

Polytetrahydrofuran Cross-Linked Polystyrene Resins for Solid-Phase Organic Synthesis

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Currently, divinylbenzene cross-linked polystyrene (DVB-PS) is the polymer of choice for use in solid-phase organic synthesis (SPOS). While much research has been directed toward the optimization of linker groups for the attachment of compounds to the polymer, the development of new polymers themselves has been relatively neglected. In an attempt to overcome the shortcomings of DVB-PS and to develop new polymers with optimum properties for use in organic synthesis, we have prepared a series of polystyrene polymers that incorporate flexible polytetrahydrofuran (PTHF) based cross-linkers. The objective of incorporating PTHF into the polymers was to slightly increase the overall polarity of the polymer and thus render the resins more organic solvent-like. Since the degree to which a resin swells in and absorbs a particular solvent correlates to how well substrates attached to the polymer are solvated, we compared the swelling of our new resins to commercially available DVB-PS resins. In all cases, we found that our resins swelled to a much greater extent than do DVB-PS resins, and their use should therefore allow for SPOS reaction conditions that more closely mimic homogeneous solution-phase conditions. It was also found that the PTHF chain length of the cross-linker does not affect the level of swelling since all of our cross-linkers afford resins with comparable levels of increased swelling. Furthermore, we have examined the utility of our resins in directed ortho-metalation reactions and found that the increased swelling of our resins allows for isolation of reaction products in yields comparable to what is achieved using standard solution-phase conditions.

Introduction

Demands of the drug discovery process and the advent of combinatorial chemistry have spurred renewed interest in polymer assisted organic chemistry.¹ The use of polymers to assist organic synthesis generally occurs via two different strategies. In one strategy, polymers are used as carriers upon which molecules are synthesized. Historically, insoluble polymer resins have been used for such applications,² but soluble polymers have also found utility.³ The second approach involves the use of polymer supported reagents to simplify purification of solution-phase chemical reaction products.⁴ For such applications, the polymer supported reagent may be a selective reaction component⁵ or it may be relatively nonselective and used to react with, and thereby remove, excess solution-phase reagents.⁶

In terms of insoluble polymer supported organic synthesis, the resin predominantly used is the one originally introduced by Merrifield for solid-phase peptide synthesis (SPPS),⁷ divinylbenzene cross-linked polystyrene (DVB-PS). While substantial research has been dedicated toward optimizing linker groups for the attachment of organic molecules to

resins,⁸ relatively little effort has been made toward identifying new insoluble polymeric supports with improved physical and chemical properties.⁹ The vast majority of work along this line has been aimed at developing new supports for the synthesis of peptides and other highly polar oligomeric biomolecules by making the polymer more compatible with highly polar solvents and reagents. These polymers generally incorporate polyester,¹⁰ polyamide,¹¹ poly(ethylene glycol) (PEG),¹² or polysaccharide¹³ matrixes to increase the overall polarity of the support. These materials are hydrophilic and contain many reactive functional groups that potentially limit their utility in solid-phase organic synthesis (SPOS) applications involving anhydrous reaction conditions, organometallic reagents, strong bases, or mineral and Lewis acids.

The optimization of polymeric supports for SPOS through the design of materials with optimal properties for interaction with organic solvents and reagents has only recently begun to be addressed. Some of the materials examined as potential SPOS supports include macroporous polystyrene resins,¹⁴ and polystyrene grafted onto fluoropolymer¹⁵ and polypropylene¹⁶ surfaces. Also, polystyrene resin beads have been derivatized by tentacles formed through grafting of linear polystyrene¹⁷ and various norbornene derivatives.¹⁸ One notable class of new gel-type polymer resins was introduced by Itsuno¹⁹ and later studied by Pillai,²⁰ Meldal,²¹ and Kurth²² in which polystyrene is lightly cross-linked by PEG derivatives **1**. In

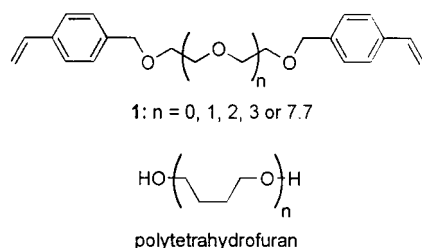
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these polymers (PEG-PS), PEG chains of various lengths are capped with styrene groups and these bifunctional PEG derivatives are used as cross-linkers in the polymerization of styrene. Resins incorporating **1** were found to be superior to DVB-PS in terms of their ability to swell in common organic solvents and their mechanical stability, and in the work of Itsuno,^{19b,c} their use afforded higher enantioselectivity in catalytic asymmetric reactions. These properties of the PEG-PS polymers prompted our work in the area of SPOS resin development, and herein we describe the preparation and study of polytetrahydrofuran (PTHF) cross-linked polystyrene (PTHF-PS) SPOS resins.^{23,24} PTHF has a linear acyclic structure and is formed through the cationic ring-opening polymerization of tetrahydrofuran (THF).

