973 (s), 1600 (s), 1156 (s), 1116 (s), 822 (s).

3.1.54. (4′-Methoxybiphenyl-3-yl)methanol (45a). From resin **44a** (495 mg), compound **45a** was obtained as a white solid (48 mg, 0.22 mmol, 70% overall yield from the loading of silyl chloride resin **3**). R_f: 0.51 (hexane/EtOAc, 2:1); mp 92–93 °C (hexane/EtOAc) (literature: 94 °C).[36] Spectroscopic data were consistent with the literature.[36]

3.1.55. (3-Thiophen-3-yl-phenyl)methanol (45b). Starting from resin **44b** (476 mg), compound **45b** was obtained as a white solid (39 mg, 0.20 mmol, 67% overall yield from the loading of silyl chloride resin **3**). R_f: 0.34 (hexane/EtOAc, 3:1); mp 88–90 °C (hexane/EtOAc); FTIR ($CHCl_3$) ν_{max}: 3319 (br s), 3102 (w), 2927 (w), 1016 (s), 770 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (br s, 1H), 7.56–7.20 (m, 6H), 4.70 (d, J=5.8 Hz, 2H), 1.96 (t, J=5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.8 (s), 140.1 (s), 134.9 (s), 127.8 (d), 125.1 (d), 125.0 (d), 124.6 (d), 124.5 (d), 123.8 (d), 119.2 (d), 64.1 (t); CIMS m/z (abundance): 190 $[M]^+$ (100%), 173 $[M-OH]^+$ (27%); HR EIMS exact mass calculated for $C_{11}H_{10}OS$: 190.0452; found: 190.0453; elemental analysis: anal. calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85; found: C, 69.39; H, 5.33; S, 16.97.

3.1.56. Resin 47. The silyl chloride resin **3** (246 mg, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (5 mL). Et_3N (0.13 mL, 0.96 mmol) was added followed by 4-hydroxybenzaldehyde (78 mg, 0.64 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was shaken for 1 h. The resin was then drained and washed with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min), and dried under high vacuum (40 °C at 10 mmHg) for 24 h. FTIR (on-bead) ν_{max}: 3058 (s), 2923 (s), 2733 (m), 1699 (s), 1121 (s), 1059 (s), 838 (s).

3.1.57. Resin 48.

3.1.57.1. Imine formation. Resin **47** (245 mg, 0.16 mmol) was suspended in dry $(MeO)_3CH$ (3 mL). Benzylamine (90 μL, 0.80 mmol) was then added and the resulting suspension was shaken at rt for 9 h. After this period the resin was drained, washed with $(MeO)_3CH$ (3×3 mL, 5 min), dry CH_2Cl_2 (3×3 mL, 5 min) and used immediately in the next step.

3.1.57.2. Reduction. The resin was suspended in dry CH_2Cl_2 (3 mL). $Me_4NB(OAc)_3H$ (168 mg, 0.64 mmol) was then added, followed by CH_3CO_2H (27 μL, 0.48 mmol) and the resulting suspension was shaken at rt for 30 h. After this period the resin was drained, washed with CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h.

3.1.58. 4-[(Benzylamino)methyl]phenol (49). Resin **48** (274 mg) was pre-swollen in THF (3 mL). The solvent was drained and fresh THF was added (3 mL), followed by a solution of TBAF in THF (0.48 mmol, 3 equiv with respect to the loading of resin **3**). The resulting suspension was shaken for 1 h at rt. The solution was then collected and the resin was washed with THF (3×5 mL, 5 min). The solution and the washings were combined and Et_2O (20 mL) was added. The organic phase was washed with brine (4×15 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **49** as an oil (23.4 mg, 0.11 mmol, 70% from resin **3**). Spectroscopic data were consistent with the literature.[38]

3.1.59. Resin 51. The silyl chloride resin **3** (100 mg, 0.65 mmol/g Cl) was suspended in dry CH_2Cl_2 (4 mL) and then Et_3N (133 μL, 0.96 mmol) was added, followed by Fmoc-L-Ser-OAllyl (235 mg, 0.64 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was shaken for 1 h at rt. The resin was drained and washed thoroughly with dry CH_2Cl_2 (10×5 mL, 5 min) and dried under high vacuum (40 °C at 10 mmHg) for 24 h. FTIR (on-bead) ν_{max}: 3440 (s), 3063 (s), 2972 (s), 1727 (s), 1601 (s), 1196 (s), 1123 (s); gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.0 (s), 155.8 (s), 143.8 (s), 141.1 (s), 118.8 (t), 75.3 (s), 67.1 (t), 66.1 (t), 63.5 (t), 55.7 (d), 47.0 (d), 30.3 (s).

