# Selenium-Linking Strategy for Traceless Solid-Phase Synthesis: Direct Loading, Aliphatic C−H Bond Formation upon Cleavage and Reaction Monitoring by Gradient MAS NMR Spectroscopy

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*Received April 6, 1998*

The development of a novel traceless linking strategy for the solid-phase synthesis of small non-peptide compounds by the use of resin-bound selenium is described. Compounds were attached by direct loading without the requirement of an auxiliary spacer. We demonstrate the synthesis of a small [2 × 3]-sized library of single alkyl aryl ethers with two points of diversity by the Mitsunobu reaction. The selenium−alkyl bond that attaches the alkyl aryl ethers to the resin was smoothly cleaved under radical conditions by homolysis with tributylstannane and catalytic amount of AIBN to generate an aliphatic C−H bond in the liberated ethers. The selenium atom remains immobilized during the entire synthesis, and in the cleavage step, tributylstannyl phenyl selenide is scavenged on the resin. Reaction monitoring was facilitated by the use of gradient high-resolution magic angle spinning 2D-NMR. This new linking method can be applied to solid-phase synthesis of many classes of organic compounds under a broad variation of reaction conditions.

## Introduction

The current development of new methods for the solid-phase synthesis (SPS) of non-peptide combinatorial libraries can be considered as a renaissance period following the pioneering work of Merrifield,[1] Leznoff,[2] Frechet,[3] and Rapoport.[4] Triggered by publications of Ellman and DeWitt[5] in the early 1990s, a large number of technologies for SPS have appeared in recent years.[6] Whenever a solid-phase strategy for a combinatorial library is considered, the key question is the most suitable choice of linker. The linker has to be stable to all reaction conditions during the synthesis and, after assembly is complete, must liberate the target molecules selectively and without causing degradation or side products.

Among the versatile linker strategies so far developed, the traceless linkers are particularly attractive because the final target compounds are cleaved without leaving a specific functional group behind and bear therefore only those functionalities which have been chosen, for example, for biological activity.

Our interest was devoted to C−H bond-forming traceless linkers. For aromatic C−H bond formation, polystyrene-based silicon[7,8]- and germanium[7]-linking methods have been developed. For aliphatic C−H bond formation, poly(ethylene glycol)-based sulfur-linking[9,10,11] strategies have been reported. In the latter strategies, attachments were indirectly achieved in a multistep procedure and with the help of an auxiliary amide-containing spacer (Figure 1), which is sensitive, for example, to reducing reagents such as $LiAlH_4$. Target compounds were liberated upon C−S bond cleavage by hydrogenolysis with $H_2$/Raney-nickel[10,11] or by homolysis either with tributylstannane/AIBN at elevated temperature[10] or under irradiation.[9] Hydrogenolysis with $H_2$/Raney-nickel proceeds smoothly, but its application is neither very suitable for automated SPS nor compatible with functional groups sensitive to reduction. Homolysis turned out either to be very slow with tributylstannane/AIBN or unselective under irradiation.

Due to these limitations, there is a need for a more generally applicable aliphatic C−H bond-forming, traceless linker. It is well documentated that homolysis with tributylstannane/AIBN of aryl alkyl selenides proceeds faster than for the corresponding sulfides,[12] suggesting alkanes to be more smoothly released from a resin-bound selenide than from resin-bound sulfides previously described. This prompted us to elaborate a C−H bond-forming, traceless linker based on selenium. With the lack of an auxiliary spacer, this strategy offers addition-

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10.1021/jo9806310 CCC: $15.00 © 1998 American Chemical Society
Published on Web 11/17/1998

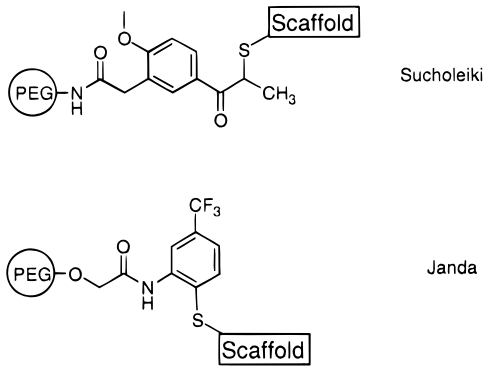


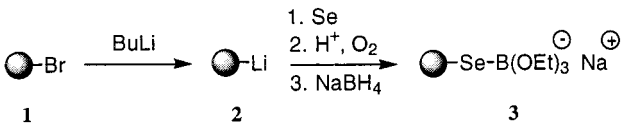

**Figure 1.**

ally the advantage of attachments in a single step by direct loading.

Twenty-two years ago, derivatives of polystyrene-bound selenium were described by Heitz et al.[13,14,15] for use as resin-bound oxidation reagents. Additionally, the authors demonstrated the coupling of polystyrene-bound selenium to the α-position of a carbonyl compound. Cleavage of the corresponding α,β-unsaturated carbonyl compound was achieved by oxidation of the resin-bound selenide to selenoxide and subsequent spontaneous β-elimination.[15] They thus demonstrated the utility of polystyrene-bound selenium as a suitable linker for the attachment and cleavage of compounds. Retrospectively, their work has therefore been a forerunner of modern combinatorial SPS.

In the present paper, we describe a new protocol for the preparation of polystyrene-bound selenium and demonstrate its first application in SPS by the synthesis of a library of single aryl alkyl ethers using the Mitsunobu reaction. Each reaction step was monitored by high-resolution magic angle spinning (HR-MAS) $^1$H NMR spectroscopy, which has been established in recent years for the nondestructive analysis of intermediate resins.[16] In addition, we describe the analysis of intermediate resins by gradient HR-MAS 2D-NMR experiments with the help of an HR-MAS double resonance probehead equipped with a one-axis pulsed field gradient coil.

**Scheme 1**




## Results and Discussion

The preparation of polystyrene-bound selenium **3** used as starting material for the library synthesis is outlined in Scheme 1. The preparation of the resin-bound selenium, following the procedure described by Heitz et al.,[15] was not successful in our hands. Successful preparation was achieved by modifing the procedure elaborated by Farrall and Fréchet[17] for the preparation of polystyrene-bound sulfur from bromopolystyrene **1**. Bromopolystyrene **1** was obtained through thallium acetate-catalyzed bromination of commercially available polystyrene (cross-linked with 1% divinylbenzene).[17] The loading of the resulting resin was determined by elemental analysis for bromine to be 3.7 mmol/g. After lithium−bromine exchange on resin **1** with excess butyllithium (BuLi) in hexane/toluene (1:1) and subsequent removal of the solvents by decantation, the lithiated polystyrene **2** was suspended in THF and treated with selenium powder.

