ACS Combinatorial Science

Research Article

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Synthesis and Application of Monodisperse Oligo(Oxyethylene)-Grafted Polystyrene Resins for Solid-Phase Organic Synthesis

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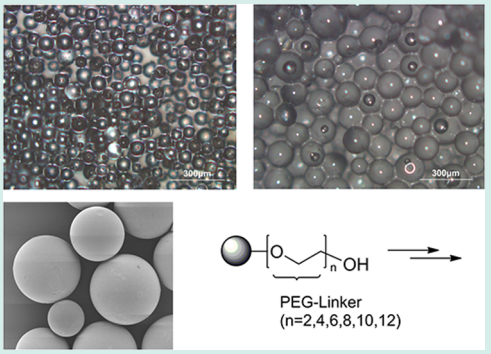
Supporting Information

ABSTRACT: In a preliminary investigation by our group, we found that poly(styrene-oxyethylene) graft copolymers (PS-PEG), for example, TentaGel resins, are advantageous for gel-phase ^{13}C NMR spectroscopy. Because of the solution-like environment provided by the PS-PEG resins, good spectral quality of the attached moiety can be achieved, which is useful for nondestructive on-resin analysis. The general drawbacks of such resins are low loading capacities and the intense signal in the spectra resulting from the PEG linker (>50 units). Here, we describe the characterization of solvent-dependent swelling and reaction kinetics on a new type of resin for solid-phase organic synthesis (SPOS) that allows an accurate monitoring by gel-phase NMR without the above disadvantages. A series of polystyrene-oligo-(oxyethylene) graft copolymers containing monodisperse PEG units (n = 2−12) was synthesized. A strong correlation between the linker (PEG) length and the line widths in the ^{13}C gel-phase spectra was observed, with a grafted PEG chain of 8 units giving similar results in terms of reactivity and gel-phase NMR monitoring to TentaGel resin. Multistep on-resin reaction sequences were performed to prove the applicability of the resins in solid-phase organic synthesis.



KEYWORDS: *PS-PEG resin, SPOS, gel-phase NMR spectroscopy, nondestructive on-resin analysis, on-resin reaction monitoring*

INTRODUCTION

For the synthesis of substance libraries, the use of combinatorial chemistry techniques is nowadays state of the art. As a result of the advantage of simplifying synthesis and product isolation, polymer-supported approaches are widely applied, and therefore suitable for potential automation. Recent developments in organic synthesis have established the applicability as a catalyst carrier (e.g., cross-coupling chemistry) enabling practicable recycling of expensive compounds.[1−4]

As a matter of fact, solid-phase organic synthesis (SPOS) plays a major role in combinatorial chemistry.[5,6] The success of any SPOS strategy strongly depends on the properties of the applied resin. Cross-linked polystyrene resins (PS) were initially used, with the disadvantage of limited swelling properties in polar solvents, like methanol or water. To obtain beads with a more universal swelling behavior, PS-based resins have been modified with poly(ethylene glycol) (PEG) chains as spacer (PS−PEG) or cross-linking units.

The PS−PEG supports (TentaGel), first reported by Bayer and Rapp,[7] show good swelling properties in a variety of solvents from medium to high polarity. Furthermore, the resins provide high quality ^{13}C gel-phase NMR spectra, a convenient technique for nondestructive on-resin analysis.[8−16] The copolymers are produced by grafting ethylene oxide to the PS backbone, creating long flexible polydisperse chains (the commercial resins TentaGel and ArgoGel bear about 60−70 PEG units) to provide a "solution-like" environment for attached moieties. The main drawback of such resins is the low degree of loading capacity (about 0.2−0.3 mmol/g), compared to classical PS resin (e.g., Merrifield, 1−1.5 mmol/g), and an intense signal in the gel-phase spectra resulting from the long oxyethylene units.[13] Moreover, the effect of variable linker chain length on the efficiency of immobilized catalyst systems has previously been demonstrated.[17]

Our strategy relies on substituting the long PEG chains for shorter monodisperse oligo(oxyethylene) tethers (n = 2−12 units) with the goal of increasing the loading and minimizing the PEG signal in the gel-phase spectra. In our previous publication, the design and synthetic access of these PS−PEG resins has been presented,[18] conducting a systematic investigation focusing on the effects of the PEG group length on the quality of gel-phase ^{13}C NMR spectra. As a result, an optimum PEG chain length in terms of NMR properties and loading capacity has been determined. The objective of this manuscript is to demonstrate the applicability of the PS−PEG resins in SPOS compared to commercially available resins.

The contribution is divided into two subunits. First, an extension of the investigation toward an efficient synthetic route toward PS−PEG resins is described, including an advanced analytical characterization (IR, gel-phase NMR, combustion analysis, microscopy) of the obtained solid supports. Second, examples of successful application in diverse

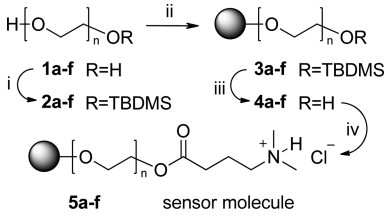
Received: February 20, 2014
Revised: June 5, 2014
Published: June 8, 2014

multistep reaction sequences are outlined (Wang-linker synthesis, palladium-catalyzed cross coupling, hydantoin synthesis). The performance of the developed resins is compared to commercially available supports (Wang resin, Reactagel, TentaGel). Hence, this study reveals the advantageous properties in terms of efficiency and reaction monitoring, as well as the broad synthetic applicability of the designed resins in the field of SPOS.

RESULTS AND DISCUSSION

Scheme 1 shows an overview of the synthesis of the resins **4a–f**. Application examples are presented in Scheme 2 and subsequently discussed in detail.

Scheme 1. Synthesis of the PS–PEG Resins 4a–f and Attachment of Sensor Molecule[a]



[a]Reaction conditions: (i) pyridine/imidazole, TBDMS-Cl, DCM, 0 °C → rt, 24 h; (ii) DEAD, PS-phenol resin, $P(C_6H_5)_3$, DCM/THF = 1/1, rt, overnight; (iii) TBAF, THF, rt, overnight; (iv) 4-(dimethylamino)-butanoic acid, hydrochloride, 1-hydroxybenzotriazole, DMAP, DIC, DCM/DMF = 9/1, rt, 2 d.