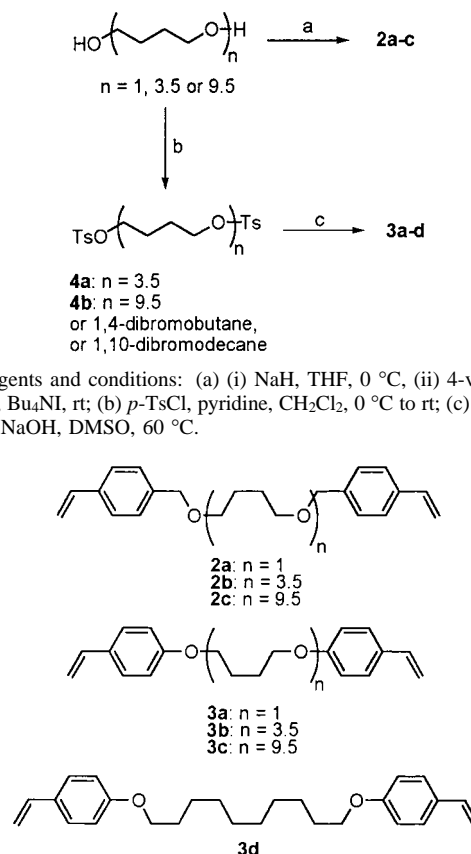


Our previous experience in using PEG as a soluble polymeric support for organic chemistry^{3c} and in developing new PEG star polymers²⁵ led us to question if PEG was the best possible cross-linker for hybrid polystyrene resins. PEG is a very hydrophilic material that has a strong tendency to form helical structures that can bind metal cations and is only sparingly soluble in cold tetrahydrofuran. These properties can limit the utility of PEG in low temperature organometallic and anionic reactions. Since such reactions are widely used in modern organic synthesis, we chose to examine the use of PTHF based cross-linkers **2a–c** and **3a–c** in gel-type polystyrene resins.²⁶ Our choice of incorporating PTHF into **2a–c** and **3a–c** was based on the fact that THF is a common solvent for reactions involving organometallic reagents and that incorporation of PTHF into resins might allow such resins to better solvate these reagents and therefore produce reaction conditions that more closely mimic solution-phase conditions.²⁷ Additionally, it has been put forth in an editorial by Czarnik that “solid-phase synthesis supports are like solvents”.²⁸ If this is true, and following the basic chemical principle that like dissolves like, the incorporation of THF into SPOS resins might begin to bridge the gap between solution- and solid-phase chemistry. Furthermore, our approach allows us to systematically examine the conversion of SPOS resins from polystyrene to PTHF through variation of the length of the PTHF chain in the cross-linkers and the level of cross-linker incorporation, progressing toward the ultimate goal of preparing SPOS supports composed entirely of PTHF.

Results and Discussion

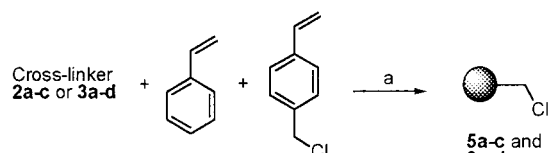
Cross-linkers **2a–c** were prepared to closely mimic cross-linkers **1** and were synthesized as outlined in Scheme 1 using standard Williamson ether synthesis conditions.²⁹ Cross-linkers **2b** and **2c** are mixtures of oligomers obtained from PTHF of molecular weight 250 and 650 Da, respectively.

Scheme 1^a



^a Reagents and conditions: (a) (i) NaH, THF, 0°C , (ii) 4-vinylbenzyl chloride, Bu_4NI , rt; (b) p -TsCl, pyridine, CH_2Cl_2 , 0°C to rt; (c) 4-acetoxystyrene, NaOH, DMSO, 60°C .

These are the lowest molecular weight PTHF grades commercially available and were chosen as a convenient starting point. Since **2a–c** all contain chemically labile benzylic ether linkages between the styrene units and the flexible tether chains, it was anticipated that there would be chemical incompatibilities of resins prepared with them. Furthermore, their large-scale synthesis requires laborious purification, limiting their potential commercial use. We therefore prepared **3a–d**, which did not require difficult purification and contain more chemically robust phenyl ether linkages, by modification of the procedure reported by Crivello for the synthesis of **3a** (Scheme 1).³⁰ Cross-linker **3d** was prepared to study the effect of decreased oxygenation of the tether between the styrene moieties. In the synthesis of **3a** and **3d**, 1,4-dibromobutane and 1,10-dibromodecane were alkylated with sodium 4-vinylphenoxide (Scheme 1). The synthesis of **3b** and **3c** required conversion of the hydroxyl functionality of the PTHF chains to leaving groups, and p -toluenesulfonyl groups were found to be the most convenient. Thus, **4a–b** were prepared and used without purification for incorporation into **3b** and **3c**, respectively. The original procedure for phenoxide alkylation was modified to allow for simple and economical isolation of pure **3a–d** in large quantities. The crude reaction mixture was poured into water, and the resulting suspension was continuously extracted with ether. Removal of the ether afforded crude product that was recrystallized to high purity. It should be noted that even **3b** and **3c**, which are mixtures of oligomers, recrystallized to afford compound mixtures that contained only the desired products. Proton NMR analysis showed that the product

Scheme 2^a

^a Reagents and conditions: (a) chlorobenzene, benzoyl peroxide, water, acacia gum, NaCl, 85 °C.