To liberate the resin from excess selenium, the mixture was treated several times with $NaBH_4$ in MeOH. After drying in vacuo, an orange resin was obtained which displayed no visible swelling properties in any solvent. It is very likely that Se−Se bonds were formed by oxidation under air exposure during the workup procedure.[17] The Se−Se bond formation has probably caused a high degree of cross-linking, which explains the poor swelling property.[18] In EtOH, however, within 1−2 h after addition of $NaBH_4$, the resin became distinctly swollen and almost colorless. Simultaneously, an intensive gas generation occurred.

Recently, Miyashita et al.[19] proved that the reaction between diphenyl diselenide and $NaBH_4$ in EtOH results in the formation of hydrogen and the sodium phenylseleno(triethyl)borate complex, $Na[PhSeB(OEt_3)]$, but not of sodium phenyl selenide as previously proposed. Consequently, we suggest the analogous structure **3** for the polystyrene-bound selenide anion after reduction with $NaBH_4$ in EtOH. This also explains our observation of strong and delayed hydrogen generation during reduction and the striking swelling property of the resin in EtOH.

Even though selenium is almost insoluble in THF, the desired reaction with lithiated polystyrene **2** took place. A plausible explanation might be that selenium was solubilized by the formation of soluble lithium butyl polyselenides. The source for lithium butyl polyselenides is possibly the reaction of selenium and lithium butyl selenide formed by reaction of excess BuLi with selenium. The formation of soluble polyselenides after treatment of selenium with, for example, alkali diselenides is well documented and supports the explanation.[20]

To determine the loading of polystyrene-bound selenium, resin **3** was converted into **4** through alkylation with chloro-*N*,*N*-dimethylacetamide using the reaction conditions decribed below (Scheme 2). Elemental analysis for nitrogen revealed a loading of 1.8 mmol/g. No bromine was found by elemental analysis, indicating that the previously performed lithium−bromine exchange has gone to completion. The difference between the initial loading of bromopolystyrene **1** (3.7 mmol/g) and polystyrene-bound selenium (1.8 mmol/g) reveals either that the

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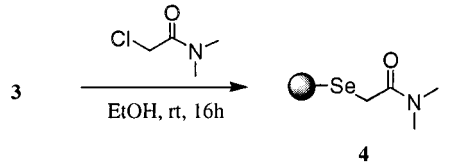
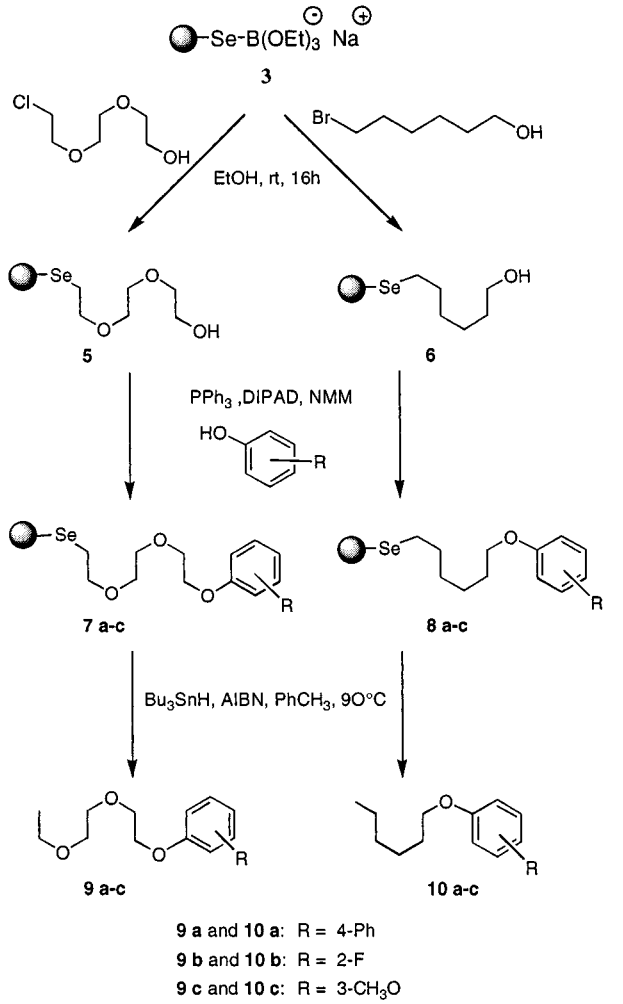
**Scheme 2**




**Scheme 3**




reaction between lithiated polystyrene and selenium was incomplete or that the selenium linker is only partially available for reactions.

The solid-phase synthesis of a [2 × 3]-sized alkyl aryl ether library is outlined in Scheme 3. The first point of diversity was introduced by alkylation of polystyrene-bound selenium with 2-[2-(2-chloroethoxy)ethoxy]ethanol and 6-bromohexanol, respectively, yielding resin-bound alcohols **5** and **6**. Prior to alkylation, the resin was treated with $NaBH_4$ in EtOH to ensure that cross-linking diselenides were reduced. The second point of diversity was introduced by ether formation with phenols by means of the Mitsunobu reaction. The reaction was carried out with triphenylphosphine and diisopropylazadicarboxylate (DIPAD) as reagents in *N*-methyl-morpholine (NMM) as solvent as previously reported.[21] Coupling of each of the resin-bound alcohols **5** and **6** with 4-phenyl-, 2-fluoro-, and 3-methoxy-phenol furnished the six

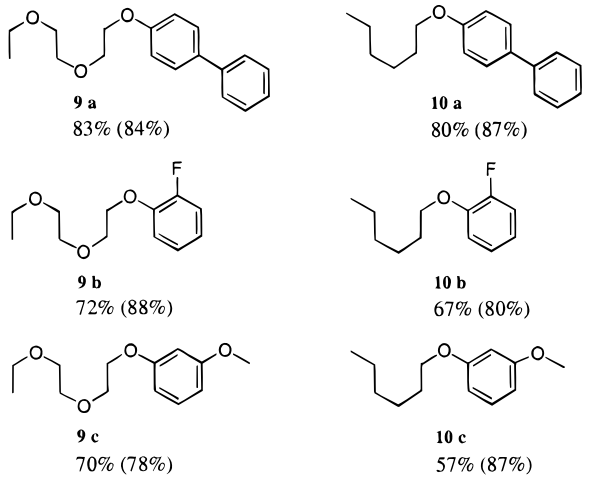



**Figure 2.** Aryl alkyl ether derivatives released from the resins **7 a**−**c** and **8 a**−**c**. The yields are reported for isolated material after purification by solid-phase extraction and are based on the initial loading of resin-bound selenium. The purities measured by GC are given in brackets.

polymer-bound alkyl aryl ethers **7a**−**c** and **8a**−**c**. No resin-bound alcohol was detected by HR-MAS $^1$H NMR, indicating that the coupling went to completion (Figure 4a). Cleavage of the products was achieved with tributylstannane and a catalytic amount of AIBN in toluene at 90 °C for 12 h. HR-MAS $^1$H NMR analyses of the resin after cleavage showed only very pure resin-bound tributylstannyl selenide **11** (Figure 4b) and no traces of the intermediate resin-bound aryl alkyl ethers, revealing that the cleavage was quantitative (see below).