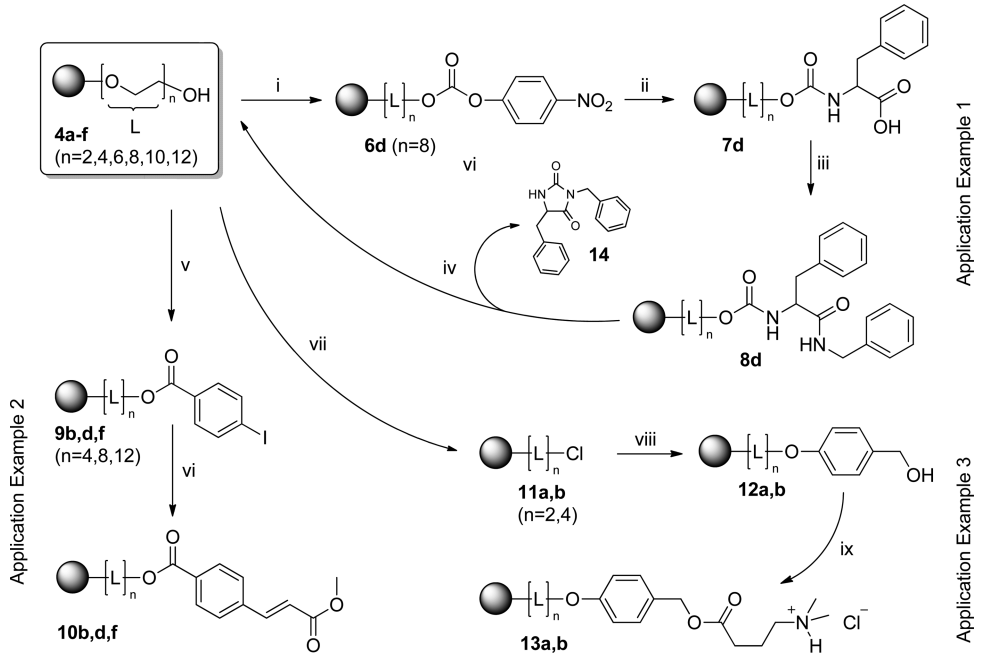
Synthesis of the PS–PEG Resin (4a–f). Starting from accessible reagents, the intention of our strategy was the design of a modular synthetic route based on monodisperse oligo(ethylene glycols) and polymer-bound phenol, leading to tailor-made resins for SPOS. Finally, we present a convenient three-step synthesis: monoprotection of glycols, attachment to solid-phase and deprotection. This synthetic approach as well as the implications of the linker length for the ^{13}C gel-phase NMR spectroscopy have previously been reported by our group.[18] However, the full experimental details and a characterization of the resins are given in this manuscript.

Glycols **1a–c** (n = 2, 4, 6) are commercially available. Higher homologues have been synthesized according to a recently published procedure.[19] As shown in Scheme 1, the initial step in the resin synthesis was the monoprotection of glycols **1a–f** (n = 2, 4, 6, 8, 10, 12) by conversion with *tert*-butyldimethylsilyl chloride (TBDMS-Cl).[20] This protective group has been proved to show the best performance in terms of stability and cleavage behavior. By comparison, in the next reaction step (Mitsunobu reaction), trimethylsilyl was not suitable for reasons of stability. Furthermore, the synthetic approach toward mono-TMS-protected oligo(oxyethylene glycols) is inconvenient (formation of azeotropic mixtures[21]). The triphenylmethyl group was appropriate for Mitsunobu conditions, but deprotection on solid-phase could not be accomplished.

As a second step, protected glycols **2a–f** were attached to polymer-bound phenol by applying Mitsunobu reactions.[22] As a result of this strategy, an aryl-alkyl linkage was formed, instead of a benzylic ether PS-graft linkage (e.g., TentaGel), which is known to be unstable in strongly acidic conditions.

Finally, for the deprotection, resins **3a–f** were swollen in THF and treated with a solution of TBAF in THF to give monodisperse PEG-grafted resins **4a–f** in quantitative yield as

Scheme 2. Application Examples 1–3[a]



[a]Reaction conditions: (i) 4-nitrophenyl-chloroformate, Et_3N, rt, 60 h; (ii) L-phenylalanine, BSA, DMAP, DMF, rt, 48 h; (iii) 1-hydroxybenzotriazole, DIC, benzylamine, DMF, rt, overnight; (iv) 1,1,3,3-tetramethylguanidine, MeOH, reflux, 24 h; (v) 4-iodobenzoic acid, 1-hydroxybenzotriazole, DMAP, DIC, DCM/DMF = 9/1, rt, overnight; (vi) methylmethacrylate, $P(C_6H_5)_3$, tetra-*n*-butylammoniumchloride, $Pd(OAc)_2$, DMF/H_2O/NEt_3, 40 °C, overnight; (vii) $SOCl_2$, toluene, 75 °C, overnight; (viii) 4-hydroxybenzyl alcohol, NaH, DMF, 75 °C, overnight, (ix) 4-(dimethylamino)butanoic acid, hydrochloride, 1-hydroxybenzotriazole, DMAP, DIC, DCM/DMF = 9/1, r.t., 2 d.

dx.doi.org/10.1021/co500028h | ACS Comb. Sci. 2014, 16, 367–374

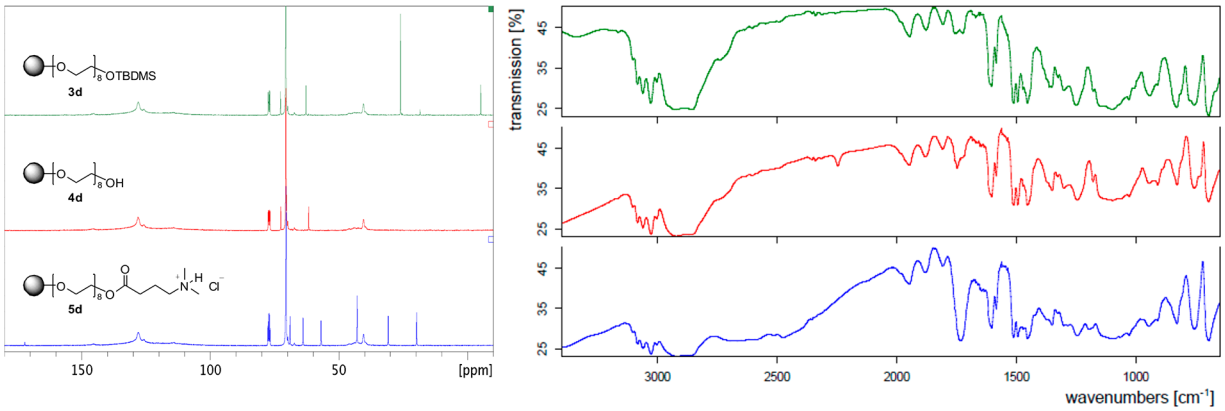


Figure 1. Reaction monitoring on solid-phase of resins **3d**–**5d** via ^{13}C gel-phase NMR and FT-IR spectroscopy. For a detailed view of the NMR spectra see associated content.