Table 1. Volumes of Swollen Resins

resin	cross-linker—percent	volume of swollen resin (mL/g) ^a				
		dioxane	THF	DMF	benzene	CH ₂ Cl ₂
Merrifield ^b	DVB-1	6.0	6.4	4.8	6.6	6.0
Merrifield ^b	DVB-2	5.4	5.4	4.2	6.6	5.8
TentaGel-HMP ^b	DVB-1	4.8	4.4	4.4	4.0	5.8
5a	2a-1	11.8	13.4	8.8	12.6	11.8
5a	2a-2	7.0	7.0	5.0	7.6	6.6
5b	2b-1	10.4	10.4	8.0	12.2	10.6
5b	2b-2	7.4	8.2	5.6	9.6	7.8
5c	2c-1	12.6	12.6	8.2	13.8	12.4
5c	2c-2	8.4	8.4	5.4	8.0	7.8
6a	3a-1	14.8	14.0	10.4	14.6	15.0
6a	3a-2	7.8	7.4	6.0	8.2	7.4
6b	3b-1	12.6	13.4	8.6	15.0	13.0
6b	3b-2	9.8	10.0	7.0	11.6	9.6
6c	3c-1	16.2	16.8	10.2	16.6	16.4
6c	3c-2	10.8	10.6	7.0	11.0	10.8
6d	3d-1	13.2	13.6	9.6	15.0	14.6
6d	3d-2	7.4	8.6	5.6	9.0	8.0

^a Volumes were measured in syringes equipped with a sintered frit after equilibrating for 1 h. Resins **5a-c** and **6a-d** did exhibit modest swelling in ethyl ether and 1:1 THF:water. Water, acetonitrile, and ethanol were also examined, but no significant swelling was observed. All resins had dry volumes of approximately 1.5 mL/g. ^b Resin was purchased from Novabiochem and used as received.

oligomer distributions were identical to those of the starting oligomer mixtures.

With **2a-c** and **3a-d** in hand, a series of resins, **5a-c** and **6a-d**, were prepared by suspension copolymerization³¹ of styrene, 4-vinylbenzyl chloride, and **2a-c** and **3a-d**, respectively (Scheme 2). The polymerization reactions were performed according to the procedure described by Kurth using a flanged reaction vessel equipped with a floating magnetic stirrer.²² Resins **5a-c** were prepared with 1, 2, 5, and 10 mol % cross-linking, while resins **6a-d** were prepared with 1 and 2 mol % cross-linking.

The degree to which a resin absorbs a particular solvent and swells is considered to be a good measure of site accessibility and thus resin functionalization.³² Table 1 compares the swelling of 1 and 2% cross-linked **5a-c** and **6a-d** to three commonly used supports of the same bead size (100–200 mesh) and approximately the same loading level (ca. 0.9 mmol/g) in solvents typically used for organic synthesis.³³ From Table 1, it is clear that utilization of cross-linkers **2a-c** and **3a-d** allows for resins **5a-c** and **6a-d** to exhibit superior swelling and solvent absorption compared to the commercial DVB cross-linked resins in all solvents where swelling was observed. Interestingly, resin swelling does not appear to be dependent on the length of the cross-linker. However, swelling does decrease with increased cross-

Table 2. Comparison of Swollen JandaJel and DVB Cross-Linked Resins

resin—cross-linking (%)	loading (mmol/g)	volume of swollen resin (mL/g) ^a				
		dioxane	THF	DMF	benzene	CH ₂ Cl ₂
JandaJel-Cl-2 ^b	1.00	11.4	11.6	9.0	10.8	10.8
PS/DVB-Cl-2 ^c	1.00	5.0	5.0	4.0	5.4	5.4
PS/DVB-Cl-2 ^d	1.00	7.0	7.4	5.8	7.0	7.0
JandaJel-OH-2	0.85	10.0	9.4	7.8	8.4	10.2
PS/DVB-OH-1 ^e	1.10	6.8	7.0	5.6	4.8	7.6
JandaJel-NH ₂ -2	1.30	17.6	12.0	14.0	12.0	11.8
PS/DVB-NH ₂ -2 ^f	1.10	9.4	8.0	5.2	8.2	7.4
JandaJel-Wang-2	0.90	11.4	12.0	10.0	9.8	11.4
PS/DVB-Wang-2 ^g	0.87	6.2	6.6	4.4	5.0	5.4

^a Volumes were measured in syringes equipped with a sintered frit after equilibrating for 1 h. The JandaJels did exhibit modest swelling in ethyl ether and 1:1 THF:water. Water, acetonitrile, and ethanol were also examined, but no significant swelling was observed. All resins had dry volumes of approximately 1.5 mL/g.