Due to the high selectivity for the cleavage of the bond between selenium and an aliphatic carbon compared with that between selenium and an aromatic carbon,[12] it is expected that selenium remains immobilized on the resin after the cleavage reaction. Accordingly, no contamination with organoselenium impurities was observed in the NMR spectra of the isolated products.

The purification of products from the reduction of alkyl phenyl selenides with tributylstannane in solution is described to be hampered by the presence of the generated tributylstannyl phenyl selenide[22] but not by the presence of excess tributylstannane.[23] Whereas tributylstannane is easily removable, tributylstannyl phenyl selenide causes a problem due to its tendency to hydrolyze on silica gel. In the present cleavage reaction, this interfering byproduct is immobilized on the resin as resin-bound tributylstannyl selenide **11**, and excess of tributylstannane is removed by solid-phase extraction. The generation of **11** is documented by HR-MAS $^1$H NMR of the resin after cleavage (see below).

The alkyl aryl ethers (**9a**−**c** and **10a**−**c**) were obtained as single, discrete compounds in 57−83% yield and 78−88% purity (GC) after purification by solid-phase extraction (Figure 2). The automation of solid-phase extraction makes it possible to purify even large libraries prepared by this method. As documented by GC, tributylstannane is undetectable in the isolated products. According to GC and $^1$H NMR, other residual Sn impurities are either undetectable or at most very low. The linking strategy

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(22) (a) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328−2337. (b) Schlatter, H.-R.; Lüthy, C.; Graf, W. *Helv. Chim. Acta* **1974**, *63*, 1044−1052.

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described is consequently useful for the synthesis of combinatorial libraries with potential use within a number of research areas including material sciences and biological sciences.

Even small traces of organostannyl compounds in the isolated products might cause problems for biological evaluation in screening assays using living cells due to the potent toxicity properties of these substances. In contrast to receptor binding and enzyme assays, this type of assay is, however, seldom used for evaluation of combinatorial libraries. Because the use of proper solid-phase extraction procedures eliminates this problem, the linking strategy has potentially a broad application in the solid-phase synthesis of combinatorial libraries. Alternatively, the removal of the tin reagent could possibly be simplified by, for example, the use of catalytic strategies or by the use of stannanes substituted with fluorinated alkyl groups. These and their byproducts are subsequently removed by extraction into a fluorinated solvent.[24]

The HR-MAS $^1$H NMR spectra of resins **7a** and **11** are shown in Figures 4−7, and the letter coding used in the interpretation of the spectra is shown in Figure 3. HR-MAS $^1$H NMR spectroscopy was carried out at a spinning rate of 4 kHz with 4−5 mg of swollen resin in $CD_2Cl_2$. Interfering backbone signals were sufficiently suppressed by the Carr−Percell−Meibom−Gill spin−echo sequence; however, due to decreases of T2 relaxation times, the signal intensity of protons very close to the backbone were also reduced. Because *J* couplings remained unresolved, full interpretation of the obtained HR-MAS $^1$H NMR spectra is difficult (Figure 4).

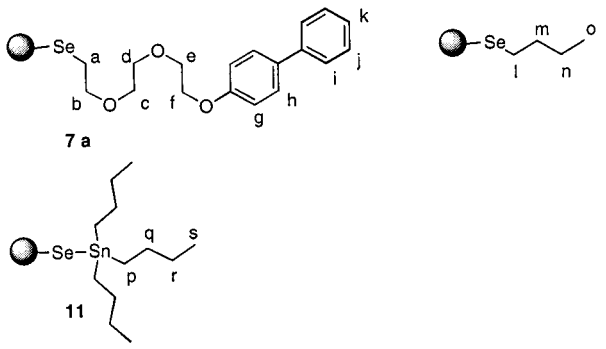


**Figure 3.**

Information about coupling constants in poorly resolved spectra may be obtained from f2 projections of 2D-JRES spectra[25] or from a 2D-E.COSY variant.[26] However, by use of an HR-MAS probehead equipped with a magic angle pulsed field gradient coil, it was found that for these relatively high loaded resin samples sufficient structural information was achieved with fast 2D-COSY45 and optionally 2D-HSQC and 2D-HMBC experiments using gradient coherence selection. The total acquisition time for each of the presented 2D spectra in Figures 5−7 was less than 6 min by use of standard one-axis solution gradient pulse programs. The high quality and short acquisition times obtained make these methods

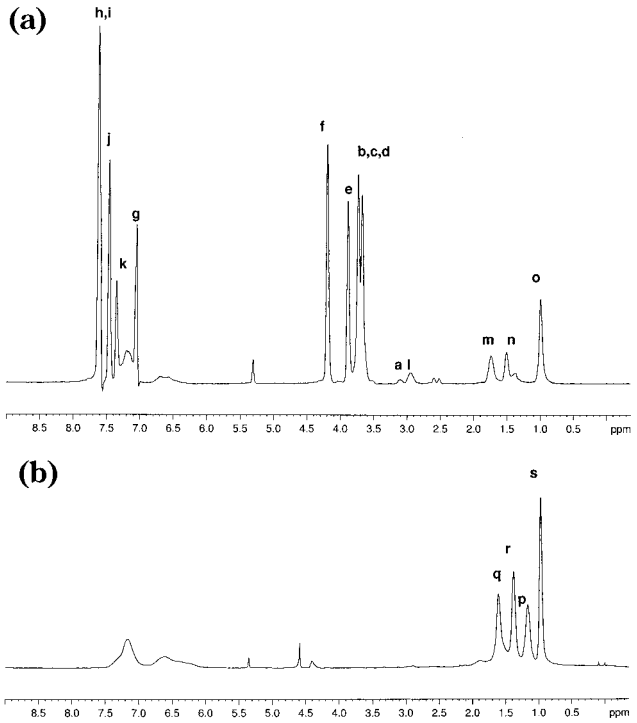


**Figure 4.** MAS $^1$H NMR spectra of **7a** (a) and **11** (b). In each case, 16 scans were acquired. In the case of **7**, a Carr−Percell−Meibom−Gill sequence with 50 cycles and a refocusing delay of 0.0015 s was applied for backbone suppression. The assignment letters refer to Figure 3.

superior for routine analysis of samples with poorly resolved 1D-$^1$H NMR spectra.

