Novel Non-PEG Derived Polyethers as Solid Supports. 2. Solid-Phase Synthesis Studies

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Novel non-PEG derived polyether resins, coined SLURPS (Superior Liquid Uptake Resins for Polymer-supported Synthesis), were studied for their performance in solid-phase synthesis. Novel amino functional resins, SLURPS-NH_2, were prepared with a loading of up to 8.5 mmol/g and employed successfully in the solid-phase synthesis of Leu-Enkephalin. The peptide was obtained with the same purity when compared to its synthesis with commercial standard poly(dimethyl acrylamide) resins. Furthermore we show loading and cleavage of aromatic carboxylic acids in excellent yield. The advantageous solvent compatibility of our support was demonstrated through the biphasic dihydroxylation of alkenes with OsO_4 in *t*-BuOH/water mixtures producing bound 1,2-diols and synthesis and removal of a bound oxime using ethanol/water mixtures both in excellent yields. Reactions were easily monitored by gel-phase NMR and FTIR. These results show that SLURPS are very well suited for organic transformations using highly polar solvent mixtures and reagents and at much higher loading levels than standard amphiphilic resins of similar solvent compatibility.

Introduction

We recently reported on the synthesis, functionalization and swelling studies of novel, non-PEG derived polyethers as supports for solid-phase synthesis.[1] These novel supports were prepared via cationic polymerization of vinyl ethers as shown in Scheme 1. The use of vinyl ethers as monomers for polymer supports is attractive due to the fact that they combine side-chain functionality leading to high and controllable loading levels, as opposed to end-chain functionalized or telomeric amphiphilic ether scaffolds such as polyethylene glycol (PEG), without compromising solvent compatibility and chemical stability.[1] We demonstrated that the synthesis of cross-linked poly(vinyl ethers) based on 1,4-butanediol vinyl ether (BDVE, **1**) as a functional monomer resulted in a support reaching a maximum level of loading of 8.5 mmol/g. In addition, acetate **2**, required to incorporate **1** into a cross-linked polymer via the cationic copolymerization with cross-linker **3**, could be quantitatively copolymerized with the structural monomer methyl ether **4**. Thus loading levels can be controlled precisely by simple adjustment of monomer feed ratios. [1] Cross-linked polymers based on acetate **2** and methyl ether **4** exhibited excellent swelling performance across a wide range of solvents. In particular a gel derived from **4** with 2 mol % of **3** exhibited high degrees of swelling in all solvents studied, with the exception of water, with moderate variation of swelling levels among different solvents (swelling in alcohols, DMF, and MeCN was on the order of 7 mL/g). Moreover, this methyl ether gel, providing a model for the generic support structure (excluding linker or substrate contributions) exhibited good chemical stability when exposed to a wide range of common chemical reagents and conditions.[1] As seems de rigueur in this field we also developed an acronym for our supports, SLURPS (Superior Liquid Uptake Resins for Polymer-supported Synthesis), based on their exceptional response to solvent and solvent changes. The combination of outstanding swelling performance in a wide range of solvents with high chemical stability and tunable loading levels of up to 8.5 mmol/g sets these polymer gels apart from other polymer supports and in particular polyether resins currently investigated for combinatorial chemistry.

Deleuze and co-workers also reported on the synthesis of similar poly(vinyl ether) supports (Scheme 2).[2] Their data are consistent with our observations of chemical stability and unusually beneficial balance of levels of swelling in diverse solvents. As we see the potential of SLURPS to be developed into a "universal" support one crucial piece of information is the performance of these gels in solid-phase peptide synthesis, with another being the performance of the gel with organic transformations which have failed on other supports usually selected for solid-phase transformations such as ubiquitous variants of PS supports.[1] The hydrolysis of acetate groups on SLURPS-Ac, **5**, is already a case in point which