determined by ^{13}C gel-phase NMR spectroscopy (Figure 1). For a systematic investigation of the effect of the PEG group length on the quality of gel-phase ^{13}C NMR spectra, a sensor molecule (4-(dimethylamino)-butanoic acid, hydrochloride) was attached and resulted in resins **5a**–**f**.[18] The sensor molecule was attached to the resins' hydroxyl groups using a carbodiimide-based coupling method.[23]

Figure 1 shows the reaction monitoring of each synthetic step on solid-phase (**3d**–**5d**), applying two different analytical techniques (FT-IR and ^{13}C gel-phase NMR spectroscopy). Allowing a precise determination of the reaction progress, NMR spectroscopy has proved to be superior. For instance, the deprotection of **3d** can be clearly monitored via the signals from the TBDMS-group (3 signals in the region <30 ppm). The formation of NMR signals, particularly in the region of 15–35 ppm, allows to examine the attachment of the sensor molecule toward **5d**. By comparison, a significant difference in the FT-IR spectra is the C═O peak in the range of 1700 cm^{-1} corresponding to the ester in substance **5d**.

As shown in preliminary research, swelling properties, loading (Table 1) and gel-phase NMR characteristics have been demonstrated to be excellent.[18] As a result, resin **4d** with eight ethylene glycol units has shown the best performance in terms of loading capacity combined with spectral quality. The surface morphology and spherical behavior of the developed resins was investigated by polarized optical microscopy and scanning electron microscopy (SEM). The images demonstrate homogeneous and spherical properties of the beads; in addition, the good swelling properties in chloroform are clearly visible (Figure 2).

Table 1. Swelling Volume [mL/g] of Selected Resins at 25 °C in Different Solvents (Data Extracted from Preliminary Research)[18]

entry	resin	loading [mmol/g]	MeOH	DMF	THF	DCM
1	Merrifield	1.5	0.7	4.3	7.5	7.3
2	**4b** (n = 4)	1.1	1.5	6.8	8.5	7.8
3	**4d** (n = 8)	0.9	2.1	6.7	7.1	8.0
4	**4f** (n = 12)	0.7	2.1	6.0	7.3	8.6
5	TentaGel	0.3	2.7	4.1	4.2	5.7

Application Examples of Monodisperse PS–PEG Resin. In the next step, we intended to demonstrate the applicability of the presented resins to SPOS. Complex multistep syntheses require a solid support that performs in both polar and nonpolar solvents. This was the major selection criterion of our on-resin sequence examples. To evaluate the resin performance, we induced the identical reaction sequences on commercially available resins (Wang, TentaGel).

In application example 1, the developed resin **4d** (PEG 8 spacer) was compared to a commercially available resin (TentaGel) in a multistep synthesis involving various reactants, solvents and conditions. For this purpose, a published synthetic route toward hydantoin **14** was chosen.[24]

Figure 3 shows the corresponding ^{13}C gel-phase NMR spectra. Because polar solvents are involved in the sequence, TentaGel, which shows a chemically comparable spacer structure, was used as a reference resin. The synthesis was performed by starting from identical amounts of the respective resin leading to 14 mg (TentaGel) and 44 mg (resin **4d**) substance **14**. This result, a more than 3-fold amount of isolated hydantoin **14**, impressively reveals the effect of higher loading of the resin due to a shorter spacer unit. Thus, a substantially lower amount of resin **4d** is needed to obtain an intended quantity of a target substance. After the reaction, the recovered

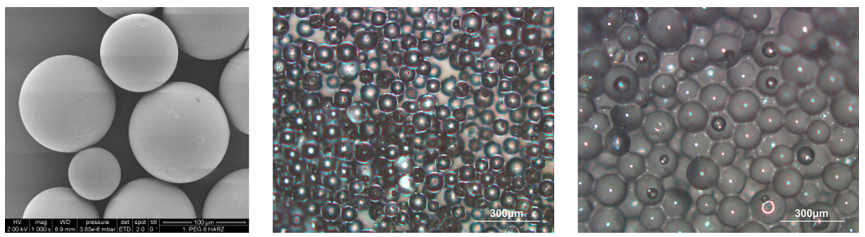


Figure 2. Microscopy images of resin **4d**. SEM image (left); polarized optical microscopy image of **4d**, dry (middle) and swollen in chloroform (right).

dx.doi.org/10.1021/co500028h | ACS Comb. Sci. 2014, 16, 367–374

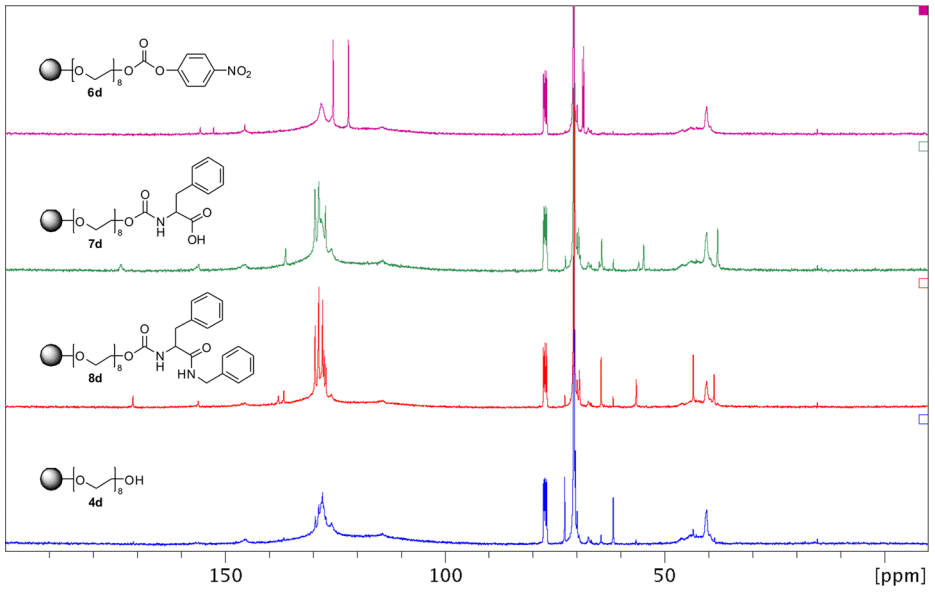


Figure 3. On-resin reaction monitoring of the hydantoin route (application example 1).