From the COSY45 spectrum in Figure 5a, it is possible to identify and assign all protons of polymer-bound aryl alkyl ether **7a** as indicated in Figure 4a. Figure 8 shows the solution-phase 1D-$^1$H NMR of the corresponding liberated aryl alkyl ether **9a**, which correlates well with the 1D-HR-MAS $^1$H NMR for the resin-bound aryl alkyl ether **7a**. As demonstrated in Figure 5a, it would have been very difficult to identify the signal of the methylene group adjacent to selenium without the COSY45 experiment. It appears as a small and broad signal at 3.1 ppm. The assignment of this signal was confirmed by its strong correlation to a superimposed signal at 3.8 ppm and additionally by its weak intensity and broad line shape that correlates to the proximity of this methylene group to the resin backbone.

$^{13}$C chemical shifts of resin-bound intermediates were not available by HR-MAS $^{13}$C NMR spectra due to low signal-to-noise ratios. However, as shown in Figures 6 and 7, valuable information about $^{13}$C chemical shifts were obtained indirectly by 2D-HSQC and 2D-HMBC NMR experiments for proton-bearing carbons and quaternary carbon atoms, respectively.

In all spectra, we found a weak signal pattern of a common impurity. On the basis of the HR-MAS $^1$H NMR spectra of **7a,** the structure of this byproduct was determined to be polymer-bound butyl phenyl selenide, with a broad signal at 2.9 ppm for the selenium-bound methylene group (Figure 4a).[27] This byproduct may have

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(26) Meissner, A.; Bloch, P.; Humpfer, E.; Spraul, M.; Sørensen, O. W. *J. Am. Chem. Soc.* **1997**, *119*, 1787−1788.

(27) The chemical shifts for the aliphatic protons of an authentic sample of butyl phenyl selenide measured by solution-phase $^1$H NMR ($CD_2Cl_2$) are in the range of 0.1 ppm, the same as that for the observed resin-bound impurity.

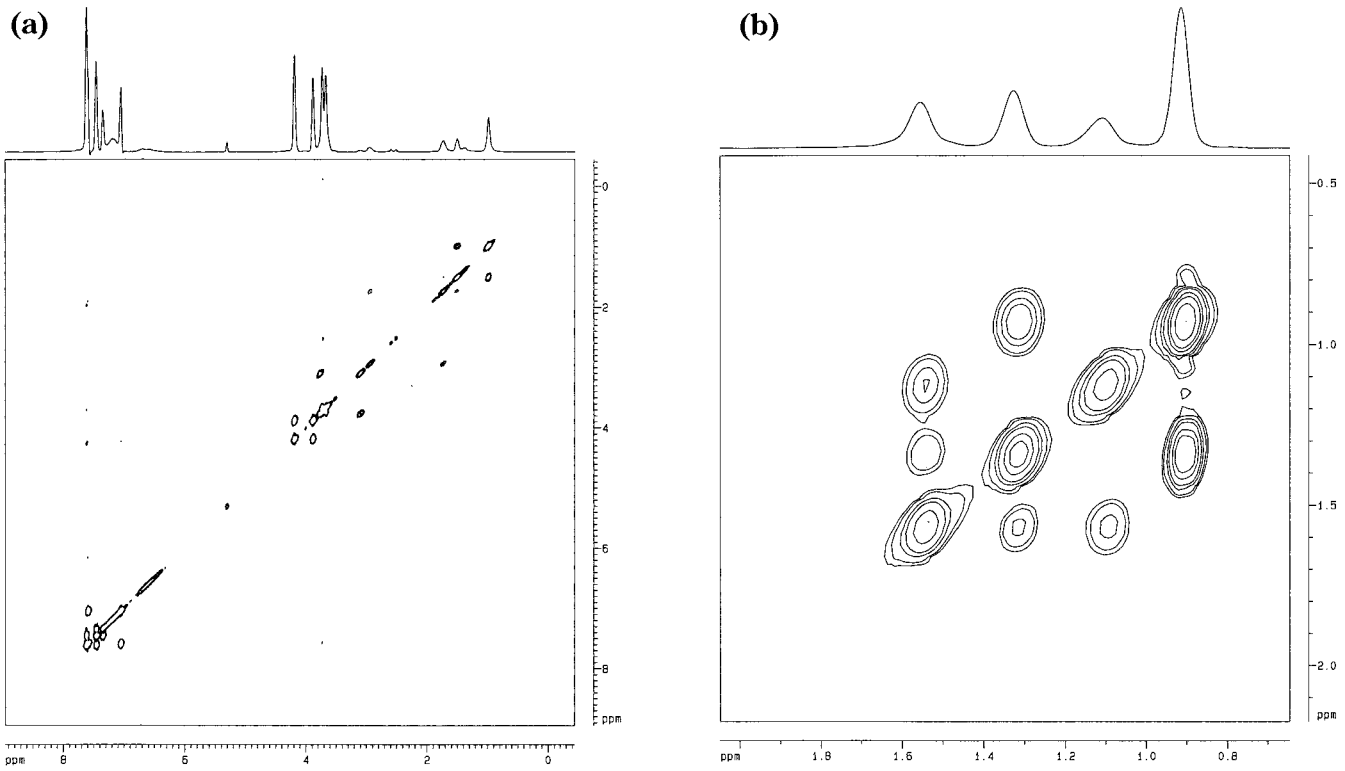


**Figure 5.** Magnitude gradient COSY45 spectra of **7a** (a) and **11** (b). The relaxation delay was 1.5 s. 2048 × 128 point matrixes with one scan per increment were aquired. The total acquisition times were 4 min. In F1, linear prediction to 256 points was performed followed by zero filling to 512 points. A sine bell window function was applied in both dimensions. For **11**, only the high-field aliphatic area is shown.

