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Synthesis and application of polytetrahydrofuran-grafted polystyrene (PS–PTHF) resin supports for organic synthesis

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Abstract—Cross-linked polystyrene (PS) with polytetrahydrofuran (PTHF) chains were prepared for use in solid phase organic synthesis (SPOS). The resins were prepared from styrene, styrene–PTHF macromonomers and cross-linkers 1,4-bis[4-vinylphenoxy]butane or divinylbenzene by suspension polymerization. The styrene–PTHF macromonomers were prepared by cationic polymerization of 4-vinylbenzyl bromide and 4-(4-vinylphenoxy)butyl iodide activated by silver hexafluoroantimonate and 4-(5-hydroxypentyl)styrene activated by triflic anhydride. Alternatively, polytetrahydrofuran–grafted polystyrene (PS–PTHF) resins could also be directly prepared from 5-hydroxypentyl *J*anda*J*el by cationic polymerization using triflic anhydride as the initiator. These PS–PTHF resins exhibited good swelling characteristics across a wide spectrum of polar and non-polar solvents. These resins were used in the synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one, which requires β-ketoester formation at low temperature (−78 °C), resulting in good yield and product purity; whereas the same synthesis carried out on PEG–grafted PS (PS–PEG) resin resulted in incomplete synthesis.

1. Introduction

Solid-phase organic synthesis (SPOS) continues to be important in the development of libraries of new molecules.[1] As more complex syntheses are investigated, specialized solid-phase supports are needed to allow facile library development. In essence, the research chemist needs to have a 'menu' of resins to choose from so as to adapt solution-phase synthesis with little or no modification to the solid-phase. The physical and chemical properties of the solid support play an important role in successful implementation of a SPOS strategy. Commercially available Merrifield and *J*anda*J*el resins have proven to be robust supports and allow access to reactive sites because of their good swelling characteristics. These resins are lightly cross-linked styrene-based polymers. *J*anda*J*els (JJ) have improved swelling when evaluated against Merrifield Resins (MF) by virtue of the more flexible cross linker 1,4-bis[4-vinylphenoxy] butane (**7**) compared to the divinylbenzene cross-linker for Merrifield resin.[2] These resins swell well in low polarity solvents such as benzene, toluene, THF, and chlorinated hydrocarbons, as well as DMF. Because of the excellent swelling of *J*anda*J*el resins (e.g., 8–10 ml/g in THF depending on resin functionalization), the environment of the resins becomes more 'solution-like' and thus provides easy access to the reactive sites, and therefore solution phase synthesis conditions can readily be adapted to SPOS.[3] However, polar protic solvents such as alcohols and water do not swell these resins and therefore limits their application, especially in terms of on-bead screening.

Complex multi-step synthesis requires a solid support that can function in both polar and non-polar solvents. Any new solid support needs to provide access to reactive sites in polar as well as non-polar solvents and be robust in severe chemical environments. PEG–grafted polyacrylamide[4] (PAM–PEG; e.g., PEGA) polymer beads as well as PEG–grafted polystyrene[5] (PS–PEG; e.g., TentaGel (TG), ArgoGel) resins have been designed to have utility in polar solvents and have limited swelling in non-polar solvents. However, PEG–grafted polyacrylamide resins have intrinsic limitations since these are not compatible with some common reagents because of the vulnerable amide bond. The grafted PEG chains provide a hydrophilic component to the hydrophobic polystyrene backbone, and exhibit more uniform swelling in both polar and non-polar

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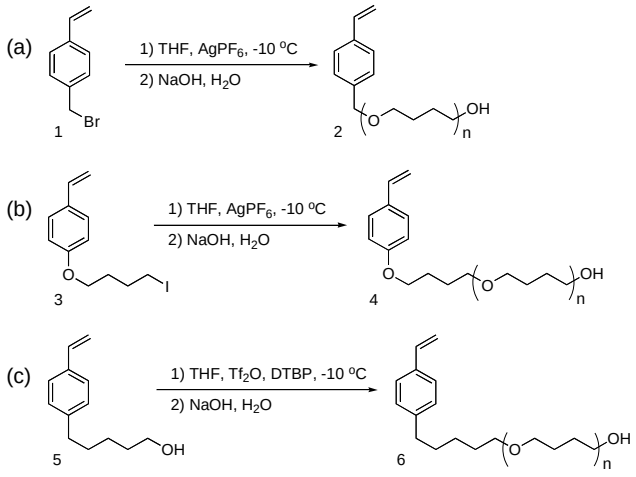
solvents, but the swelling is low compared to the Merrifield and *J*anda*J*el resins, especially in non-polar solvents. PS–PEG resins have superior performance in reactions involving salts and in peptide synthesis. However, studies conducted by Li et al. indicate that the PS resins have superior or equivalent kinetics in many chemical reactions compared to PS–PEG resins.[6] Furthermore, these PS–PEG resins generally have low loading capacity, tend to aggregate and have poor stability in some chemical environments, for example, in acidic media.