3.1.60. General procedure for *N*-Fmoc deprotection of resin-bound amino acids and peptides. The initial resin **51** (500 mg) was treated twice with a 20% solution of piperidine in DMF (5.00 mL each, 10 min). Positive ninhydrin test[39] on the resin indicated the presence of the free amino group. Then, the *N*-deprotected amino-resin was washed with DMF (3×5 mL, 5 min) and used immediately for the coupling with the next Fmoc-AA-OH.

3.1.61. General procedure 1 for the solid-phase peptide coupling reactions with Fmoc-AA-OH. To a stirred solution of the Fmoc-AA-OH (3.20 mmol) in a mixture of dry CH_2Cl_2 and DMF (9:1, 10 mL), HOBt (432 mg, 3.20 mmol) was added and stirring was continued for 10 min. DIC (500 μL, 3.20 mmol) was added dropwise and the reaction mixture was stirred for additional 10 min. The resulting solution was then added to the previously *N*-deprotected resin and the corresponding suspension was shaken for 3 h. After this period the ninhydrin test[39] on the resin was negative, indicating substantially no free amino group.

3.1.62. General procedure 2 for solid-phase peptide coupling reactions with Fmoc-AA-OH. Coupling involving the terminal nitrogen of the L-Proline[40] residue was performed with PyBrop (1.50 g, 3.20 mmol) and DIPEA (700 μL, 4.00 mmol) instead of the DIC/HOBt system, employing the same mixture of solvents. The reaction was allowed to run until chloranil test was negative.[41]

3.1.63. Resin-bound dipeptide 52. Resin-bound dipeptide **52** was prepared from resin **51** using the general procedure 1 for peptide coupling described above. FTIR (on-bead)

ν_{max}: 3302 (s), 3026 (s), 2926 (s), 1643 (br s), 1154 (s), 1118 (s).

3.1.64. *N*-Fmoc-L-Phe-L-Ser(OH)-(*O*-Alloc) (53). To resin **52** (524 mg) pre-swollen in CH_2Cl_2 (5 mL) was added TFA (30% in CH_2Cl_2 containing 6% of triethylsilane). The resulting suspension was rapidly stirred for 2 h at rt. After this period the solution was filtered through glass wool and the resin was further washed with CH_2Cl_2 (5×5 mL, 5 min). The washings and the original solution were collected and the excess of TFA was removed under reduced pressure to give an oily residue. Chromatography on silica and precipitation with cold Et_2O afforded **53** as a white amorphous solid (157 mg, 0.30 mmol, 90% overall yield based on the loading of resin **3**). R_f: 0.36 (hexane/EtOAc, 1:1); mp 188–190 °C (hexane/EtOAc); $[\alpha]_D^{25}$: −14.0 (*c* 0.25, MeOH); FTIR ($CHCl_3$) ν_{max}: 3293 (br), 3065 (w), 1741 (s), 1726 (s), 1662 (s), 1545 (s), 1293 (s), 1046 (s); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.45 (d, J=7.5 Hz, 1H), 7.86 (d, J=7.5 Hz), 7.67–7.56 (m, 3H), 7.43–7.05 (m, 9H), 5.95–5.81 (m, 1H), 5.33 (dd, J=17.0, 1.5 Hz, 1H), 5.18 (dd, J=10.5, 1.5 Hz, 1H), 5.12 (t, J=5.5 Hz, 1H), 4.58 (d, J=5.0 Hz, 2H), 4.50–4.32 (m, 2H), 4.20–4.00 (m, 3H), 3.78 (m, 1H), 3.67 (m, 1H), 3.04 (dd, J=13.5, 3.0 Hz, 1H), 2.76 (dd, J=13.5, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.1 (s), 170.3 (s), 155.9 (s), 143.8 (s), 140.7 (s), 138.3 (s), 132.5 (d), 129.4 (d), 128.1 (d), 127.7 (d), 127.2 (d), 126.3 (d), 125.4 (d), 120.2 (d), 117.6 (t), 65.8 (t), 65.0 (t), 61.3 (t), 56.0 (d), 54.9 (d), 46.7 (d), 37.6 (t); ESMS *m*/*z*: 537 $[M+Na]^+$; HR ESMS exact mass calculated for $C_{30}H_{30}N_2O_6Na$ $[M+Na]^+$: 537.1996; found: 537.1982.