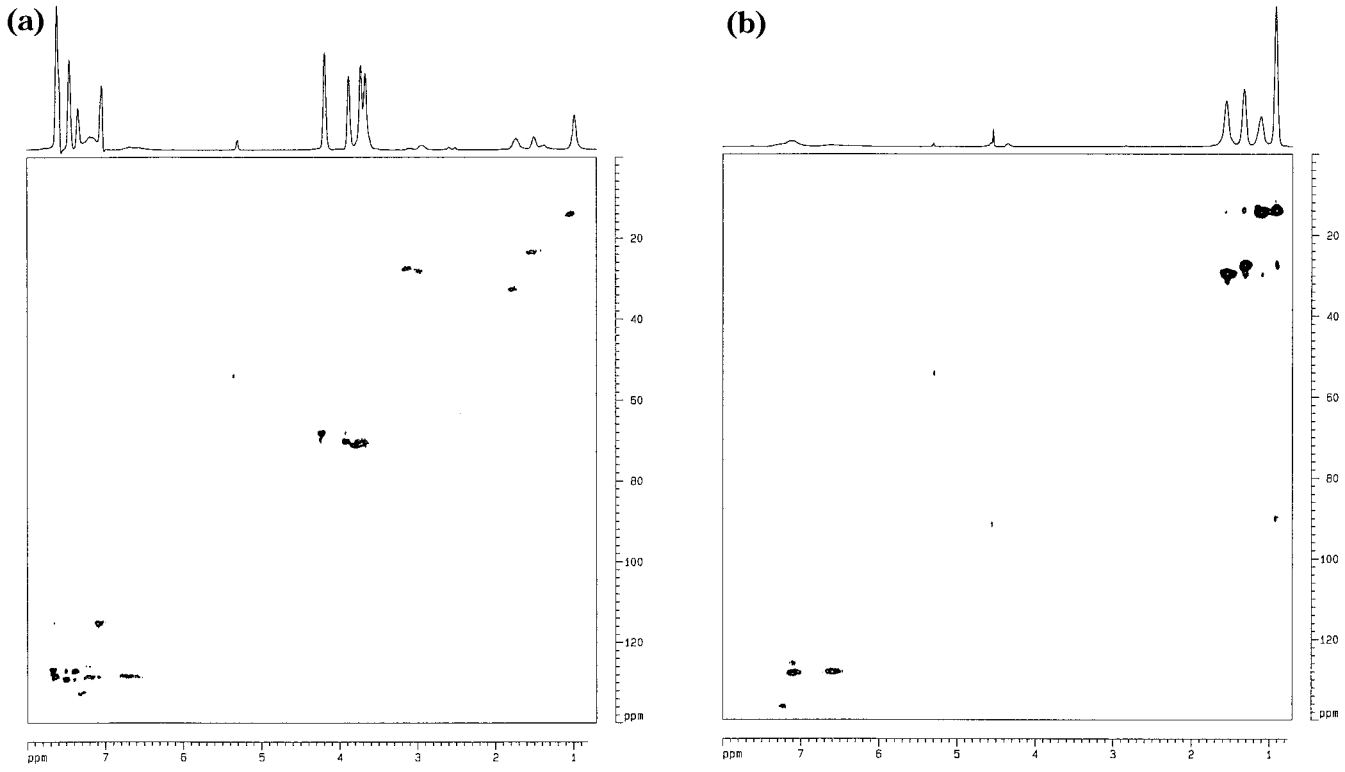


**Figure 6.** Phase-sensitive gradient HSQC spectra of **7a** (a) and **11** (b) with echo−antiecho coherence selection. The relaxation delay was 1.1 s, and the evolution delay for $J_{CH}$ couplings was 0.00185 s. 2048 × 128 point matrixes with two scans per increment were acquired. The total acquisition times were 5 min 35 s. In F1, linear prediction to 256 points was performed followed by zero filling to 512 points. A squared cosine window function was applied in both dimensions. Only positive levels are plotted.

been formed in the synthesis of resin-bound selenium by alkylation of polystyrene-bound lithiumselenide with butylbromide, the latter generated by lithium−bromine exchange between butyllithium and bromopolystyrene.

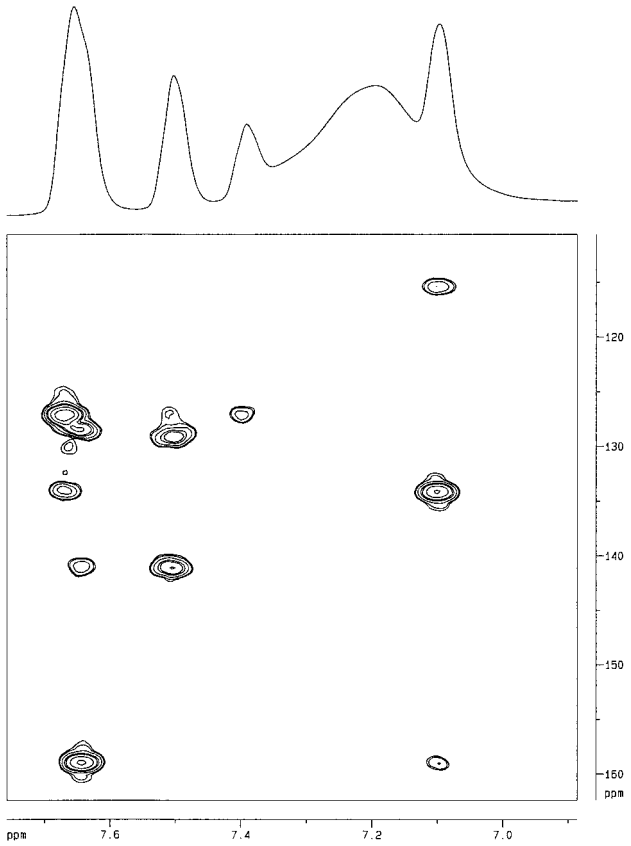


**Figure 7.** Magnitude gradient HMBC spectrum of **7a**. The relaxation delay was 1.0 s, and the evolution delay for long-range $J_{CH}$ couplings was 0.05 s. 2048 × 128 point matrixes with two scans per increment were acquired. The total acquisition times were 5 min 54 s. In F1, linear prediction to 256 points was performed followed by zero filling to 1024 points. A squared cosine window function was applied in both dimensions. Only the aromatic area is shown.

Assignment of the proton chemical shift for resin-bound tributylstannyl selenide **11**, obtained after cleavage of the ethers **9**, could be done unambiguously by either analyzing the COSY45 spectrum (Figure 5b) or the line width in the 1D-$^1$H NMR spectrum (Figure 4b) taking advantage of the decreasing T2 relaxation time with the distance to the backbone. The aliphatic part of the $^1$H spectrum of **11** is similar to that of the published solution-phase spectrum of tributylstannyl phenyl selenide.[22]

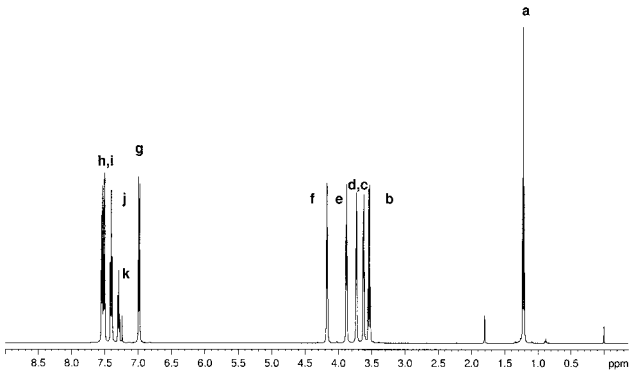


**Figure 8.** Solution $^1$H NMR spectrum in $CDCl_3$ of **9a** after cleavage from the resin and purification by solid-phase extraction. The assigment letters refer to Figure 3 for compound **7a**.