In considering new resins that could be adapted to SPOS, we chose to focus on tetrahydrofuran-based resins since tetrahydrofuran is a good organic solvent and is partially miscible with water. Therefore, we speculated that styrene-based resins containing PTHF chains could therefore provide resins with good swelling in a broad spectrum of solvents and increased chemical resistance compared to the PS–PEG resins. Polymerization of THF has been studied over the last 50 years and an extensive body of literature is available on polymeric techniques for preparing THF-based polymers. Based on the literature, two approaches to preparing PS–PTHF resins can be formulated: (1) preparation of macromonomers of styrene–PTHF, followed by suspension polymerization, and (2) grafting of PTHF chains to pre-formed resins similar to the preparation of PS–PEG resins. Evidence for the implementation of the second approach is the reported successful partial graft polymerization of PTHF on polyvinyl chloride (PVC), brominated poly-butadiene and random polymers of styrene and methacryloyl chloride.[7] Styrene–PTHF macromonomers of varying chain length also have been prepared, and successfully used in suspension polymerizations.[8–11] These macromonomers are prepared by cationic ring opening polymerization using initiators prepared from styrene derivatives or end capping of the living polymerization of THF with a styrene compound. For example, vinyl phenoxide PTHF macromonomers have been prepared with low polydispersity by the living polymerization of THF initiated by triethyloxonium tetrafluoroborate and then terminated by end capping with sodium vinyl phenoxide.[8] In another example, macromonomers were prepared by polymerizing THF from vinyl benzyl halides activated by reacting with silver (I) hexafluoroantimonate. PTHF macromonomers have also been prepared from triflic esters of butyl or allyl alcohols.[12]

Herein, we report the preparation of macromonomers 4-vinylbenzyloxy–PTHF **2**, 4-(4-vinylphenoxy)butyl–PTHF **4**, 5-(4-vinylphenyl)pentanoxy–PTHF **6** and suspension polymerization with styrene and styrene-based cross-linkers to produce PS–PTHF resins. We also report the preparation of PS–PTHF resins by a grafting protocol. The synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one **18** using these resins was used as a test case to evaluate these resins as a support for organic synthesis, particularly to examine the stability of these resins in acidic medium and metallation chemistry at low temperatures (−78 °C).

2. Results and discussion

Macromonomers of 4-vinylbenzyloxy PTHF **2** were prepared from 4-vinylbenzyl bromide **1** activated with silver (I) hexafluoroantimonate (Scheme 1a).[13] The cationic polymerization of THF was carried out in THF at −10 °C, and then terminated by quenching with dilute sodium hydroxide solution, resulting in macromonomers with hydroxyl end groups in quantitative yield.[14]



Scheme 1. Preparation of macromonomers.

The number of PTHF chains, n, was found to be directly proportional to the reaction time and macromonomers of specific chain length were obtained by controlling the reaction times. Two macromonomers of average chain lengths of $n=7.1$ and 13.6 were obtained. The average number of PTHF chains in the macromonomers was calculated by analysis of ^{1}H NMR spectra (Fig. 1), through comparison of the peak ratio of benzyl protons (a: 4.48 ppm) and methylene protons (c: 1.62 ppm). Although the NMR measurement gives an average chain length, these macromonomers contain a statistical distribution of macromonomers with varying chain length (verified by a GPC analysis) and a polydispersity of 1.1 for $n=7.1$ was calculated from the measured distribution.

Since the benzylic carbon of **2** might be susceptible to attack under acidic conditions, two other macromonomers were also prepared, 4-(4-vinylphenoxy)butyl–PTHF **4** and 5-(4-vinylphenyl)pentanoxy–PTHF **6**. Using $AgPF_6$ or $AgBF_4$ activation, 4-(4-vinylphenoxy)butyl iodide was readily converted to the corresponding macromonomers (Scheme 1b). Macromonomers containing $n=17.0$ and 34.0 were prepared using this procedure. However, we were unsuccessful in preparing macromonomer **6** by silver (I) activation from either 4-(5-bromopentyl)styrene or 4-(5-iodopentyl)styrene as precursors, presumably due to lower activity of these aliphatic type halides. We succeeded in making macromonomer **6** from 4-(5-hydroxypentyl) styrene **5** activated with triflic anhydride (Scheme 1c). A macro monomer of number-average molecular weight (M_n) of 689, weight-average molecular weight of (M_w) 747, and polymerization dispersity (M_w/M_n) of 1.1 was prepared (obtained by ESI-TOF, previously calibrated with polyethylene glycol (PEG)) by controlling the reaction time, resulting in a macromonomer with an average chain length of $n=6.9$. All the macromonomers were generally unstable even at low temperature having a shelf life of a few

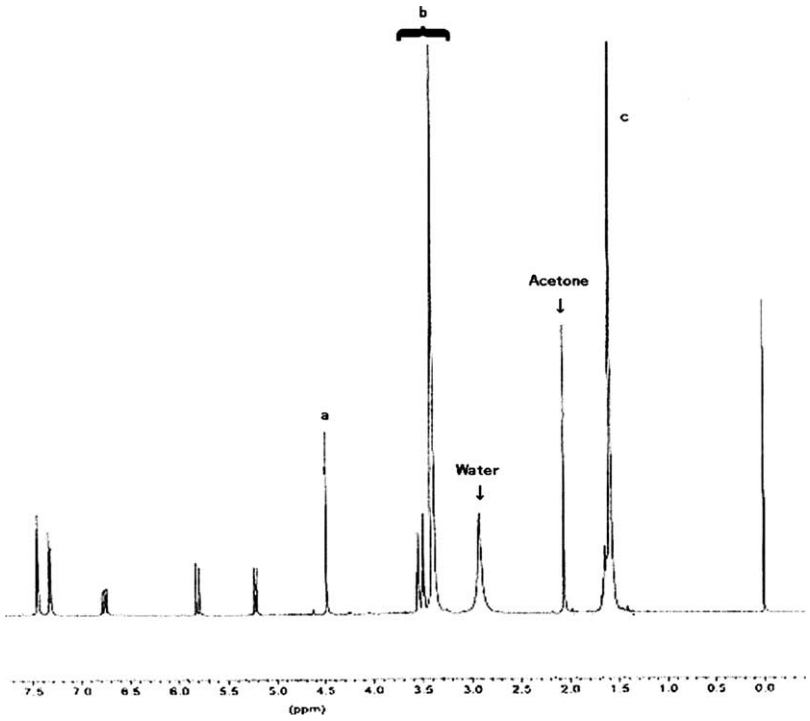
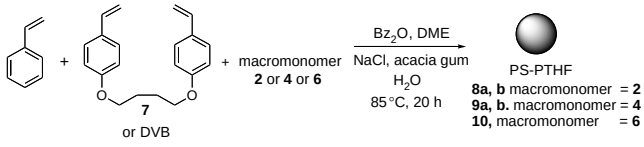


Figure 1. [1]H NMR Spectrum of macromonomer **2**.