beads feature ^{13}C gel-phase NMR spectra comparable to the starting material, which is an important factor for resin recycling. Both higher loading and the possibility of recycling are essential for efficient industrial scale syntheses.

Application example 2 points out the applicability in heterogenic catalytic systems (Heck coupling[25]). After conversion of resin **4b,d,f** with 4-iodobenzoic acid, the palladium catalyzed cross-coupling step (methacrylate as coupling reagent) was performed. The evaluation of the ^{13}C gel-phase NMR spectra showed an increased conversion by applying extended length of the PEG tether, which is supported by the swelling behavior (low conversion for **9b** (n = 4), good result for **9d** (n = 8), quantitative conversion for **9f** (n = 12)). In comparison with the result obtained from TentaGel, cross coupling of resin **9f** yielded the same performance (similar reaction progress as determined by gel-phase NMR spectroscopy), with the advantage of higher loading and improved on-resin analysis.

In application example 3 (Scheme 2), an end-group modification to a Wang-Linker system[26] (conversion using thionyl chloride and 4-hydroxybenzyl alcohol) was performed to achieve resin **12a−b**. The goal was to investigate the stability of our PEG linker in harsh reaction conditions (thionyl chloride) and to allow a comparison with commercially available Wang and TentaGel resins. The attachment of the Wang linker enables the application of the developed PS−PEG resins in the field of peptide synthesis as a result of mild cleavage conditions for the target peptides. Subsequently, the attachment of a sensor molecule (4-(dimethylamino)butanoic acid, hydrochloride) to obtain resin **13a−b** enabled the comparison of the characteristics of gel-phase NMR spectroscopy of **13a−b** with commercially available beads (the functionalization of the reference beads with the sensor has been previously described[13]). To characterize each spectrum by a single value, an average half-height line width of all nonquaternary carbon peaks of the immobilized sensor molecule was determined. Small values correspond to high-quality spectra, resulting in a better line shape. The values for the commercially available resins are 28.4 Hz for Wang and 7.3 Hz for TentaGel.[13] By comparison, the half-hight line widths of resins **13a** and **13b** were determined as 24.4 and 19.2 Hz, respectively, which is a clear improvement relative to Wang.

The above-mentioned sensor was chosen for the present work due to its high polarity, which makes it a very demanding sensor for attachment and gel-phase NMR. The polarity of the sensor is a key criterion for the achievable quality of the gel-phase spectrum on a given resin. Highly polar sensor molecules (like the (4-(dimethylamino)butanoic acid, hydrochloride) can only be measured in good quality if bound to a solid-phase via a suitable PEG linker: no signals were obtained for these molecules on Merrifield resin.[13] The acid was bound to the hydroxyl groups of the resins as described before (carbodiimide method); quantitative conversions for each step could be observed.

CONCLUSION

In conclusion, we have shown that polystyrene resins grafted with short, monodisperse PEG units (n = 2−12) can easily be synthesized in a modular synthetic route from polymer-bound phenol by Mitsunobu coupling. The resulting solid supports offer advantageous properties for gel-phase NMR spectroscopy and are excellent resins for SPOS. In order to prove the applicability, three reaction sequences on solid-phase have been performed (Wang-linker synthesis, palladium catalyzed cross coupling, hydantoin synthesis). Compared to commercially available PS−PEG resins, our support offers equal swelling properties in polar and apolar solvents, better on-resin analytic properties and significantly higher loading, thus being a suitable choice for industrial application. This approach to tailor-made resins enables the adjustment of the resin properties by a proper linker selection depending on the respective field of application.

EXPERIMENTAL PROCEDURES

All reactions were conducted under an atmosphere of argon in oven-dried glassware with magnetic stirring. Unless otherwise stated, reagents were purchased from commercial sources and purified in the usual manner. DEAD (diethyl azodicarboxylate), 4-(dimethylamino)butanoic acid, hydrochloride, hexa(ethylene glycol) and TBDMS-Cl (*tert*-butylchlorodimethylsilane) were

dx.doi.org/10.1021/co500028h | ACS Comb. Sci. 2014, 16, 367−374

purchased from Aldrich and used without prior purification. Di(ethylene glycol) **1a** and tetra(ethylene glycol) **1b** were obtained from Merck and used as purchased. Oligo(ethylene glycols) **1c**–**f**[19] (n = 6, 8, 10, 12) and mono-TBDMS protected glycols **2a**–**c**[20] were prepared in analogy to literature.

The resins used were as follows: polymer-bound phenol (1.7 mmol/g, 1% divinylbenzene, 100–200 mesh) was purchased from Aldrich; TentaGel resin (0.3 mmol/g, 1% divinylbenzene, 80–100 μm), and Reactagel-OH resin (0.7 mmol/g, 1% divinylbenzene, 100–200 mesh) were purchased from Advanced ChemTech. All resins were dried prior to usage.

Anhydrous DMF was purchased from Acros. Tetrahydrofuran was dried over and distilled from sodium/benzophenone ketyl. Dichloromethane was dried over and distilled from CaH_2. Technical grade solvents were distilled prior to usage. Analytical TLC was performed on Merck silica gel 60 F254 plates. Chromatographic separations at preparative scale were carried out on silica gel (Merck silica gel 60, 40–63 um).

Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker DPX-200 or Avance DRX-400 Fourier transform spectrometer operating at the following frequencies: DPX-200:200.1 MHz (^{1}H) and 50.3 MHz (^{13}C); DRX-400:400.1 MHz (^{1}H) and 100.6 MHz (^{13}C). All ^{13}C gel-phase spectra were performed at the Avance DRX-400 spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane using solvent residual signals for calibration. Coupling constants are reported in Hertz (Hz); multiplicity of signals is indicated by using following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, b = broad. Multiplicities of ^{13}C signals were obtained by measuring JMOD spectra. Significant peaks corresponding to compounds attached to solid-phase are indicated in the NMR code. IR spectra were recorded on a BioRad FTS 135 FT-IR spectrometer from KBr pellets or using the ATR technique. Elemental analyses were carried out at the Microanalytical Laboratory, University of Vienna.

Synthesis of TBDMS-Protected Glycols. *General Procedure.* A solution of glycol **1a**–**f** in anhydrous DCM was cooled to 0 °C and the base (imidazole or anhydrous pyridine) was added slowly. The solution was stirred for 5 min before a solution of TBDMS-Cl in anhydrous DCM was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and after it was warmed to room temperature, it was stirred for an additional 24 h. Water was added to the formed suspension, and after phase separation, the organic layer was consecutively washed with 10% aqueous HCl, saturated $NaHCO_3$ solution and brine. After it was dried over $MgSO_4$, the solvent was distilled off under reduced pressure to give the crude product, which was subjected to column chromatography for further purification leading to monoprotected glycols **2a**–**f**.

2,2,3,3-Tetramethyl-4,7,10,13,16,19,22,25-octaoxa-3-sila-heptacosane-27-ol ***2d***. According to the general procedure, octa(ethylene glycol) (19.20 g, 51.8 mmol, 1.7 eqiv.), imidazole (2.13 g, 31.3 mmol, 1.0 eqiv.), TBDMS-Cl (4.69 g, 31.1 mmol, 1.0 eqiv.), and ~70 mL of anhydrous DCM were used. Column chromatography: 400 g of silica gel, gradient elution using hexanes/ethyl acetate = 1/5 → ethyl acetate → ethyl acetate/MeOH = 4/1. The title compound **2d** was obtained as slightly yellow oil (6.92 g, 46%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80–3.45 (m, 32H), 2.80 (bs, 1H), 0.87 (s, 9H), 0.04 (s, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.6 (t), 72.5 (t), 70.7 (t), 70.6 (t), 70.5 (t), 70.3 (t), 62.7 (t), 61.7 (t), 25.9 (q), 18.3 (s), −5.3 (q) ppm. Anal. Calcd for $C_{22}H_{48}O_9Si$: C, 54.52; H, 9.98. Found: C, 54.48; H, 9.72; N, <0.05.

2,2,3,3-Tetramethyl-4,7,10,13,16,19,22,25,28,31-decaoxa-3-silatritriacontane-33-ol ***2e***. According to the general procedure, deca(ethylene glycol) (5.60 g, 12.2 mmol, 1.0 equiv), imidazole (0.82 g, 12.0 mmol, 1.0 equiv), TBDMS-Cl (1.81 g, 12.0 mmol, 1.0 equiv), and ~100 mL of anhydrous DCM were used. Column chromatography: 200 g of silica gel, gradient elution using $CHCl_3$/MeOH = 25/1 → $CHCl_3$/MeOH = 5/1 → $CHCl_3$/MeOH = 4/1. Compound **2e** was obtained as colorless oil (2.19 g, 32%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75–3.43 (m, 40H), 1.91 (bs, 1H), 0.83 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.6 (t), 70.7 (t), 70.5 (t), 70.2 (t), 62.6 (t), 61.6 (t), 25.9 (q), 18.3 (s), −5.3 (q) ppm. Anal. Calcd for $C_{26}H_{56}O_{11}Si$: C, 54.52; H, 9.85. Found: C, 54.59; H, 9.70; N, <0.05.

2,2,3,3-Tetramethyl-4,7,10,13,16,19,22,25,28,31,34,37-do-decaoxa-3-silanonatriacontane-39-ol ***2f***. According to the general procedure, dodeca(ethylene glycol) (9.83 g, 18.0 mmol, 1.2 equiv), anhydrous pyridine (1.50 g, 19.0 mmol, 1.3 equiv), TBDMS-Cl (2.26 g, 15.0 mmol, 1.0 equiv), and ~50 mL of anhydrous DCM were used. Column chromatography: 400 g of silica gel, gradient elution using $CHCl_3$/MeOH = 30/1 → $CHCl_3$/MeOH = 20/1. Pure compound **2f** was obtained as a colorless oil (4.36 g, 44%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.74–3.44 (m, 48H), 2.13 (bs, 1H), 0.83 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.6 (t), 72.5 (t), 70.7 (t), 70.5 (t), 70.3 (t), 62.7 (t), 61.7 (t), 25.9 (q), 18.3 (s), −5.3 (q) ppm. Anal. Calcd for $C_{30}H_{64}O_{13}Si$: C, 54.52; H, 9.76; Found: C, 54.10; H, 9.47; N, <0.05.

General Procedure for Mitsunobu Reaction on Solid-Phase. DEAD (5.0 equiv) was added dropwise to a mixture of 1.0 equiv of polymer-bound phenol (100–200 mesh, 1% divinylbenzene, Aldrich, 1.7 mmol/g) in dry DCM/THF = 1/1 (50 mL/g resin) under argon. In the next step, the corresponding monoprotected glycols **2a**–**f** (5.0 equiv), dissolved in dry THF, and finally triphenylphosphine were added slowly. The reaction mixture was stirred overnight and filtered, and the solid residue was washed 3 times with DCM/THF = 1/1, DCM, isopropanol, DCM, and finally with methanol. The resulting resin **3a**–**f** was dried to constant weight in vacuo. To complete the conversion, the whole procedure was repeated.

PS-PEG(2)-O-TBDMS ***3a***. Starting from 999.8 mg (1.70 mmol) of polymer-bound phenol, we isolated 1.2069 g of yellow resin.

PS-PEG(4)-O-TBDMS ***3b***. Starting from 1.1413 g (1.94 mmol) of polymer-bound phenol, we isolated 1.5156 g of yellow resin.

PS-PEG(6)-O-TBDMS ***3c***. Starting from 513 mg (0.87 mmol) of polymer-bound phenol, we isolated 733 mg of pink resin.