## Conclusion

In the present investigation, we demonstrate the use of polystyrene-bound selenium as a novel C−H bond-forming traceless linker in the SPS of an aryl alkyl ether library. Without the requirement of an auxiliary spacer, the first building block was attached in a single step to the polymer, and the final compounds were cleaved selectively under mild conditions. Even though toxic substances are used in the presented linking strategy, the contamination of the isolated products is reduced to a minimum by solid-phase extraction facilitated by the immobilization of selenium and interfering organostannyl compounds onto the resin. Fast purification of the cleaved products can be achieved by automated solid-phase extraction. The broad stability of alkyl phenyl selenides toward various reaction conditions and the high loading of 1.8 mmol/g make this resin very suitable in SPS of non-peptide compounds. Extensions of our basic strategy to the preparation of the homologous polystyrene-bound tellurium, oxidative cleavage strategies, and the SPS of heterocycles are under active investigation in our laboratory. Additionally, we have shown that very short acquisition times for gradient HR-MAS 2D-NMR experiments on resin-bound intermediate resin can be achieved, thus demonstrating the full benefit of gradient coherence selection.

## Experimental Section

**General Methods.** All reactions were carried out under positive pressure of nitrogen. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under $N_2$ from sodium/benzophenone immediately prior to use. Flash column chromatography was carried out according to the procedure described by Still.[28] For flash column chromatography and for solid-phase extraction, Scharlau 60 230−400 mesh silica gel (sorbil) was used. Thin-layer chromatography (TLC) was performed on Merck 60 $F_{254}$ 0.25 $\mu$m silica gel plates. Unless otherwise stated, TLC $R_f$ values given were determined with the solvent used for column chromatography. $^1$H NMR and $^1$H-decoupled $^{13}$C NMR spectra were recorded at 500.13 and 125.67 MHz, respectively, on a Bruker Avance DRX 500 instrument. NMR spectra of polymer-bound substances were recorded with a 4 mm $^1$H/$^{13}$C double resonance high-resolution MAS probehead optimized for proton resonance and equipped with a one-axis pulsed field gradient coil. Unless otherwise noted, compounds were measured in deuterated chloroform (99.8%). Chemical shifts for $^1$H NMR are reported in ppm with TMS as internal reference. Chemical shifts for $^{13}$C NMR and high-resolution MAS NMR are reported in ppm relative to chemical shifts of deuterated solvents. Coupling constants ($J$ values) are in hertz. For GC, samples were dissolved in methylene chloride ($c$ = approximately 1 mg/mL). GC was performed on a Varian Star 3400 CX instrument using an injector temperature of 200 °C, detector temperature of 325 °C, gas flow of 4.9 mL/min at 65 °C, a split flow of 150 mL/min, and a Restek Rtx-5 column with a length of 15 m, inner diameter of 0.32 mm, and a cross-bonded phase of 0.50 mm. A temperature gradient of 15 deg/min from 65 °C to 275 °C was used. Retention times ($R_t$ values) are in minutes. High-resolution mass spectra (HRMS) were performed at the University of Odense, Department of Chemistry (Odense, Denmark) with the peak-matching method using a Varian MAT 311A mass spectrometer. Elemental analyses were performed at the University of Vienna, Department of Physical Chemistry (Vienna, Austria) with a Perkin-Elmer 2.400 CHN elemental analyzer. Polystyrene for the preparation of bro-

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

mopolystyrene according to the procedure described by Ferrall and Fréchet[17] was purchased from Rapp Polymere GmbH (Tübingen, Germany) (H 1000, 100−200 mesh, cross-linked with 1% divinylbenzene).

**Preparation of Resin-Bound Selenium.** Bromopolystyrene[17] (24.0 g, 2.94 mmol/g)[29] was preswollen in dry toluene (200 mL) for 15 min, and BuLi (100 mL, 160 mmol, 1.6 M in hexane) was added. The mixture was stirred for 2 h at room temperature, and the resin was allowed to settle. After the solvents were carefully removed by decantation, BuLi (200 mL, 320 mmol, 1.6 M in hexane) and dry toluene (200 mL) were added. The suspension was heated at 60 °C for 3 h. After the mixture cooled to room temperature, the solvent was removed by decantation without further washing. After the temperature was reduced to 0 °C, dry THF (250 mL) was added. Immediately afterwards, selenium powder (25.1 g, 318 mmol, 100 mesh) was carefully added in small portions (1−2 g) under intensive stirring (CAUTION: generation of heat). The addition of selenium was complete within approximately 5 min. After the black suspension was heated at 50 °C for 12 h, the mixture was cooled to room temperature and filtered. The black residue was washed with THF (1 × 250 mL), methanol (1 × 250 mL), 2 N aqueous HCl/THF (1:2, 1 × 250 mL), and water (3 × 250 mL). For safety reasons, the excess selenium was removed from the residue bit by bit. Small portions of the residue (2−3 g) were suspended in methanol (250 mL) in a 3-L Erlenmeyer flask and treated carefully in small portions with excess of fine granulated sodium borohydride (5 g, 132 mmol) (CAUTION: generation of heat, hydrogen, and toxic sodium selenides). Immediately after the gas evolution ended, the resin was filtered and washed with methanol (1 × 250 mL). The procedure was repeated for each resin fraction until the excess selenium was removed. The combined fractions were suspended in methanol (500 mL) and treated with sodium borohydride (5 g, 132 mmol) as described above for each single portion. The procedure was repeated about 20 times until the filtrate did not contain any more selenium. After every fourth treatment with sodium borohydride, the resin was additionally washed with 2 N aqueous NaOH/THF (1:2, 1 × 250 mL), water (1 × 250 mL), 2 N aqueous HCl/THF (1:2, 1 × 250 mL), water (1 × 250 mL), THF (1 × 250 mL), and methanol (1 × 250 mL) (washing with methylene chloride should be omitted because the solvent could couple to the resin). Finally, the pale yellow resin and sodium borohydride (5 g, 132 mmol) were refluxed in ethanol/methanol (20:1, 500 mL) for 2 h. The resin was filtered and washed as described above with the exception that THF (2 × 250 mL) was used in the last washing step. After drying in vacuo at room temperature, an orange resin (24.3 g) was obtained.