^b The JandaJel resins contain 2 mol % cross-linker **3a**. ^c Resin was purchased from Aldrich, catalog number 22,150-3. ^d Resin was prepared in our lab under conditions identical to those used to prepare the JandaJel resins. ^e Resin was purchased from Novabiochem, catalog number 01-64-0110. ^f Resin was purchased from Sigma, catalog number 08564. ^g Resin was purchased from Novabiochem, catalog number 01-64-0105.

linking. We have also prepared hydroxymethyl, aminomethyl, and Wang resins containing 2 mol % **3a** (JandaJels) and compared their swelling to analogous commercially available DVB cross-linked resins of approximately equal loading levels (Table 2). Again, all resins containing cross-linker **3a** exhibit significantly enhanced swelling compared to the analogous DVB-PS resins. It is likely that our method of resin preparation differs from the commercial processes and that the method of polymerization could be responsible for the observed superior swelling of JandaJel. To examine this possibility, we have prepared 2% divinylbenzene cross-linked polystyrene under conditions identical to those used for the JandaJels. While these DVB-PS resins did, in fact, swell slightly better than commercial DVB-PS resins, they swelled 35–40% less than the corresponding JandaJel resins in most solvents (compare lines 1, 2, and 3, Table 2). Therefore we conclude that the increased swelling is due to the structure of our cross-linker.

We have recently reported the results of a study in which two spectroscopic tools, EPR and fluorescence spectroscopy, were used to probe the microenvironments of chloromethyl JandaJel and Merrifield resins.^{32e} These techniques gave conflicting results in predicting which resin would exhibit greater solvation and, thus, swelling. Additionally, Hildebrand solubility parameters (δ) were calculated for each resin, and based on these values it was difficult to predict which resin would swell to a greater extent in a given solvent. We have therefore suggested that any interpretation of a resin's microenvironment based on a single phenomenon is subject to question.

To assess the synthetic utility of resins containing the new cross-linkers under strongly basic reaction conditions and their compatibility with organolithium reagents, we have prepared aminomethyl resins containing cross-linkers **2a-c** and **3a-d** and used these resins in directed ortho-metalation reactions³⁴ to prepare a library of phthalide compounds.³⁵ Traditionally, aminomethyl resins have been prepared by

Table 3. Aminomethyl Resins and the Synthesis of Phthalide Compounds

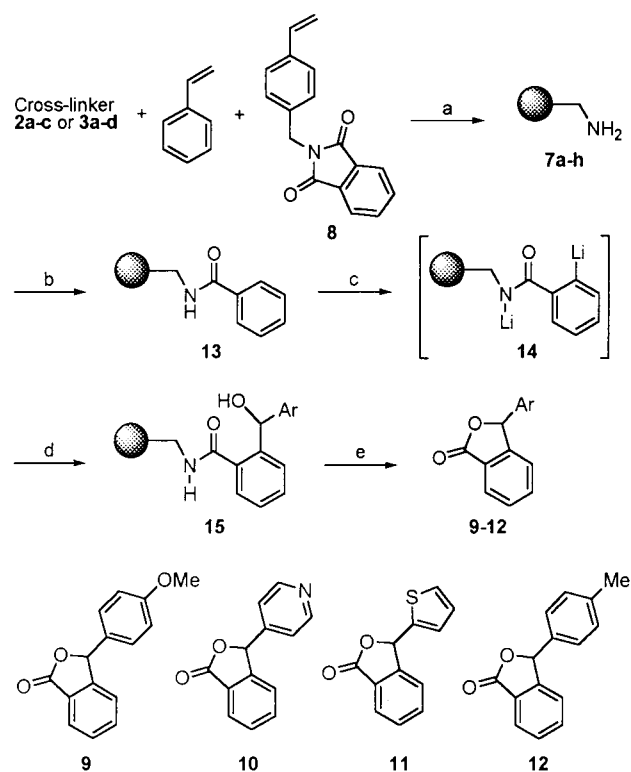
resin	cross-linker—percent	yield of phthalide product (%) ^a				
		9	10	11	12	avg
7a	3a-2	63	59	57	49	57
7b	3a-5	38	47	46	42	43
7c	3b-2	46	52	63	51	53
7d	3b-5	44	55	57	42	50
7e	3c-2	53	58	63	59	58
7f	3c-5	39	55	57	50	50
7g	3d-2	50	61	66	52	57
7h	3d-5	46	50	58	44	50

^a Yields are of crude reaction products found to be greater than 95% pure by ¹H NMR.

derivatization of preformed chloromethylated resin beads.³⁶ We chose to exploit an alternative route that involves the incorporation of the amine group through the use of a functionalized monomer in the polymerization reaction.³⁷ It was felt that this approach would result in resins of more defined composition and potentially more uniform functionality distribution, since reaction conditions used to introduce aminomethyl functionality on preformed resin beads often lead to side reactions, including unwanted additional cross-linking, and occur predominantly at the surface of the resin.³⁸ Furthermore, variation of the proportion of the functionalized monomer in the polymerization monomer mixture would allow for simple control of the resin's functional group loading levels.