Scheme 2. Preparation of macromonomers.

days, however, macromonomer **6** was found to be more unstable and had to be used immediately in resin preparation.

Having the three macromonomers in hand, we prepared PS–PTHF resins **8a**,**b**, **9a**,**b** and **10** (Scheme 2) by suspension polymerization of styrene, PTHF macromonomers **2**, **4** and **6**, and cross linkers divinylbenzene (DVB) and **7**.

The polymers were filtered and washed to obtain the resins in 69, 70, 48, 57 and 40% yield, respectively. In order to avoid problems with emulsions, a 10% higher concentration of NaCl was used with DVB as the cross-linker in the production of the resin **10**. The presence of PS and PTHF in resin **8a** was confirmed by ^{13}C NMR. The NMR spectrum of **8a** (Fig. 2) shows the presence of the methylene protons neighboring the hydroxyl group, the protons labeled as **e** and **f** can be attributed to the peaks at 62.6 and 30.3 ppm, respectively, confirming the presence of both PS and PTHF in the resin.[15] Similarly, magic angle spinning (MAS) [1]H NMR of resin **10** showed very defined peaks at 3.4 and 1.6 ppm, corresponding to the PTHF backbone, confirming the formation of PS–PTHF resins. The loading of the resins **8a**,**b**, **9a**,**b** and **10** was determined to be 0.55, 0.35, 0.29, 0.17 and 0.34 mmol/g, respectively, by Fmoc-glycine loading and quantitation of dibenzofulvene release. Resins **9a**,**b** obtained from 4-(4-vinylphenoxy)butyl PTHF were found to be sticky, presumably because of the long chain lengths ($n=17.0$, 34.0) of the macromonomer **4**; alternatively, resins **8** and **10** were isolated as free flowing powders.

Even though we succeeded in producing resin **10** from 5-(4-vinylphenyl)pentoxy PTHF **6**, precautions were necessary in the preparation of the resin due to the instability of macromonomer **6**. Therefore, we searched for an alternative procedure for making this resin. Since we were successful in activating 4-(5-hydroxypentyl)styrene **6** using triflic anhydride, we hypothesize that this approach could be applied to

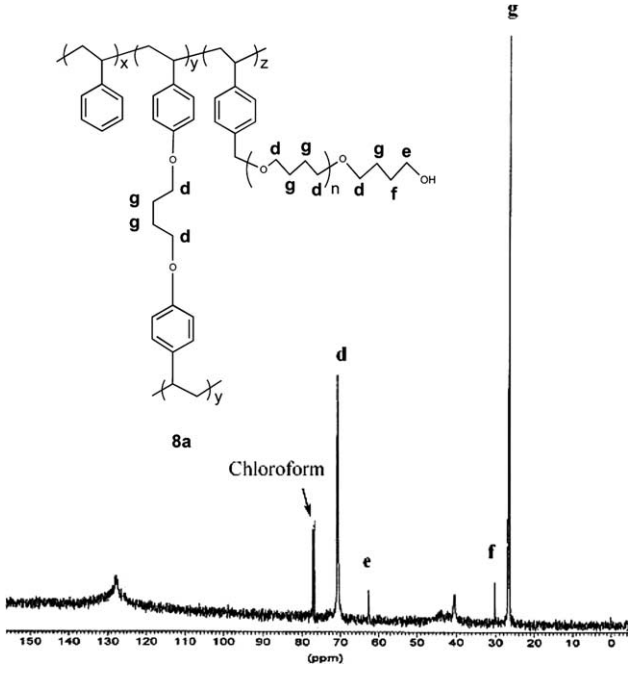
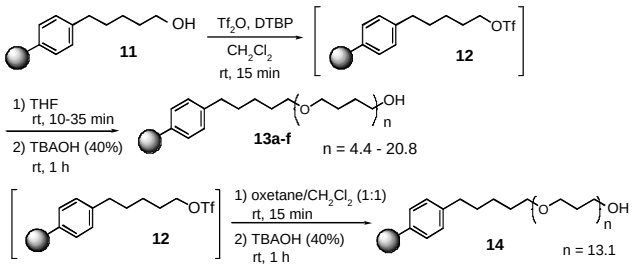


Figure 2. ^{13}C NMR of PS–PTHF resin **8a**.

graft PTHF macromer to 5-hydroxypentyl *J*anda*J*el resin (5-HPJJ resin), a resin previously prepared in our laboratory.[16] Gratifyingly, we were successful in activating this resin with triflic anhydride, and this method proved to be reproducible, reliable and easy to use (Scheme 3).



Scheme 3. Preparation of PTHF–grafted polystyrene from 5-hydroxypentyl *J*anda*J*el.