The loading of the resin was calculated to be 1.84 mmol/g determined by elemental analysis for nitrogen after alkylation with chloro-*N*,*N*-dimethylacetamide as described below.

**Alkylation of Resin-Bound Selenium. *N*,*N*-Dimethylformylmethylselanyl Polystyrene (4).** The procedure for a typical experiment follows. Polymer-bound selenium (50 mg) was suspended in ethanol/methanol (40:1, 0.5 mL) and treated with sodium borohydride (40 mg, 1 mmol) at room temperature. After approximately 1 h, gas and heat generation occurred and the resin became swollen and almost colorless. The mixture was stirred for approximately 3 h until the gas evolution stopped. The resin was allowed to settle, and the above solution was removed by a pipette. After being washed with ethanol under an $N_2$ atmosphere (1 × 20 mL), the resin was treated with chloro-*N*,*N*-dimethylacetamide (207 mg, 1.7 mmol) in ethanol (0.5 mL), and the mixture was stirred for 12 h at room temperature. The almost colorless resin was filtered, washed with ethanol (2 × 25 mL), water (2 × 25 mL), THF (1 × 25 mL), ethanol (1 × 25 mL), water (1 × 25 mL), acetone (1 × 25 mL), and methylene chloride (3 × 25 mL) and dried in vacuo at room temperature. Anal. Found: C, 67.97; H, 6.46; N, 2.22; Br, < 0.1. According to the elemental analysis for N, a loading of 1.59 mmol/g was calculated for resin **4**, which corresponds to a loading of 1.84 mmol/g for the initial loading of polystyrene-bound selenium, assuming that the alkylation went to completion.

The resins **5** and **6** were prepared according to the procedure described above by alkylation with 2-[2-(2-chloroethoxy)ethoxy]-ethanol and 6-bromohexanol, respectively.

**Alkyl Aryl Ether Synthesis by the Mitsunobu Reaction. 2-[2-[2-(3-Methoxy-phenoxy)ethoxy]ethoxy]ethylselanyl Polystyrene (7c).** The procedure for a typical experiment follows. Resin-bound alkyl alcohol **5** (500 mg, 0.74 mmol) was preswollen in 4-methylmorpholin (5 mL) for 5 min. Neat 3-methoxyphenol (571 mg, 4.60 mmol) and triphenylphosphine (1.21 g, 4.61 mmol) were added at room temperature. After complete dissolution, neat diisopropyl azodicarboxylate (930 mg, 4.60 mmol) was added in small portions over a period of 15 min at room temperature. After the suspension was stirred for 12 h at room temperature, the resin was filtered and subsequently washed with THF (3 × 10 mL), DMSO (2 × 10 mL), THF (2 × 10 mL), water (2 × 10 mL), methanol (2 × 10 mL), and methylene chloride (3 × 10 mL) and dried in vacuo at room temperature for 12 h. Resin **7c** was calculated to have a loading of 1.28 mmol/g, assuming the Mitsunobu reaction went to completion.

The resins **7a**, **7b**, **8a**, **8b**, and **8c** were prepared according to the procedure described above.

**Cleavage by Homolysis. 1-[2-(2-Ethoxyethoxy)ethoxy]-3-methoxybenzene (9c).** The procedure for a typical experiment follows. Resin **7c** (1.00 g, 1.28 mmol) was preswollen in toluene (10 mL) for 5 min. Neat tributylstannane (1.62 g, 5.6 mmol) and AIBN (20 mg, 0.12 mmol) were added, and the mixture was heated in a sealed tube to 90 °C for 12 h. After cooling to room temperature, the resin was filtered and washed with THF (2 × 2 mL), acetone (1 × 2 mL), and methylene chloride (2 × 2 mL). The filtrates were combined, and the solvents were evaporated in vacuo. The residue was purified by solid-phase extraction using silica gel (approximately 50 g). Nonpolar tin impurities were removed by washing the column with pure heptane. Subsequently, elution with heptane/ethyl acetate (15:1) gave 213 mg (70%) of the desired product **9c** as a clear oil (78% purity by GC, $R_t$ = 9.3). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate, 5:1) and subsequent microdistillation (0.1 mmHg, 90−95 °C): TLC (heptane/ethyl acetate, 2:1) $R_f$ = 0.41; $^1$H NMR $\delta$ 1.21 (t, 3H, $J$ = 7.0), 3.52 (q, 2H, $J$ = 7.0), 3.60 (t, 2H, $J$ = 4.8), 3.70 (t, 2H, $J$ = 4.8), 3.76 (s, 3H), 3.84 (t, 2H, $J$ = 4.9), 4.12 (t, 2H, $J$ = 4.9), 6.50 (m, 3H), 7.15 (t, 1H, $J$ = 8.1); $^{13}$C NMR $\delta$ 15.5, 55.6, 67.0, 67.8, 70.1, 70.2, 71.3, 101.6, 106.9, 107.1, 130.2, 160.5, 161.2; HRMS calcd for $C_{13}H_{20}O_4$, 240.1362; found, 240.135. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.90; H, 8.65.

The aryl alkyl ethers **9a**, **9b**, **10a**, **10b** and **10c** were prepared according to the procedure described above.

**1-Hexyloxy-3-methoxybenzene (10c).** This compound was cleaved from resin **8c** (924 mg, 1.23 mmol). Solid-phase extraction (heptane and then heptane/ethyl acetate, 15:1) gave 146 mg (57%) of the desired product as a clear oil (87% purity by GC, $R_t$ = 8.0). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate 30:1) and subsequent microdistillation (0.1 mmHg, 50−55 °C): TLC $R_f$ = 0.32; $^1$H NMR $\delta$ 0.90 (t, 3H, $J$ = 6.6), 1.33 (m, 4H), 1.44 (m, 2H), 1.76 (p, 2H, $J$ = 7.1), 3.76 (s, 3H), 3.91 (t, 2H, $J$ = 6.6), 6.46 (m, 1H), 6.48 (m, 2H), 7.15 (t, 1H, $J$ = 8.1); $^{13}$C NMR $\delta$ 14.5, 23.1, 26.2, 29.7, 32.0, 55.6, 68.4, 101.4, 106.5, 107.1, 130.2, 160.9, 161.3; HRMS calcd for $C_{13}H_{20}O_2$, 208.1463; found, 208.145. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.93.