We have previously reported the incorporation of **2a–c** into aminomethyl resins and the use of resin incorporating **2c** in the preparation of a 24-member phthalide library.³⁵ Unfortunately, when **2a–c** were used as cross-linkers, the resins had to be highly cross-linked to ensure their stability to butyllithium. We postulated that the phenyl ether linkages in **3a–d** would render resins prepared from them more stable at lower cross-linking levels under the basic reaction conditions. Thus, aminomethyl resins **7a–h** (Table 3) were prepared by suspension copolymerization of **3a–d** with **8**³⁹ and styrene (Scheme 3), and each was used to synthesize a subset of our original library (**9–12**) to determine any possible effects of cross-linker length and the degree of cross-linking. We previously observed a dramatic decrease in yield when going from 5 to 10 mol % cross-linking during the optimization of the reaction conditions for the library synthesis.

The amine group was deprotected by treatment with hot hydrazine. Resins **7a–h** were acylated with benzoyl chloride and triethylamine to afford the benzamide **13**, which served as the lithiation substrate. Treatment of **13** with 7 equiv of butyllithium afforded **14**, which was treated immediately with an arylaldehyde (*p*-anisaldehyde, 4-carboxypyridine, 2-carboxythiophene, or *p*-tolualdehyde) to afford alcohols **15**. The product phthalides (**9–12**) were cleaved from the resin by heating **15** in toluene and were found to be greater than 95% pure, as determined by ¹H NMR in yields that are comparable to what is observed in solution-phase chemistry.^{34,40} Inspection of Table 3 reveals that there does not appear to be any benefit to using the longer cross-linkers **3b–d** or from increasing the level of cross-linking from 2 to 5 mol %. Since **3a** is the most facile and economical to prepare of the cross-linkers studied, we have adopted its incorporation at 2 mol

Scheme 3^a

^a Reagents and conditions: (a) (i) chlorobenzene, benzoyl peroxide, water, acacia gum, NaCl, 85 °C, (ii) hydrazine hydrate, EtOH, reflux; (b) benzoyl chloride, Et₃N, THF, rt; (c) BuLi, THF, 0 °C; (d) ArCHO, 0 °C to rt; (e) toluene, reflux.

% as the standard for the resins that we currently prepare and use in our laboratory.²⁴

Summary

As SPOS rapidly becomes a more widely used tool of the organic chemistry community, the limitations of the currently used supports are becoming apparent. Up to this point, the supports used for SPPS have been adopted for use in SPOS. In comparison to SPOS, SPPS is a relatively simple process in which a limited number of different reactions are repetitively performed. These reactions require polar reagents and solvents. On the other hand, modern organic synthesis utilizes a much broader range of reagents, catalysts, solvents, and reaction conditions, and therefore supports used for SPOS must be much more versatile in their compatibility. Thus, to exploit the full catalog of organic reactions in SPOS, there is a need for new materials that are designed specifically to more closely mimic solution-phase organic reaction solvents.

In an attempt to prepare resins that more closely mimic THF in their polarity, we have introduced a series of flexible PTHF derived cross-linkers and incorporated these into SPOS resins. These resins, regardless of cross-linker length, exhibit superior swelling and solvent absorption compared to commercially available DVB cross-linked materials. The utility of the new resins in anhydrous anion chemistry was demonstrated through the synthesis of **9–12** in good yield. Furthermore, we have also successfully used a hydroxymethyl resin⁴¹ containing 2 mol % **3a** as a reusable, recyclable support for a Jacobson asymmetric epoxidation catalyst⁴² and

in a multipolymer REM resin⁴³ system for the synthesis of tertiary amines.⁴⁴ We expect that these resins will be useful for a wide array of SPOS applications and are currently exploring the scope of their utility.

Experimental Section

General. Polytetrahydrofuran 250 and 650 were purchased from Polymer Laboratories. Tetrahydrofuran was distilled from sodium prior to use. Technical grade 4-vinylbenzyl chloride was distilled in vacuo prior to use. All other chemicals were obtained from the Aldrich Chemical Co. and were used without further purification. Standard NMR spectra were recorded on either a Bruker AC-300 or AMX-400 spectrometer.