The procedure for the preparation of the PTHF–grafted polystyrene (PS–PTHF) required activation of 5-hydroxypentyl *J*anda*J*el (**11**) with triflic anhydride and in the presence of 2,6-di-*tert*-butylpyridine (DTBP) to give triflate resin **12**. The terminal triflate acts as an active intermediate for living polymerization of THF. The activated 5-HPJJ complex **12** was isolated and the grafting of PTHF macromer was achieved by adding anhydrous THF to the isolated complex. A series of PTHF–grafted polystyrene resins **13a–f** with varying number of PTHF chain length were prepared by adjusting the reaction time from 10 to 35 min (Table 1). However, when the same procedure was applied to hydroxymethyl polystyrene resins, grafting of PTHF did not take place and PS–PTHF resins were not obtained.

The chain lengths of **13a–f** were calculated from the weight increase, and verified by measuring the hydroxyl loading by 4,4′-dimethoxytrtyl chloride (DMT) titration.[17] The number of grafted PTHF units were found to have a linear correlation with reaction time (Fig. 3), resulting in zero order kinetics, suggesting that the number of PTHF units did not have an effect on the reactivity of the activated triflate end unit. IR spectra of the grafted resin showed two new peaks (C–O bond stretching) at 1028 and 1103 cm^{-1} and one enhanced peak (aliphatic C–H bond stretching) at 2852 cm^{-1} in comparison to 5-HPJJ. We also prepared resin **14** from oxetane, with $n=13.1$ and an –OH loading of 0.57 mmol/g, to determine if these resins may have properties similar to PS–PEG resins. Unlike TentaGel where several ethylene oxide units (more than 30) can be grafted onto the polystyrene polymer, PTHF and oxetane grafted resins with $n>13$ were found to be sticky in consistency. The morphology of PTHF derived resins is

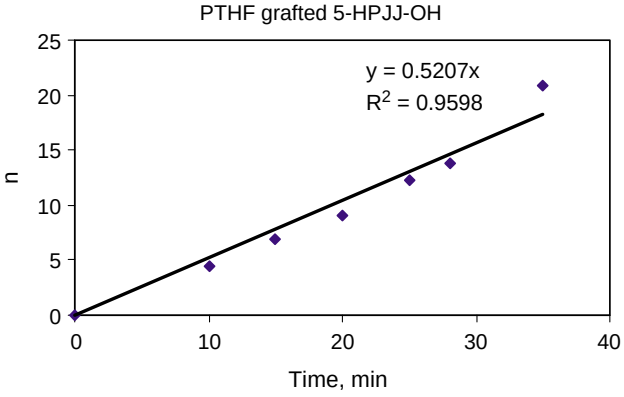


Figure 3. Kinetics for the preparation of PTHF–grafted 5-HPJJ resins.

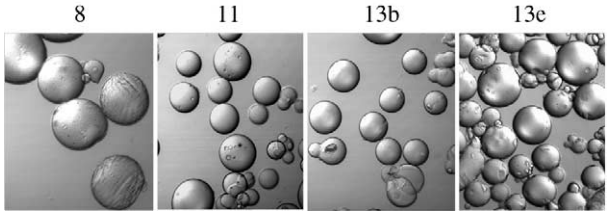


Figure 4. Microscopic images of resins.

shown in optical microscopic images (Fig. 4), demonstrating that the resins were spherical and free-flowing.

The stability of the PS–PTHF resins was examined under severe acidic and basic conditions, and the stability of these resins compared with commercially available hydroxymethyl Merrifield (MF), hydroxymethyl *J*anda*J*el (JJ) and hydroxyl-TentaGel (TG) resins. All resins were stable under strong basic conditions as measured by weight loss (Table 2). However, PEG or PTHF grafted resins were not stable under acidic conditions. Merrifield resin was shown to be inert under all conditions. Among the PTHF derived resins, the pentyl resins **13b**,**e** were found to be more stable than the benzyl resin **8** in TFA (condition C). The IR spectrum of the treated resins confirmed the findings based on weight loss.

The swelling property of resin supports is an essential feature for site accessibility in solid-phase organic synthesis. We measured swelling of these resins in several common solvents used in organic synthesis (Table 3). Unfortunately, none of the PTHF-derived resins showed any swelling in water, whereas TentaGel swells in water. When swelling of resins **13a–f** was examined, it was generally found to mirror the swelling obtained in 5-HPJJ. The best swelling results were obtained in resins **13b** and **13e** ($n=$ 6.9, 13.8, respectively). In methanol and diethyl ether resins

Table 1. Loading and chain lengths of grafted 5-HPJJ resins

Resin		**11**	**13a**	**13b**	**13c**	**13d**	**13e**	**13f**
Time (min)		0	10	15	20	25	28	35
n		—	4.4	6.9	9.1	12.2	13.8	20.8
Weight increase (%)		—	31.8	50.1	65.5	88.3	99.5	150.3
PTHF (wt%)		—	24.1	33.4	39.6	46.9	49.9	60.0
–OH loading (mmol/g)	Calculated	—	0.76	0.67	0.60	0.53	0.50	0.40
	Measured[a]	1.00		0.67			0.44	

[a] Measured by a DMT protocol.