**2-[2-(2-Ethoxyethoxy)ethoxy]-1-fluorobenzene (9b).** This compound was cleaved from resin **7b** (950 mg, 1.24 mmol). Solid-phase extraction (heptane and then heptane/ethyl acetate, 5:1) gave 200 mg (72%) of the desired product as a clear oil (88% purity by GC, $R_t$ = 7.4). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate, 4:1) and subsequent microdistillation (0.1 mmHg, 70−75 °C): TLC

(29) The loading of bromopolystyrene was determined by elemental analysis for bromine: Anal. found: C, 63.72; H, 5.03; Br, 29.32.

$R_f$ = 0.15; $^1$H NMR $\delta$ 1.20 (t, 3H, $J$ = 7.0), 3.52 (q, 2H, $J$ = 7.0), 3.60 (t, 2H, $J$ = 4.8), 3.72 (t, 2H, $J$ = 4.8), 3.87 (t, 2H, $J$ = 5.0), 4.19 (t, 2H, $J$ = 5.0), 6.89 (m, 1H), 7.02 (m, 3H); $^{13}$C NMR $\delta$ 15.9, 67.4, 69.9, 70.5, 70.7, 71.8, 116.4, 117.0 (d, $J_{C,F}$ = 18.3), 122.2 (d, $J_{C,F}$ = 6.8), 125.0 (d, $J_{C,F}$ = 3.5), 147.8 (d, $J_{C,F}$ = 10.6), 153.7 (d, $J_{C,F}$ = 245.6); HRMS calcd for $C_{12}H_{17}FO_3$, 228.1162; found, 228.118. Anal. Calcd for $C_{12}H_{17}FO_3$: C, 63.14; H, 7.51. Found: C, 63.36; H, 7.35.

**1-Fluoro-2-hexyloxybenzene (10b).** This compound was cleaved from resin **8b** (985 mg, 1.33 mmol). Solid-phase extraction (heptane) gave 174 mg (67%) of the desired product as a clear oil (80% purity by GC, $R_t$ = 5.9). An analytical sample was obtained by flash chromatography (heptane) and subsequent microdistillation (15 mmHg, 95−105 °C): TLC $R_f$ = 0.31; $^1$H NMR $\delta$ 0.90 (t, 3H, $J$ = 6.9), 1.34 (m, 4H), 1.47 (m, 2H), 1.81 (p, 2H, $J$ = 7.1), 4.02 (t, 2H, $J$ = 6.6), 6.86 (m, 1H), 6.95 (t, 1H, $J$ = 7.8), 7.05 (m, 2H); $^{13}$C NMR $\delta$ 14.6, 23.2, 26.3, 29.9, 32.2, 70.1, 115.7, 116.8 (d, $J_{C,F}$ = 18.4), 121.5 (d, $J_{C,F}$ = 6.8), 124.8 (d, $J_{C,F}$ = 3.4), 147.9 (d, $J_{C,F}$ = 10.6), 153.6 (d, $J_{C,F}$ = 245.4); HRMS calcd for $C_{12}H_{17}FO$, 196.1263; found, 196.126.

**1-[2-(2-Ethoxyethoxy)ethoxy]-4-phenylbenzene (9a).** This compound was cleaved from resin **7a** (997 mg, 1.21 mmol). Solid-phase extraction (heptane and then heptane/ethyl acetate, 5:1) gave 285 mg (83%) of the desired product as a solid (84% purity by GC, $R_t$ = 12.7). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate, 4:1). Recrystallization from heptane gave white crystals: mp 62−63 °C; TLC $R_f$ = 0.17; $^1$H NMR $\delta$ 1.22 (t, 3H, $J$ = 7.0), 3.54 (q, 2H, $J$ = 7.0), 3.62 (t, 2H, $J$ = 4.8), 3.73 (t, 2H, $J$ = 4.8), 3.88 (t, 2H, $J$ = 4.9), 4.17 (t, 2H, $J$ = 4.9), 6.98 (d, 2H, $J$ = 8.6), 7.28 (t, 1H, $J$ = 7.3), 7.40 (t, 2H, $J$ = 7.6), 7.51 (d, 2H, $J$ = 8.6), 7.54 (d, 2H, $J$ = 7.6); $^{13}$C NMR $\delta$ 15.6, 67.1, 67.9, 70.2, 70.3, 71.4, 115.3, 127.1, 127.2, 128.5, 129.1, 134.3, 141.2, 158.8; HRMS calcd for $C_{18}H_{22}O_3$, 286.1569; found, 286.157. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.27; H, 8.00.

**1-Hexyloxy-4-phenylbenzene (10a).**[30] This compound was cleaved from resin **8a** (1.02 g, 1.29 mmol). Solid-phase extraction (heptane and then heptane/ethyl acetate, 15:1) gave 262 mg (80%) of the desired product as a solid (87% purity by GC, $R_t$ = 11.7). An analytical sample was obtained by flash chromatography (heptane/ethyl acetate, 30:1). Recrystallization from heptane gave white crystalls: mp 61−62 °C (lit.[30] 63.0−63.5 °C); TLC $R_f$ = 0.42; $^1$H NMR $\delta$ 0.91 (t, 3H, $J$ = 6.2), 1.34 (m, 4H), 1.46 (m, 2H), 1.78 (p, 2H, $J$ = 7.1), 3.97 (t, 2H, $J$ = 6.6), 6.94 (d, 2H, $J$ = 8.5), 7.27 (t, 1H, $J$ = 7.4), 7.38 (t, 2H, $J$ = 7.6), 7.49 (d, 2H, $J$ = 8.5), 7.53 (d, 2H, $J$ = 7.8); $^{13}$C NMR $\delta$ 14.5, 23.1, 26.2, 29.7, 32.1, 68.5, 115.3, 127.0, 127.1, 128.5, 129.1, 134.0, 141.4, 159.2; HRMS calcd for $C_{18}H_{22}O$, 254.1670; found, 254.166. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.73; H, 8.97.

**Note Added in Proof.** After the submission of the present manuscript, an account of polymer-supported selenium reagents and their use in organic synthesis has been published by Nicolaou et. al. (Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Wissinger, N. *Chem. Commun.* **1998**, 1947−1948).

**Acknowledgment.** The very skillful technical assistance by Mr. Jens Schiøtt and Mr. Johnny Angelsø is gratefully acknowledged. The preparation of the manuscript by Ms. V. Nielsen is highly appreciated.

**Supporting Information Available:** $^1$H NMR spectra and GC chromatograms of isolated products and GC chromatogram of tributylstannane after heating to 90 °C according to the cleavage procedure to document the efficient removal of this substance by the workup procedure used (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9806310

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