MAS NMR samples were prepared by swelling a few milligrams of each sample inside the NMR tube by the addition of CDCl₃. MAS NMR spectra were acquired on a Varian INOVA spectrometer operating at 599.7 MHz for proton and 150.8 MHz for carbon. The MAS frequency was about 2000 Hz in all cases. For 1D proton spectra, the sweep widths were 6000 Hz, and the time domain signals were apodized using a cosine function prior to Fourier Transforms. For the HMQC spectrum, the carbon sweep width was 45225.8 Hz, and a WALTZ sequence was employed to decouple carbon during the acquisition time. A squared sinebell function was applied along both frequency domains prior to the 2D transform. Proton frequencies were referenced to the residual signal from the solvent set at 7.24 ppm. Carbon frequencies were arbitrarily referenced by setting the lowest field, broad aromatic signal to 128 ppm.

SEM samples were mounted onto a SEM sample holder (Aquadag colloidal graphite, Ted Pella, Inc., Redding, CA) using graphite paint, and a thin coating of gold (10 nm) was applied under high vacuum. Samples were removed and placed into the SEM vacuum chamber and imaged using an accelerating voltage setting of 8 kV.

General Procedure for Cross-Linker 2a–c Synthesis. To a solution of PTHF 250 (10.0 g, 40.0 mmol) in anhydrous THF (150 mL) under a nitrogen atmosphere and cooled to 0 °C was added NaH (2.2 g, 91.7 mmol). After 1 h, 4-vinylbenzyl chloride (13.7 g, 90.0 mmol) and Bu₄NI (0.74 g, 2.0 mmol) were added, and the reaction mixture was allowed to stir at room temperature for an additional 24 h. The reaction mixture was quenched with water, poured into water (500 mL), and extracted with Et₂O (3 × 200 mL). The combined organic layer was washed with brine (300 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel (10% EtOAc/90% hexanes to 40% EtOAc/60% hexanes) to afford **2b** (16.7 g, 34.6 mmol, 87%) as a pure mixture of oligomers. 1,4-Butanediol and PTHF 650 were used to prepare **2a** and **2c**, respectively.

2a: ¹H NMR (400 MHz, CDCl₃) δ 1.70–1.73 (m, 4H), 3.47–3.50 (m, 4H), 4.49 (s, 4H), 5.24 (d, 2H, *J* = 10.9 Hz), 5.75 (d, 2H, *J* = 17.6 Hz), 6.72 (dd, 2H, *J* = 10.9 and 17.6 Hz), 7.29 (d, 4H, *J* = 8.2 Hz), and 7.39 (d, 4H, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 26.5, 70.0, 72.5, 113.7, 126.2, 127.8, 136.5, 136.8, and 138.2.

2b: ¹H NMR (400 MHz, CDCl₃) δ 1.60–1.67 (m, 14H), 3.39–3.49 (m, 14H), 4.48 (s, 4H), 5.22 (d, 2H, *J* = 10.9

Hz), 5.73 (d, 2H, *J* = 17.6 Hz), 6.70 (dd, 2H, *J* = 10.9 and 17.6 Hz), 7.28 (d, 4H, *J* = 8.2 Hz), and 7.37 (d, 4H, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 26.4, 70.1, 70.4, 70.5, 72.5, 113.6, 126.1, 127.7, 136.5, 136.8, and 138.2.

2c: ¹H NMR (400 MHz, CDCl₃) δ 1.62–1.67 (m, 38H), 3.41–3.49 (m, 38H), 4.48 (s, 4H), 5.21 (d, 2H, *J* = 10.9 Hz), 5.73 (d, 2H, *J* = 17.6 Hz), 6.70 (dd, 2H, *J* = 10.9 and 17.6 Hz), 7.28 (d, 4H, *J* = 8.2 Hz), and 7.37 (d, 4H, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 26.3, 70.0, 70.4, 70.5, 72.4, 113.5, 126.0, 127.6, 136.4, 136.7, and 138.1.

General Procedure for Bistosylate 4a–b Synthesis. To a solution of PTHF 250 (25.0 g, 0.10 mol) in pyridine (50 mL) and CH₂Cl₂ (450 mL) cooled to 0 °C was added *p*-TsCl (41.9 g, 0.22 mol). This was stirred for 16 h at room temperature and then diluted with additional CH₂Cl₂ (750 mL). The organic solution was washed successively with water (400 mL), 1 N HCl (400 mL), saturated NH₄Cl (400 mL), and brine (400 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford **4a** (52.1 g, 93.0 mmol, 93%) which was used directly without further purification. PTHF 650 was used to prepare **4b**.

4a: ¹H NMR (300 MHz, CDCl₃) δ 1.54–1.70 (m, 38H), 2.45 (s, 6H), 3.33–3.43 (m, 34H), 4.03 (dd, 4H, *J* = 10.5 and 4.1 Hz), 7.34 (d, 4H, *J* = 9.3 Hz), 7.78 (d, 4H, *h* = 9.3 Hz).