Table 2. Stability test (weight change (%))

Conditions		MF	TG	JJ	PTHF–grafted JJ			
					8a	**11**	**13b**	**13e**
A	10% TBAOH (40%)/THF, 60 °C, 3.5 h	—	—	—	—	—	—	—
B	3% NaH/THF, room temperature, 3.5 h	—	—	—	—	—	—	—
C[a]	50% TFA/toluene, room temperature, 5 h	+10	+4	+10	−24[b]	−10	+6	+6
D	1 M BBr_3/CH_2Cl_2, room temperature, 3 h	—	−25[c]	x[d]	x[d]	x[d]	x[d]	x[d]
E	1 M $SnCl_4/CH_2Cl_2$, room temperature, 3 h	—	−10[e]	—	−30[b]	—	−30[b]	−36[b]

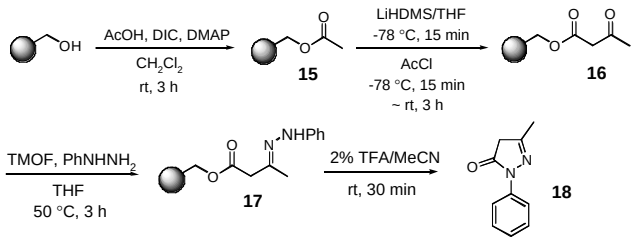
[a] Hydroxyl groups were protected with trifluoroacetyl group.
[b] All PTHF units were cleaved.
[c] All PEG units were cleaved.
[d] Resin dissolved.
[e] Partial cleavage of PEG units.

Table 3. Swollen volume (mL/g) of various resins

		CH_2Cl_2	THF	Dioxane	Toluene	DMF	MeOH	Acetone	Et_2O	*n*-Hexane	H_2O
5-HPJJ	**11**	8.9	8.7	8.3	7.6	6.8	2.4	4.3	4.6	2.4	—
	8a	8.9	8.7	7.8	8.3	5.2	2.4	4.1	4.7	2.6	—
	13a	6.3	6.1	5.6	7.0	4.1	2.6	3.5	3.7	2.5	—
	13b	9.1	8.6	7.9	7.9	5.3	3.0	4.1	4.9	3.0	—
	13c	6.8	6.1	5.3	6.0	3.5	2.6	3.3	3.7	2.6	—
PS–PTHF	**13d**	5.1	4.5	4.1	4.4	2.8	2.2	2.8	2.2	2.5	—
	13e	9.4	8.8	7.3	8.0	4.4	2.8	3.8	5.1	3.2	—
	13f	7.4	6.8	5.9	6.6	3.4	2.5	3.3	4.1	3.2	—
	14	7.7	7.1	6.2	4.8	4.2	2.3	4.0	4.6	3.1	—
	MF	5.9	6.7	6.5	4.5	5.7	2.7	3.7	3.2	2.1	—
	TG	6.9	5.1	5.5	4.6	5.1	3.7	4.0	2.0	—	3.0
	JJ	8.2	8.1	8.0	7.1	6.3	2.2	4.1	3.9	—	—

13b and **13e** exhibited slightly higher swelling compared to 5-HPJJ and JJ. Resin **14** prepared from oxetane showed similar behavior as the PTHF derived resins. We also measured swelling of resins **13b**, **13e** and TG at −78 °C in THF. Compared to swelling at room temperature, a significant reduction in swelling volume (~40%) was found for TG at −78 °C, whereas the PTHF derived resins retained the same degree of swelling obtained at room temperature. Resin **10** exhibited swelling behaviour equivalent to resin **13b**, whereas, resins **9a** and **9b** swelling could not be determined precisely because of the stickiness of the resins. Even though PS–PTHF resins exhibited only a marginal improvement in swelling especially in polar solvents, nevertheless, we decided to test these new resins in a synthetic application.

We chose the synthesis of a β-ketoester to demonstrate the application of these new resins in SPOS and compare their performance to the PEG based resin. The synthesis involves the use of LiHMDS at −78 °C and these conditions have been shown to be problematic for SPOS. Scheme 4 shows the synthesis using TentaGel and PS–PTHF resins **8b**, **13b** and **13e**. The resins were reacted with acetic acid by using 1,3-diisopropylcarbodiimide (DIC) as a condensation reagent to afford **15**, which was reacted with LiHMDS at −78 °C and treated with acetyl chloride to afford β-ketoester **16**.[18] Treatment of **16** with phenylhydrazine afforded **17**, which was cleaved with TFA in acetonitrile at room temperature to obtain **18**. No reaction was obtained with TentaGel, however, with all three PS–PTHF resins **18** was obtained in 42–48% yield with a purity ranging between 91 and 96% (Table 4). PEG-based resins proved ineffective under these conditions, probably due to low solubility of PEG in organic solvents,[19] and as discussed previously, TentaGel was shown to have much lower swelling at low temperature, presumably resulting in inaccessibility of reactive sites for this reaction. The fact that successful synthesis of **18** was achieved suggests that PS–PTHF resins are capable of generating carbanions at low temperatures.



Scheme 4. Preparation of 3-methyl-1-phenyl-2-pyrazolin-5-one **18**.

3. Conclusion

In summary, styrene-based PTHF macromonomers were prepared from the cationic polymerization of THF from styrene-based precursors activated with either silver (I) or

Table 4. Yields and purity of 3-methyl-1-phenyl-2-pyrazolin-5-one **18**

		TG	PS–PTHF		
			8b	**13b**	**13e**
OH loading (mmol/g)	Theoretical[a]	0.44		0.67	0.50
	Measured[b]	0.32	0.35	0.67	0.44
Purity (%)		—	94	96	91
Yield (%)		1	48	47	42

[a] Loading for TG based on reported value from manufacturer and for **13b** and **13e** by weight increase.
[b] Measured by a DMT protocol.