3.1.65. Heptapeptide 54. Heptapeptide **54** was prepared from resin **51** using the general deprotection, coupling and cleavage procedures described above. The following amino acids were used: (1) Fmoc-L-PheOH; (2) Fmoc-L-IleOH; (3) Fmoc-L-LeuOH; (4) Fmoc-L-ProOH; (5) Fmoc-L-IleOH; (6) Fmoc-L-ProOH. Following TFA cleavage, chromatography on silica and final precipitation with cold Et_2O afforded **54** as a white amorphous solid (230 mg, 0.22 mmol, 60% overall yield from the loading of **3**). R_f: 0.50 (EtOAc/MeOH, 60:1); mp 150–153 °C (dec); FTIR ($CHCl_3$) ν_{max}: 3300 (br), 2964 (m), 2878 (m), 1642 (s), 1528 (s), 1188 (s), 1131 (s), 740 (s); NMR analysis was complicated by the presence of different rotamers. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.32 (d, J=7.5 Hz, 1H), 8.05–7.92 (m, 2H), 7.86 (d, J=6.5 Hz, 2H), 7.70–7.60 (m, 2H), 7.53 (d, J=8.0 Hz, 1H), 7.40 (t, J= 7.5 Hz, 2H), 7.30 (d, J=5.0 Hz, 2H), 7.26–7.08 (m, 6H), 5.85 (m, 1H), 5.32 (dd, J=17.0, 1.5 Hz, 1H), 5.18 (dd, J=10.5, 1.5 Hz, 1H), 5.12 (t, J=5.0 Hz, 1H), 4.65 (m, 1H), 4.57 (d, J=5.0 Hz, 2H), 4.42–4.15 (m, 7H), 4.13–3.95 (m, 2H), 3.79–3.60 (m, 3H), 3.58–3.40 (m, 3H), 3.05 (dd, J=14.0, 4.0 Hz, 1H), 2.76 (dd, J=14.0, 10.0 Hz, 1H), 2.10–0.91 (m, 17H), 0.89–0.69 (m, 15H), 0.67 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.2 (s), 171.8 (s), 171.6 (s), 171.5 (s), 171.4 (s), 170.7 (s), 170.2 (s), 154.1 and 154.0 (s), 144.1, 143.9 and 143.6 (s), 140.9, 140.8 and 140.7 (s), 137.8 (s), 132.5 (d), 129.2 (d), 128.1 (d), 127.8 (d), 127.3 (d), 126.3 (d), 125.8 (d), 125.4 (d), 125.3 (d), 120.2 (d), 117.7 (t), 67.1 and 66.7 (t), 65.0 (t), 61.4 (t), 59.5 (d or q), 59.2 (d or q), 56.9 (d or q), 55.0 (d or q), 54.8 (d or q), 53.4 (d or q), 51.3 (d or q), 47.4 (t), 47.3 (t), 46.8 (d or q), 46.6 (t), 40.0 (t), 37.7 (t), 36.9 (d or q), 36.4 (d or q), 31.6 (t), 30.8 (d or q), 30.0 (t), 29.1 (t), 24.6 (t), 24.4 (t), 24.1 (t), 23.3 (d or q), 21.8 (d or q), 15.3 (d or q), 15.1 (d or q), 15.0 (d or q), 11.0 (d or q), 10.8 (d or q); ESMS *m*/*z*: 1070 [M+Na].

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References and notes

1. (a) Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2109–2135; (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, 1994; (c) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, NY, 1999.
2. For selected linker reviews, see: (a) Wills, A. J.; Balasubramanian, S. *Curr. Opin. Chem. Biol.* **2003**, *7*, 346–352; (b) James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946; (c) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
3. For some reviews of solid-phase synthesis and combinatorial chemistry, see: (a) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2289–2337; (b) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293–3320; (c) Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623–679; (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600.
4. Chan, T. H.; Huang, W. Q. *J. Chem. Soc., Chem. Commun.* **1985**, 909–910.
5. Randolph, J. T.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5712–5719.
6. Nakamura, K.; Ishii, A.; Ito, Y.; Nakahara, Y. *Tetrahedron* **1999**, *55*, 11253–11266.
7. Thompson, L. A.; Moore, F. L.; Moon, Y. C.; Ellman, J. A. *J. Org. Chem.* **1998**, *63*, 2066–2067.
8. Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315–3319.
9. Lindsley, C. W.; Chan, L. K.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 422–423.
10. Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716–3722.
11. (a) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999–12000; (b) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006–6007; (c) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076–7077; (d) Schuster, M.; Lucas, N.; Blechert, S. *Chem. Commun.* **1997**, 823–824.
12. (a) Lee, Y.; Silverman, R. B. *Org. Lett.* **2000**, *2*, 3743–3746; (b) Gu, W.; Liu, S.; Silverman, R. B. *Org. Lett.* **2002**, *4*, 4171–4174; (c) Gu, W.; Silverman, R. B. *J. Org. Chem.* **2003**, *68*, 8774–8779.
13. Lipshutz, B. H.; Shin, Y. J. *Tetrahedron Lett.* **2001**, *42*, 5629–5633.