4b: ¹H NMR (300 MHz, CDCl₃) δ 1.54–1.72 (m, 38H), 2.45 (s, 6H), 3.31–3.39 (m, 10H), 4.04 (t, 4H, *J* = 7.5 Hz), 7.34 (d, 4H, *J* = 10.1 Hz), 7.78 (d, 4H, *J* = 10.1 Hz).

General Procedure for Cross-Linker 3a–c Synthesis. To a solution of 4-acetoxystyrene (10 mL, 65.0 mmol) in DMSO (50 mL) was added finely ground NaOH (6.6 g, 165.0 mmol). The reaction mixture was heated to 60 °C, and after 1.5 h, **4a** (17.9 g, 32.0 mmol) dissolved in DMSO (20 mL) was added dropwise over 3 h. Heating and stirring were continued for an additional 24 h. The suspension was cooled to room temperature, poured into water (250 mL), and continuously extracted with ether until TLC analysis showed that the organic material was completely removed from the aqueous layer (approximately 36 h). The ether was removed in vacuo, and the crude product was recrystallized from hot toluene to afford **3b** (10.6 g, 23.4 mmol, 72%) as a pure mixture of oligomers. 1,4-Dibromobutane, **4b**, and 1,10-dibromodecane were used to prepare **3a**, **3c**, and **3d**, respectively.

3a: ¹H NMR (400 MHz, CDCl₃) δ 1.96–1.99 (m, 4H), 4.04 (t, 4H, *J* = 5.6 Hz), 5.14 (d, 2H, *J* = 10.9 Hz), 5.62 (d, 2H, *J* = 17.6 Hz), 6.67 (dd, 2H, *J* = 10.9 and 17.6 Hz), 6.87 (d, 4H, *J* = 8.6 Hz), and 7.35 (d, 4H, *J* = 8.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 25.9, 67.4, 111.5, 114.4, 127.4, 130.3, 136.2, and 158.7.

3b: ¹H NMR (400 MHz, CDCl₃) δ 1.63–1.87 (m, 14H), 3.42–3.50 (m, 10H), 3.97 (dt, 4H, *J* = 1.5 and 6.2 Hz), 5.11 (d, 2H, *J* = 10.9 Hz), 5.59 (d, 2H, *J* = 17.6 Hz), 6.65 (dd, 2H, *J* = 10.9 and 17.6 Hz), 6.84 (d, 4H, *J* = 8.8 Hz), and 7.32 (d, 4H, *J* = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 26.4, 70.1, 70.4, 70.5, 72.5, 113.6, 126.1, 127.7, 136.5, 136.8, and 138.2.

3c: ¹H NMR (400 MHz, CDCl₃) δ 1.61–1.87 (m, 38H), 3.41–3.48 (m, 34H), 3.97 (t, 4H, *J* = 6.4 Hz), 5.10 (d, 2H,

$J = 10.9$ Hz), 5.59 (d, 2H, $J = 17.6$ Hz), 6.64 (dd, 2H, $J = 10.9$ and 17.6 Hz), 6.81 (d, 4H, $J = 8.6$ Hz), and 7.32 (d, 4H, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 26.4, 67.6, 70.3, 70.5, 70.6, 111.3, 114.4, 127.2, 130.1, 136.2, and 158.7.

3d: ^1H NMR (400 MHz, CDCl_3) δ 1.32–1.46 (m, 12H), 1.73–1.80 (m, 4H), 3.94 (t, 4H, $J = 6.6$ Hz), 5.10 (d, 2H, $J = 10.9$ Hz), 5.59 (d, 2H, $J = 17.6$ Hz), 6.65 (dd, 2H, $J = 10.9$ and 17.6 Hz), 6.84 (d, 4H, $J = 8.8$ Hz), and 7.33 (d, 4H, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 26.0, 29.2, 29.3, 29.5, 68.0, 111.4, 114.4, 127.3, 130.2, 136.2, and 158.9.

General Procedure for Resin Preparation (Janda/Jel-Cl). A solution of acacia gum (18.0 g) and NaCl (11.25 g) in water (450 mL) was placed in a 500 mL flanged reaction vessel equipped with a floating magnetic stirrer²² and deoxygenated by purging with N_2 . A solution of VBC (4.59 g, 30.0 mmol), styrene (23.4 mL, 204 mmol), **2c** (4.14 g, 4.69 mmol), and benzoyl peroxide (0.45 g) in chlorobenzene (30 mL) was injected into the rapidly stirred aqueous solution. This mixture was heated at 85°C for 16 h. The crude polymer was collected and washed in a Soxhlet extractor with water, THF, and hexanes. The beads (25.92 g, 86%) were dried *in vacuo* and sieved to afford resin in three size ranges: 50–100 mesh (11.31 g, 38%), 100–200 mesh (10.51 g, 35%), and 200–400 mesh (1.31 g, 4%). MAS ^1H NMR (600 MHz, 4 mg per mL CDCl_3 , 4 s relaxation delay with water suppressed by using a 0.5 s presaturation pulse during the relaxation delay) $\delta = 3.75$, 1.82.