triflic anhydride. PS resins with PTHF graft chains were synthesized by suspension polymerization of styrene, macromonomer and cross-linkers. Alternatively a reproducible procedure was developed for production of resins by grafting PTHF chains to pre-formed 5-hydroxypentyl *J*anda*J*el. These resins were used successfully for the synthesis of 3-methyl-1-phenyl-2-pyrazolin-5-one **18** in good yield and purity, whereas Tentagel was shown to be ineffective in this synthesis. These resins had good chemical stability and swelling characteristics, and compared to commercially available resins should provide equal or better solid supports in SPOS.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from Aldrich and were used without further purification. TG and MF resins were purchased from Novabiochem. *J*anda*J*el-OH (JJ) was purchased from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-600, DRX-500, AMX-400 or a Varian Unity-300 spectrometer using tetramethylsilane (TMS) as an internal standard. FT-IR spectra were obtained with a Nicolet Avatar 360 FT-IR spectrometer equipped with a Nicolet Smart Gate (ZnSe). Gel permeation chromatographic analyses (GPC) were carried out on a Shimadzu LC-6A preparative liquid chromatograph with a Shimadzu CR-501A integrator and a Shimadzu SPD-10AV UV–vis detector (254 nm) (Styragel® HR2, HR3, and HR4, THF as eluent) using polystyrene standards. GC–MS analyses were carried out on a Shimadzu QP-5000 equipped with GC-17A gas chromatography instrument using DB-1 (J&W scientific 30 m×0.25 mm×0.25 μm) column. Gas chromatography (GC) analyses were carried out on Shimadzu GC-17A instrument using Ultra Alloy-7 (15 m×0.25 mm×0.25 μm) column. UV analyses were carried out on a Shimadzu UV mini 1240 UV–vis spectrophotometer. Microscope pictures were obtained using a BioRad Rainbow Radiance 2100 Confocal Laser Scanning Microscope (CLSM) attached to a Nikon TE2000U Eclipsed Inverted Fluorescence Microscope equipped with Differential Interference Contrast Optics (20× Plan Apo 0.75 na). Electron spray ionization–time-of-flight determinations were obtained using an Agilent ESI-TOF mass spectrometer. MAS data was collected on a Varian Inova spectrometer at 400 MHz using Varian's nanoprobe. The polymer was suspended in solution and sample spinner was set at 2000 RPM.

4.1.1. Synthesis of 4-vinylbenzyl alcohol. 4-Vinylbenzyl alcohol was prepared by slight modification of the reported method.[20] A mixture of 4-vinylbenzyl chloride (100 ml, 0.71 mmol) and potassium acetate (80 g, 0.84 mmol) in DMSO (300 ml) was stirred at 40 °C for 48 h. The reaction mixture was poured into water (300 ml) and extracted three times with ethyl acetate (300 ml). The collected ethyl acetate layer was dried with $MgSO_4$. The ethyl acetate was evaporated to afford 4-vinylbenzyl acetate and used without further purification. Sodium hydroxide (50 g, 1.25 mol) was added to the crude 4-vinylbenzyl acetate in EtOH (300 ml)/water (50 ml) and refluxed for 1.5 h. The reaction mixture was poured into water and extracted with ethyl acetate, dried with $MgSO_4$. The ethyl acetate layer was evaporated and distilled under vacuum to obtain 4-vinylbenzyl alcohol (92.3 g, 97% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.66 (s, 2H), 5.24 (d, 1H, J=10.5 Hz), 5.75 (d, 1H, J=17.7 Hz), 6.71 (dd, 1H, J=17.4, 10.8 Hz), 7.31 (d, 2H, J=7.8 Hz), 7.40 (d, 2H, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.0, 113.8, 126.3, 127.1, 136.4, 136.9, 140.4.

4.1.2. Synthesis of 4-vinylbenzyl bromide 1. 4-Vinylbenzyl bromide **1** was prepared by slight modification of the procedure for preparation of 4-styrylbenzyl bromide from 4-styrylbenzyl alcohol.[21] Phosphorous tribromide PBr_3 (18.4 g, 6.4 ml, 68 mmol) in Et_2O (10 ml) was added to 4-vinylbenzyl alcohol (5.9 g, 44.3 mmol) in Et_2O (500 ml) at 0 °C under N_2. After 1 h, additional PBr_3 (18.4 g, 6.4 ml, 68 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. After the reaction, the reaction mixture was cooled to 0 °C and water (100 ml) was added slowly to control the temperature. The solution was extracted with Et_2O, and the Et_2O layer was washed with aqueous $NaHCO_3$, brine and dried with $MgSO_4$. The crude product was purified by vacuum distillation (0.65 mmHg) at 60 °C to obtain **1**. Yield 6.8 g (78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (s, 2H), 5.26 (dd, 1H, J=11.0, 1.0 Hz), 5.75 (dd, 1H, J=17.6, 1.0 Hz), 6.69 (dd, 1H, J=17.6, 11.0 Hz), 7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4, 114.6, 126.6, 129.2, 136.1, 137.2, 137.7.

4.1.3. Synthesis of macromonomer 2 (n=7.1). A solution of 4-vinylbenzyl bromide **1** (2.96 g, 15 mmol) in THF (10 ml) was added to a solution of silver hexafluorophosphate (4.55 g, 18 mmol) in THF (500 ml) at −10 °C and stirred for 8 min. After the reaction, NaOH (3 g, 75 mmol) in water (50 ml) was added to the reaction mixture. The solution was filtered to remove AgBr and the solution was concentrated to a volume of ca. 200 ml. The solution was then added drop-wise into water and extracted with ethyl acetate. The organic ethyl acetate layer was washed with NH_4Cl, brine, and dried with $MgSO_4$. Evaporation of the solvents afforded **2** (10.46 g, quant.) as a clear viscous oil that solidified upon standing at 4 °C, was pure according to NMR analysis, and was used without further purification (n=7.1 calculated by ^{1}H NMR). Macromonomer **2** (n=13.1) was prepared by a similar procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55–1.66 (br, 29.7H), 3.39–3.56 (br, 29.7H), 4.48 (s, 2H), 5.22 (d, 1H, J=11.0 Hz), 5.80 (dd, 1H, J=17.6, 1.0 Hz), 6.75 (dd, 1H, J=17.6, 11.0 Hz), 7.32 (d, 2H, J=8.1 Hz), 7.45 (d, 2H, J=17.6, 8.1 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 27.2, 62.3, 70.7, 71.0–71.2, 72.8, 113.9, 126.9, 128.5, 137.5, 137.6, 139.8.