PS-PEG(8)-O-TBDMS ***3d***. Starting from 1.5750 g (2.68 mmol) of polymer-bound phenol, we isolated 2.3409 g of pink resin.

PS-PEG(10)-O-TBDMS ***3e***. Starting from 354.5 mg (0.60 mmol) of polymer-bound phenol, we isolated 517.0 mg of pink resin.

PS-PEG(12)-O-TBDMS ***3f***. Starting from 584.1 mg (0.99 mmol) of polymer-bound phenol, we isolated 857.6 mg of yellow resin.

General Procedure for the Deprotection of TBDMS Group on Solid-Phase. Resins **3a**–**f** were suspended in 30 mL/g dry THF under argon. Then 5.0 equiv of 1.0 M

dx.doi.org/10.1021/co500028h | ACS Comb. Sci. 2014, 16, 367–374

tetrabutylammonium fluoride (TBAF) solution in dry THF were added dropwise. The reaction suspension, forming a brown mixture within 1 h, was stirred overnight at room temperature. Subsequently, the reaction mixture was filtered, and the solid residue was washed 3 times with THF, THF/water, THF, methanol/water, DCM, and finally with methanol. Proper washing is important to get rid of liberated substances. The resulting resin **4a**–**f** was dried to constant weight in vacuo (50 °C).

*PS-PEG(2)-OH **4a***. Resin **3a** (245.6 mg, 0.26 mmol) resulted in yellow resin **4a** (217.1 mg, 1.1 mmol/g). Anal. Found: C, 84.10; H, 7.58; N, <0.05. FT-IR (KBr): 3449, 3024, 2913, 2850, 1944, 1872, 1803, 1748, 1601, 1509, 1450, 1354, 1238, 1127, 1054, 1027, 906, 827, 754, 696 cm^{-1}.

*PS-PEG(4)-OH **4b***. Resin **3b** (924.5 mg, 0.89 mmol) resulted in yellow resin **4b** (820.4 mg, 1.1 mmol/g). Anal. Found: C, 82.41; H, 7.88; N, <0.05. FT-IR (KBr): 3460, 3025, 2916, 1945, 1876, 1805, 1747, 1602, 1510, 1493, 1452, 1349, 1244, 1108, 1064, 1028, 907, 828, 757, 697 cm^{-1}.

*PS-PEG(6)-OH **4c***. Resin **3c** (318.2 mg, 0.27 mmol) resulted in yellow resin **4c** (283.9 mg, 1.0 mmol/g). Anal. Found: C, 80.20; H, 7.90; N, <0.05. FT-IR (KBr): 3449, 3026, 2917, 1945, 1877, 1805, 1744, 1720, 1602, 1509, 1452, 1350, 1244, 1100, 943, 828, 757, 697 cm^{-1}.

*PS-PEG(8)-OH **4d***. Resin **3d** (361.5 mg, 0.25 mmol) resulted in yellow resin **4d** (327.0 mg, 0.9 mmol/g). Anal. Found: C, 78.41; H, 7.95; N, <0.05. FT-IR (KBr): 3480, 3026, 2921, 1947, 1878, 1808, 1747, 1602, 1511, 1452, 1349, 1098, 943, 908, 827, 757, 695 cm^{-1}.

*PS-PEG(10)-OH **4e***. Resin **3e** (347.0 mg, 0.19 mmol) resulted in slightly brown resin **4e** (343.6 mg, 0.8 mmol/g). Anal. Found: C, 80.32; H, 7.96; N, <0.05. FT-IR (KBr): 3480, 3025, 2915, 1946, 1877, 1805, 1747, 1602, 1509, 1493, 1349, 1243, 1099, 944, 828, 757, 697 cm^{-1}.

*PS-PEG(12)-OH **4f***. Resin **3f** (728.8 mg, 0.44 mmol) resulted in yellow resin **4f** (327.0 mg, 0.7 mmol/g). Anal. Found: C, 76.30; H, 8.06; N, <0.05. FT-IR (KBr): 3505, 3026, 2919, 1945, 1874, 1804, 1734, 1602, 1453, 1350, 1289, 1251, 1104, 948, 841, 758, 698 cm^{-1}.

General Procedure for Attachment of Sensor Molecule to Solid Support. Resins **4a**–**f** were suspended in dry DCM/DMF = 9/1 (15 mL/g resin), and then 4-(dimethylamino)butanoic acid, hydrochloride (5.0 equiv), and 1-hydroxybenzotriazole (5.0 equiv) were added in a minimum amount of dry DMF. 4-(*N*,*N*-Dimethylamino)pyridine (1.0 equiv) in dry DMF and *N*,*N*′-diisopropylcarbodiimide (5.0 equiv) were added to the mixture and stirred under argon at room temperature for 2 days. The resulting suspension was filtered and the solid residue was washed 3 times with DMF, then with DCM, and finally with methanol. The resin was dried to constant weight in vacuo.

*PS-PEG(2)-4-(dimethylamino)butanoic Acid, Hydrochloride **5a***. **4a** (165.7 mg, 1.01 mmol) resulted in yellow resin **5a** (194.0 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.1 (s, O–C═O), 63.9 (t, CH_2–O–C═O), 57.0 (t, CH_2–N), 43.0 (q, N–CH_3), 30.8 (t, CH_2–C═O), 19.8 (t, CH_2–CH_2–CH_2) ppm; assignment of the signals was supported by 2D-NMR experiments.

*PS-PEG(4)-4-(dimethylamino)butanoic Acid, Hydrochloride **5b***. **4b** (302.2 mg, 0.89 mmol) resulted in yellow resin **5b** (358.9 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.1 (s), 63.9 (t), 57.0 (t), 43.1 (q), 30.9 (t), 19.9 (t) ppm.

*PS-PEG(6)-4-(dimethylamino)butanoic Acid, Hydrochloride **5c***. **4c** (140.7 mg, 0.27 mmol) resulted in yellow resin **5c** (159.8 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.2 (s), 63.9 (t), 57.1 (t), 43.1 (q), 30.9 (t), 20.0 (t) ppm.

*PS-PEG(8)-4-(dimethylamino)butanoic Acid, Hydrochloride **5d***. **4d** (193.0 mg, 0.18 mmol) resulted in yellow resin **5d** (222.3 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.0 (s), 63.9 (t), 56.9 (t), 42.9 (q), 30.8 (t), 19.7 (t) ppm.