14. (a) Mullen, D. G.; Barany, G. *J. Org. Chem.* **1988**, *53*, 5240–5248; (b) Chao, H. G.; Bernatowicz, M. S.; Reiss, P. D.; Klimas, C. E.; Matsueda, G. R. *J. Am. Chem. Soc.* **1994**, *116*, 1746–1752; (c) Routledge, A.; Stock, H. T.; Flitsch, S. L.; Turner, N. J. *Tetrahedron Lett.* **1997**, *47*, 8287–8290.
15. Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877–3882.
16. Recently a *tert*-butyldiarylsilyl linker was prepared from metallated polystyrene, see: DiBlasi, C. M.; Macks, D. E.; Tan, D. S. *Org. Lett.* **2005**, *7*, 1777–1780.
17. Stöver, H. D. H.; Lü, P. Z.; Fréchet, J. M. J. *Polym. Bull.* **1991**, *25*, 575–582.
18. (a) Stranix, B. R.; Liu, H. Q.; Darling, G. D. *J. Org. Chem.* **1997**, *62*, 6183–6186; (b) Hu, Y.; Porco, J. A. J.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518–4521.
19. Smith, E. M. *Tetrahedron Lett.* **1999**, *40*, 3285–3288.
20. For an example of direct silylether formation from a polymer-bound silane, see: Hu, Y.; Porco, J. A. J. *Tetrahedron Lett.* **1998**, *39*, 2711–2714.
21. (a) Savin, K. A.; Woo, J. C. G.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 4183–4186; (b) Routledge, A.; Wallis, M. P.; Ross, K. C.; Fraser, W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2059–2064; (c) Paterson, I.; Temal-Laïb, T. *Org. Lett.* **2002**, *4*, 2473–2476.
22. (a) Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602–2608; (b) Guindon, Y.; Fortin, R.; Yoakim, C.; Gillard, J. W. *Tetrahedron Lett.* **1984**, *25*, 4717–4720.
23. For a preliminary communication of this work, see: Meloni, M. M.; Brown, R. C. D.; White, P. D.; Armour, D. *Tetrahedron Lett.* **2002**, *43*, 6023–6026.
24. It is possible that the spot observed on the TLC plate could be silanol or another silicon derivative formed by hydrolysis of the chlorosiloxane.
25. Hernandez, A. S.; Hodges, J. C. *J. Org. Chem.* **1997**, *62*, 3153–3157.
26. Successful formation of the 3° alcohol resin could be confirmed by the methyl red test, see: Burkett, B. A.; Brown, R. C. D.; Meloni, M. M. *Tetrahedron Lett.* **2001**, *42*, 5773–5775.
27. For reviews describing solid-phase Pd-catalysed C–C bond formation, see: (a) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885–939; (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549–1581; (c) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137–202.
28. Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811.
29. Albericio, F.; Kates, S. A. Coupling methods: Solid-phase formation of amide and ester bonds. *Solid Phase Synthesis*; Kates, S. A., Albericio, F., Eds.; Marcel Dekker: New York, NY, 2000; pp 275–330.
30. For imine formation, see: Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937–2940.
31. Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778–1784.
32. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930–5933.
33. Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954.
34. Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512–2517.
35. Berteina, S.; Wendeborn, S.; Brill, W. K. D.; De Mesmaeker, A. *Synlett* **1998**, 676–678.
36. Grether, U.; Waldmann, H. *Chem.—Eur. J.* **2001**, *7*, 959–971.
37. Wendeborn, S.; Berteina, S.; Brill, W. K. D.; De Mesmaeker, A. *Synlett* **1998**, 671–675.
38. Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V.; Kovalenko, K.; Forood, B. *J. Comb. Chem.* **2002**, *4*, 290–294.
39. Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147–157.
40. Doi, T.; Iijikuro, I.; Takahashi, T. *Synlett* **1999**, 1751–1753.
41. Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236–237.