4.1.4. Synthesis of of 4-[4-(vinyl)phenoxy]butyliodide 3. A mixture of NaOH (0.40 g, 10 mmol) and 4-acetoxystyrene (0.91 ml, 5 mmol) in DMSO (15 ml) was stirred at 60 °C for 2 h. The mixture was cooled to room temperature and 1,4-diiodobutane (1.32 ml, 10 mmol) in DMSO (15 ml) was added gradually. After 30 min, water (100 ml) was added and the solution extracted with ethyl acetate (100 ml×3). Ethyl acetate layer was washed with dilute HCl, aqueous $NaHCO_3$, and brine. The organic ethyl acetate layer was dried over Na_2SO_4, and filtered. After evaporation of the solvent, the residue was washed with methanol to

extract the 1,4-bis[4-(vinyl)phenoxy)]butane. The extract was evaporated and separated by column chromatography on silica gel to provide the desired compound in 41% yield (solvent: hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.65 (dd, J=17.4, 11.0 Hz, 1H), 5.60 (dd, J=17.7, 1.0 Hz, 1H), 5.12 (dd, J=10.8, 1.1 Hz, 1H), 3.98 (t, J=6.0 Hz, 2H), 3.26 (t, J=6.6 Hz, 2H), 1.85–2.08 (m, 4H).

4.1.5. Synthesis of macromonomer 4. The monomer 4-[4-(vinyl)phenoxy]butyliodide **3** (1.86 g, 6.0 mmol) in THF (25 ml) was added in the solution of silver hexafluorophosphate (8.99 g, 30 mmol) in THF (250 ml) at −10 °C. After 1 h, NaOH (1.5 g, 38 mmol) in water (30 ml) was added in the reaction mixture. The generated solid material (AgI) was separated by filtration and evaporated to ca. 150 ml. Ethyl acetate (200 ml) was added to the reaction mixture, and ethyl acetate layer was washed with NH_4Cl, brine, and dried with $MgSO_4$. The organic layer was filtered and evaporated. The residue was separated by column chromatography on silica gel (hexane/EtOAc: 95:5 to THF) to obtain **4** in 81% yield. The polymerization degree of PTHF was n=17.0 determined by ^{1}H NMR. Macromonomer **4** (n=34.0) was prepared by a similar procedure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J=8.4 Hz, 2H), 6.84 (d, J=9.0 Hz, 2H), 6.65 (dd, J=17.7, 11.0 Hz, 1H), 5.60 (d, J=17.7 Hz, 1H), 5.11 (d, J=12.0 Hz, 1H), 3.98 (t, J=6.3 Hz, 2H), 3.64 (t, J=6.0 Hz, 2H), 3.50–3.49 (br), 1.73–1.86 (m, 2H), 1.56–1.70 (br).

4.1.6. Synthesis of macromonomer 6. 4-(5-Hydroxypentyl)styrene **5** was prepared using literature procedure.[16] A solution of **5** (490 mg, 2.79 mmol) in CH_2Cl_2 (10 ml) was added slowly to a solution of di-*tert*-butyl pyridine (0.80 g, 4.19 mmol) and trifluoromethanesulfonic anhydride (1.04 g, 3.69 mmol) at room temperature. The solution was stirred for 1 h and then cooled to −20 °C. THF (50 ml) was then added with strong stirring for 10 min. After the reaction, NaOH (3 g, 75 mmol) was added to the reaction mixture. The resulting solution was evaporated to 20% of the initial volume. Water (25 ml) was added to the solution, followed by three extractions with ethyl acetate. The combined organic phase was washed with brine (2×25 ml) and dried over $MgSO_4$. Evaporation of the solvent afforded the macromonomer **6** (1.87 g, 93.7% as a typical result) as a clear viscous oil. Small amounts of the solvent remained in the product and the material was used without further purification immediately for resin synthesis (n=6.9, as calculated by ^{1}H NMR and ESI). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.59 (d, 2H), 7.35 (d, 2H), 6.70 (dd, 1H), 5.15 (d, 1H), 3.39 (m, 30H), 1.58–1.60 (m, 30H).

4.1.7. Preparation of 8a,b, 9a,b by suspension polymerization. Suspension polymerization was carried out by slight modification of the reported method.[2] A solution of styrene (6.8 ml, 60 mmol), **2** (6.90 g, 10.3 mmol, n=7.1), and **7** (406 mg, 1.4 mmol) in DME (16.1 ml) was heated to 45 °C until a homogeneous solution was obtained. The initiator (benzoyl peroxide, 120 mg) was added to the organic solution and the solution was added by syringe to aqueous phase (142 ml prepared by reported method[2]) under N_2 at 45 °C. The temperature of the reaction mixture was raised to 85 °C and stirring was continued for 20 h. The suspension was filtered to recover the polymer beads and washed with hot water. The resin was washed with THF in a soxhlet extractor for 20 h. The recovered beads **8a** were washed with ether and hexane and dried under vacuum for 24 h. Yield 9.39 g (69%). Sieve separation: 100–200 mesh: 5.03 g, 40–100 mesh: 1.41 g, <40 mesh: 1.54 g. Resins **8b**, **9a**, and **9b** were prepared using a similar procedure. ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.0–27.0, 30.3, 40.3, 42.0–45.0, 62.6, 70.0–72.0, 125.0–134.0.