*PS-PEG(10)-4-(dimethylamino)butanoic Acid, Hydrochloride **5e***. **4e** (198.0 mg, 0.12 mmol) resulted in yellow resin **5e** (219.2 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.2 (s), 63.9 (t), 57.2 (t), 43.1 (q), 30.9 (t), 20.0 (t) ppm.

*PS-PEG(12)-4-(dimethylamino)butanoic Acid, Hydrochloride **5f***. **4f** (228.8 mg, 0.16 mmol) resulted in yellow resin **5f** (261.8 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.2 (s), 63.9 (t), 57.0 (t), 43.1 (q), 30.9 (t), 19.9 (t) ppm.

Application Example 1 (Hydantoin Synthesis). The synthetic steps toward hydantoin **14** were accomplished following published procedures.[24] All synthetic steps are in accordance with the literature, modifications concerning reaction time and reactant amounts are noted.

Activation of the Solid Support. Resin **4d** or TentaGel S PHB (0.2 mmol/g), respectively, were activated in the presence of a 10-fold excess of 4-nitrophenyl chloroformate and Et_3N (5.0 equiv) at a reaction time of 60 h.

Polymer-Bound 4-Nitrophenylcarbonates. Resin **4d** (1.340 g) led to a white resin **6d** (1.450 g). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 155.4 (s, ArC–O), 152.4 (s, C═O), 145.3 (ArC–NO_2), 125.2 (d, ArC–H), 121.7 (d, ArC–H) ppm. TentaGel S PHB resin (1.127 g) resulted in slightly yellow resin **6g** (1.180 g). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 155.2, 152.1, 145.0, 124.9, 121.5 ppm.

Attachment of the Amino Acid. The respective resins **6d** and **6g** were treated with a solution of L-phenylalanine (4.0 equiv) in BSA (4.0 equiv) and DMF, followed by the addition of DMAP (2.0 equiv) and stirred for a reaction time of 48 h.

Polymer-Bound N-Carboxy-L-phenylalanin. PS-PEG Resin **6d** (1.141 g, 0.52 mmol) led to a white resin **7d** (1.155 g). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 173.4 (s, O═C–OH), 155.3 (s, C═O), 136.1 (ArC-CH_2), 129.3 (d, ArC–H), 128.4 (d, ArC–H), 126.9 (d, ArC–H) ppm. TentaGel resin **6g** (350 mg, 0.07 mmol) resulted in yellow resin **7g** (341 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.9, 155.8, 136.2, 129.4, 129.2, 126.4 ppm.

Addition of the Amine. Resins **7d** and **7g** were suspended in DMF; dissolved 1-hydroxybenzotriazole (4.0 equiv) was added, and subsequently, DIC (4.0 equiv) was transferred to the vessel dropwise. Then, the mixture was stirred for 1 h. Finally, benzylamine (4.0 equiv) was added, and the reaction was allowed to proceed overnight. After the filtration of the resin, the procedure was repeated to ensure full conversion.

Polymer-Bound N-Carboxy-L-phenylalanin-benzylamide. Bead **7d** (930 mg, 0.43 mmol) resulted in beige resin **8d** (935 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 170.7 (s, O═C–NR), 155.9 (s, C═O), 137.6 (ArC–CH_2), 136.4 (s, ArC–CH_2) ppm. Starting from resin **7g** (984 mg, 0.17 mmol) yellow resin **8g** (854 mg) was achieved. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 170.4, 155.6, 137.5, 136.2 ppm.

Release of the Hydantoin. The cleavage of hydantion **14** was realized by reaction of 1,1,3,3-tetramethylguanidine (2.0 equiv) in MeOH with bead **8d** (507 mg) and resin **8g** (503 mg), respectively. The reaction was allowed to proceed at reflux (65 °C) for 24 h (to complete the cleavage for **8d** the reaction

dx.doi.org/10.1021/co500028h | *ACS Comb. Sci.* 2014, 16, 367–374

was repeated at reflux overnight). After work-up, **4d** and TentaGel resin could be recovered showing ^{13}C gel-phase spectra comparable to the starting resin. The filtrates were concentrated in vacuo and purified by column chromatography (4.5 g silica gel, diethyl ether) leading to 44 mg of **14** starting from resin **8d** and 14 mg of hydantoin **14** applying TentaGel-based resin **8g**.

*3,5-Bis(phenylmethyl)-2,4-imidazolidinedione **14***. **14** was obtained as white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35−6.95 (m, 10H), 5.44 (bs, 1H), 4.62−4.43 (m, 2H), 4.18 (ddd, J = 8.5 Hz, 3.8 Hz, 1.2 Hz, 1H), 3.19 (dd, J = 14.0 Hz, 3.8 Hz, 1H), 2.78 (dd, J = 14.0 Hz, 8.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (s), 157.0 (s), 135.7 (s), 134.9 (s), 129.3 (d, 2C), 128.8 (d, 2C), 128.6 (d, 2C), 128.2 (d, 2C), 127.7 (d), 127.3 (d), 58.3 (d), 42.0 (t), 37.6 (t) ppm. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.62; H, 5.48; N, 9.71.

Application Example 2 (Heck-Coupling Route). *Loading of the Resins with 4-Iodobenzoic Acid.* Resin **4b,d,f** and Reactagel (0.7 mmol/g) were stirred in a mixture DCM/DMF (9/1) for 15 min to ensure sufficient swelling. 4-Iodobenzoic acid (5.0 equiv) and 1-hydroxybenzotriazole (5.0 equiv) dissolved in DMF, as well as DIC (5.0 equiv), were added to the resin. Finally DMAP (1.0 equiv) was transferred to the reaction vessel and the mixture was stirred overnight at room temperature under argon. The work-up of the beads was in accordance with the procedure reported in the literature; because of incomplete loading of resins **9d** and **9f** (determined by ^{13}C gel-phase NMR spectra), the reaction sequence was repeated applying a 0.2-fold amount of all reactants compared to the first loading step.