Janda/Jel- NH_2 was prepared using *N*-(4-vinylbenzyl)-phthalimide (**8**)³⁹ as the functional monomer in the polymerization reaction followed by treatment of the resin with hydrazine hydrate to remove the phthalimide protecting group. Janda/Jel-OH was prepared using 4-vinylbenzyl alcohol^{41,45} as the functional monomer in the polymerization reaction. Janda/Jel-Wang was prepared from Janda/Jel-Cl by treatment with sodium methoxide and 4-hydroxybenzyl alcohol according to the method of Merrifield.⁴⁶ The loading level of hydroxyl and amine functionalized resins was determined by Fmoc release assay.¹⁴

General Procedure for Phthalide Synthesis. Aminomethyl resin (1.0 g) was swollen in dry THF (15 mL) and treated with triethylamine (5 equiv) and benzoyl chloride (5 equiv). After 1 h at room temperature, the resin was washed with THF, 1:1 THF/ H_2O , DMF, MeOH, and hexanes (40 mL of each solvent) and dried *in vacuo*. The resin (**13**) was negative to a Kaiser amine test and was placed (0.1 mmol N) in a dry 10 mL test tube equipped with a nitrogen inlet and a magnetic stirrer. Dry THF (2 mL) was added, the reaction mixture was cooled to 0°C , and *n*-BuLi (7 equiv, 2.5 M in hexanes) was added to afford resin **14**. After 5 min, the arylaldehyde (10 equiv) was added, and the reaction mixture was allowed to stir at 0°C for an additional 30 min. The reaction mixture was warmed to room temperature, and after 1 h, the resin was washed with THF, DMF, MeOH, and hexanes (10 mL of each solvent). The resulting resin (**15**) was heated for 16 h in refluxing toluene and filtered, and the filtrate was concentrated *in vacuo* to afford the desired phthalide⁴⁰ in greater than 95% purity as determined by ^1H NMR spectroscopy.

9: ^1H NMR (300 MHz, CDCl_3) δ 3.81 (s, 3H), 6.38 (s, 1H), 6.89 (d, 2H, $J = 8.8$ Hz), 7.18 (d, 2H, $J = 8.8$ Hz), 7.32 (d, 1H, $J = 7.5$ Hz), 7.56 (t, 1H, $J = 7.5$ Hz), 7.69 (t, 1H, $J = 7.5$ Hz), and 7.97 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 55.3, 82.7, 114.3, 122.9, 125.5, 125.9, 128.2, 128.8, 129.2, 134.2, 149.7, 160.4, 170.5.

10: ^1H NMR (250 MHz, CDCl_3) δ 6.36 (s, 1H), 7.25 (d, 2H, $J = 5.9$ Hz), 7.36 (d, 1H, $J = 7.3$ Hz), 7.56 (t, 1H, $J = 7.3$ Hz), 7.63 (t, 1H, $J = 7.3$ Hz), 7.96 (d, 1H, $J = 7.7$ Hz), and 8.62 (d, 2H, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 80.4, 121.0, 121.8, 122.4, 125.0, 126.0, 129.8, 134.6, 148.1, 150.1, 169.7.

11: ^1H NMR (300 MHz, CDCl_3) δ 6.67 (s, 1H), 7.02 (m, 1H), 7.15 (d, 1H, $J = 3.1$ Hz), 7.37 (d, 1H, $J = 5.3$ Hz), 7.47 (d, 1H, $J = 7.5$ Hz), 7.60 (t, 1H, $J = 7.5$ Hz), 7.71 (t, 1H, $J = 7.5$ Hz), and 7.96 (d, 1H, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 77.8, 123.1, 125.6, 125.8, 127.0, 127.5, 127.9, 129.8, 134.3, 138.8, 148.6, 169.7.

12: ^1H NMR (300 MHz, CDCl_3) δ 2.35 (s, 3H), 6.38 (s, 1H), 7.15 (d, 2H, $J = 8.3$ Hz), 7.18 (d, 2H, $J = 8.3$ Hz), 7.32 (d, 1H, $J = 7.5$ Hz), 7.55 (t, 1H, $J = 7.5$ Hz), 7.65 (t, 1H, $J = 7.5$ Hz), and 7.96 (d, 1H, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 82.7, 122.8, 125.6, 125.7, 127.0, 129.2, 129.6, 133.3, 134.2, 139.3, 149.8, 170.5.

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Supporting Information Available. A complete table of the swelling of resins **5a–c** and **6a**; NMR spectra of **2a–c**, **3a–d**, **4a–b**, and **9–12**; MAS ^1H NMR spectra of Janda/Jel-Cl, Janda/Jel-OH, Janda/Jel- NH_2 , and Janda/Jel-Wang; MAS HMQC spectrum of Janda/Jel-Cl; and a SEM micrograph of Janda/Jel-Cl are available free of charge via the Internet at <http://pubs.acs.org>.

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