4.2. Preparation of 10 by suspension polymerization

Resin **10** was prepared using the same procedure as for resin **8**, but using a higher concentration of NaCl (10%) in water and divinyl benzene as the cross-linker to minimize problems of emulsion formation.

4.3. Measurement of swelling volume

Resins (100–200 mesh, 50 mg) were placed in a 1 ml syringe with filter and 0.8 ml of the desired solvent was added. The syringe was placed in a shaker for 1 h and the volume of the resin was measured.

4.4. Determination of the loading of 8a,b, 9a,b, and 10

The PTHF resin (100 mg), DIC (100 μL), DMAP (2 mg), and Fmoc-glycine (300 mg) in anhydrous CH_2Cl_2 (2 ml) was placed in screw-top vial, and shaken at room temperature for 1 h. The mixture was filtered and washed three times with CH_2Cl_2. The filtrate was returned to a screw-top vial and the reaction was carried out again. The mixture was washed three times each with CH_2Cl_2, THF, MeOH, Et_2O and hexanes. The produced resin was dried in vacuo overnight. Approximately 15 mg of each resin was added into 2 vials and 20% piperidine/DMF (3 ml) was added to the vial and shaked at room temperature for 1 h. A 100 μl aliquot of this solution was diluted to 3 ml with 20% piperidine/DMF and the UV adsorption at 290 nm measured.

4.5. Preparation of PTHF–grafted 5-hydroxypentyl *J*anda*J*el 13a–f

5-Hydroxypentyl *J*anda*J*el **11** (1.00 g, 1.07 mmol OH loading) was placed in a cylindrical reaction vessel, with sintered glass filter and a stopcock at one end and with a rubber-sealed screw-cap at the other end. The reaction vessel was charged with argon gas and sealed by closing the stopcock. The resin was swollen with anhydrous dichloromethane (20 ml). 2,5-Di-*tert*-butylpyridine (0.72 ml, 3.21 mmol) and trifluoromethanesulfonic anhydride (0.54 ml, 3.21 mmol) were added through syringe in sequence. The suspension was shaken for 15 min at room temperature. The solution containing excess reagents was drained through the sintered glass filter and the resin was dried by flowing argon gas. The resin was washed three times with anhydrous dichloromethane (10 ml) and dried by flowing argon gas for 5 min. THF (15 ml) was then added

into the reaction vessel via a syringe and the reaction vessel was shaken for 10–35 min at room temperature. Tetra-*n*-butylammonium hydroxide (40% in H_2O, 1 ml) was then added to terminate the living polymerization. After additional shaking for 1 h, the resulting resin was collected into a syringe equipped with polypropylene filter and washed several times with dichloromethane, Et_2O and *n*-hexane in sequence, and dried under reduced pressure to give a series of poly-THF-grafted *J*anda*J*el (**13a–f**).

4.6. Preparation of polyoxetane–grafted 5-hydroxypentyl *J*anda*J*el 14

The procedure is similar to the preparation of **13a–f**, except a 50/50 mixture of oxetane–dichloromethane (15 ml) was used instead of 15 mL of THF for grafting the activated complex.

4.6.1. Synthesis of 5-methyl-2-phenyl-2,4-dihydropyrazol-3-one 18.[22] TentaGel (0.32 mmol/g), and PTHF reins **8b** (0.35 mmol/g), **13b** (0.67 mmol/g), and **13e** (0.44 mmol/g)) were swollen in CH_2Cl_2 (12 ml) and treated with DIC (5 equiv), DMAP (1 equiv) and acetic acid (5 equiv). After shaking at room temperature for 3 h, these resins were filtered, and washed with CH_2Cl_2, MeOH and Et_2O and dried in vacuo. Under argon, 5 equiv of LiHMDS (1 M solution in THF, prepared from solid LiHMDS) was slowly added via syringe to a pre-cooled suspension at −78 °C of acetyl resin in THF, and stirred for 15 min at −78 °C. Acetyl chloride (5 equiv) was added dropwise, and the mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature. After 3 h, the resin was filtered, and washed with THF, CH_2Cl_2, MeOH and Et_2O, and dried in vacuo. These resulting resins were treated with phenylhydrazine (10 equiv) in THF (4 ml) and trimethyl orthoformate (4 ml) at 50 °C for 12 h, and filtered, and washed with THF, CH_2Cl_2, MeOH and Et_2O, and dried under vacuum. The desired product **18** was obtained by treating with 2% TFA/acetonitrile (7 ml) at room temperature for 30 min. The resulting filtrate was concentrated under reduced pressure, and purified by preparative TLC to give **18**; TentaGel (<1 mg, 1%), **8b** (15 mg, 48%), **13b** (27 mg, 47%), **13e** (16 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.37 (s, 2H), 7.13 (t, J=7.6 Hz, 1H), 7.35 (t, J=8.0 Hz, 2H), 7.81 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.0, 42.9, 43.0, 43.1, 118.7, 118.8, 125.0, 128.7, 137.9, 156.3, 170.4; FTIR (cm^{-1}): 3064, 2924, 2852, 1714, 1594, 1561, 1498; MS (ESI) m/z=175 $[M+H]^+$.

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