Polymer-Bound 4-Iodobenzoic Acid. Starting from resin **4b** (610 mg), we could isolate 691 mg of **9b** as a yellowish resin. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 166.0 (s, O═*C*−OR), 137.6 (d, ArC−H), 131.1 (d, ArC−H), 129.5 (s, Ar*C*−C═O), 100.8 (s, ArC−I). Resin **4d** (292 mg) led to 330 mg of slightly yellow beads **9d** after a second loading step. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ 165.9, 137.6, 131.1, 129.5, 100.8. **4f** (210 mg) overall resulted in 244 mg of white resin **9f**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 165.9, 137.6, 131.1, 129.5, 100.7 ppm. Starting from Reactagel (1.138 g), we could obtain 1.175 mg of white resin **9g**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 165.8, 137.5, 131.0, 129.4, 100.7 ppm.

Heck-Coupling Reactions. The different resins (**9b,d,f** and loaded Reactagel **9g**) were swollen in a mixture of DMF/H_2O/NEt_3 over a period of 15 min. Subsequently, methyl methacrylate (2.0 equiv), triphenylphosphine (0.4 equiv), tetra-*n*-butylammonium chloride (0.4 equiv) and finally palladium(II)acetate (0.2 equiv) were added. The reaction was carried out overnight at 40 °C under argon atmosphere; the isolation of the beads was carried out according to literature.[25] The black/gray color of the resin is attributed to residual palladium remaining adsorbed on the beads.

Polymer-Bound Phenylmethylmethcrylate. Resin **9b** (291 mg) leads to black resin **10b** (264 mg). ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 166.8 (s, O═*C*−O*C*HH_3), 165.9 (s, O═*C*−OR), 143.4 (d, H−*C*═C), 138.5 (s, ArC−*C*═C), 120.1 (d, H−*C*═C), 51.8 (q, *C*H_3) ppm. ^{13}C gel-phase NMR spectra indicated incomplete conversion, which is attributed to the low swelling ability in polar-solvent mixtures of the resin bearing a short PEG spacer unit. Starting from **9d** (196 mg), we could obtain 198 mg of **10d** as a black solid. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 166.8, 165.9, 143.3, 138.5, 120.1, 51.8 ppm. Beads **9f** (187 mg) resulted in 191 mg of gray resin **10f**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 166.9, 165.8, 143.4, 138.6, 120.1, 51.8 ppm. Starting from Reactagel-based **9g** (291 mg), we could isolate 272 mg of **10g** as back beads. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 166.7, 165.6, 143.2, 138.4, 120.0, 51.7 ppm.

Application Example 3 (Wang Linker Attachment). *General Procedure for the Chlorination of PS−PEG Resins.* Beads **4a−b** were suspended in anhydrous toluene. Thionyl chloride (7.0 equiv) was added, and the reaction mixture was stirred overnight at 75 °C. After it was cooled to 55 °C, the resin was filtered and washed with warm toluene (5×) and methanol (3×). The polymer-bound poly(ethylene glycol) derivatives **11a−b** were dried to constant weight in vacuo.

Chlorinated PS-PEG-Bound Linker. Resin **4a** (1.648 g) in 20 mL anhydrous toluene yielded in 0.787 g white resin **11a**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 71.5 (t), 69.9 (t), 67.4 (t), 42.7 (t, *C*-Cl) ppm. PS-PEG beads **4b** (0.904 g, 1.36 mmol) in 20 mL of anhydrous toluene resulted in 0.873 g of white resin **11b**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 71.3 (t), 70.8 (t), 69.8 (t), 67.2 (t), 42.7 (t) ppm.

Addition of the Wang Linker. General Procedure. Sodium hydride (5.0 equiv) was added to a solution of 4-hydroxybenzyl alcohol (5.0 equiv) in anhydrous DMF. After it was stirred for 30 min at room temperature, resins **11a−b** were added to the reaction mixture. The suspension was heated to 75 °C and stirred overnight at this temperature. The resin was filtered off and washed twice with each of the following solvents: DMF, DMF/H_2O, THF/H_2O, MeOH/H_2O, MeOH, alternating DCM, and MeOH. The isolated resin was dried to constant weight in vacuo overnight.

PS-PEG-Bound Wang Linker. Resin **11a** (0.516 g, 0.538 mmol) in 25 mL of anhydrous DMF resulted in 0.549 g of brown resin **12a**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 128.5 (d, Ar*C*−H), 114.6 (d, ArC−H), 69.9 (t), 67.4 (t, CH_2−O−Ar), 64.8 (t, CH_2−OH) ppm. Starting from **11b** (0.574 g, 0.599 mmol) in 25 mL of anhydrous DMF, we could isolated 0.621 g of brown resin **12b**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 128.5 (d), 114.6 (d), 70.6 (t), 69.6 (t), 67.3 (t), 64.7 (t) ppm.

Attachment of Sensor Molecule to the Wang Linker. The reaction was carried out analogous to the general procedure of the sensor attachment, except for stirring the reaction mixture overnight.

PS-PEG-Bound Sensor 4-(Dimethylamino)butanoic Acid, Hydrochloride. Beads **12a** (0.196 g, 0.193 mmol) in 7 mL of solvent yielded 0.217 g of brown polymer **13a**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.1 (s, O−*C*═O), 57.2 (t, CH_2−N), 43.3 (q, N−CH_3), 31.1 (t, CH2−C═O), 20.2 (t, CH_2−CH_2−CH_2) ppm. Starting from **12b** (0.209 g, 0.191 mmol) in 7 mL of solvent, we isolated 0.240 g of brown resin **13b**. ^{13}C gel-phase NMR (100 MHz, $CDCl_3$): δ = 172.0 (s), 57.0 (t), 43.1 (q), 30.9 (t), 20.0 (t) ppm.

■ ASSOCIATED CONTENT

Supporting Information

Gel-phase ^{13}C NMR characterization of target PS−PEG resins (**3a−f**, **4a−f**), gel-phase ^{13}C NMR spectra of compounds **4a−f**, **5a−f** and the application example 2 (Heck coupling, compounds **9b,d,f** and **10b,d,f**, Reactagel), and IR spectra of compounds **4a−f**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/co500028h | *ACS Comb. Sci.* 2014, 16, 367−374

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to G. Ebner, C. Gorsche, H. Gschiel, C. Trimmel, and B. Waldner for supporting the synthetic experiments. Prof. H. Hutter and M. Holzweber are acknowledged for assistance in performing the microscopy.

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