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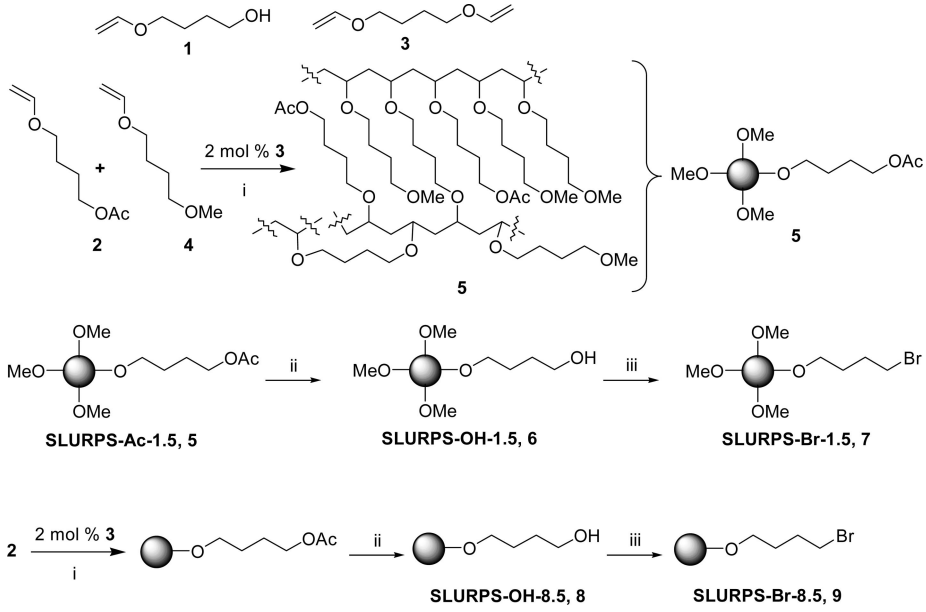
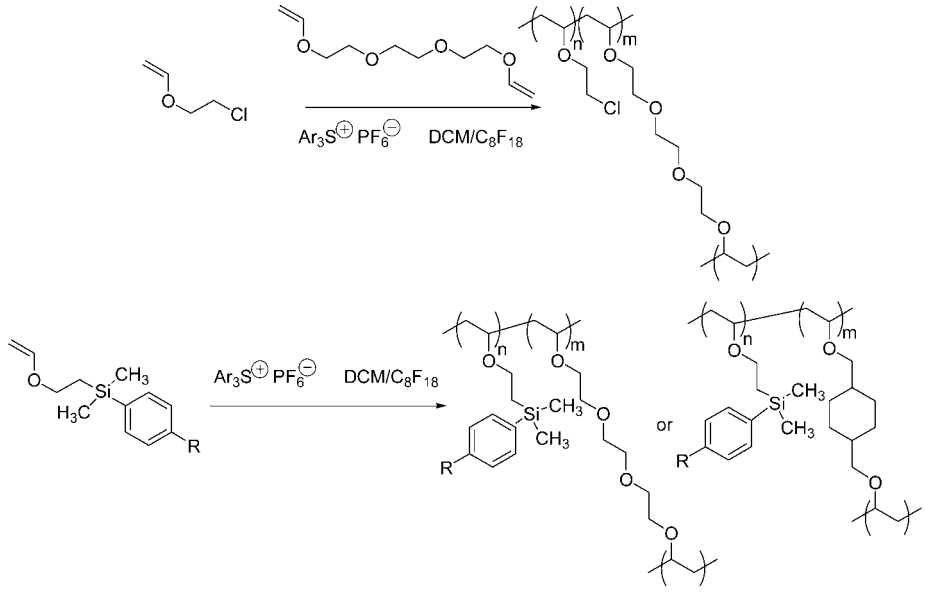
Scheme 1. Synthesis of SLURPS[1]: (i) catalytic BF_3–OEt_2, CH_2Cl_2, –78 to 0 °C, N_2, 3 h, 100%; (ii) 6 equiv KOH, methanol/H_2O, reflux, 24 h, 100%; (iii) PPh_3, Br_2, imidazole, DCM, 10 °C, overnight, 100%



Scheme 2. Poly(vinyl ether) supports for Birch reductions developed by Deleuze[2]



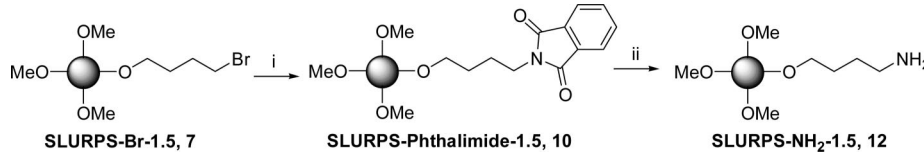
reaches completion to give alcohol **6** in ethanol/water mixture under which PS gel supports collapse and perform poorly.[3–13] As relevant transformations, we identified the dihydroxylation of alkenes using catalytic amounts of OsO_4 in the presence of stoichiometric oxidants,[14] a key transformation in natural product synthesis and aldoximes formation, a vital intermediate step in synthetic sequences leading to important heterocyclic cores.[15–19]

Results and Discussion

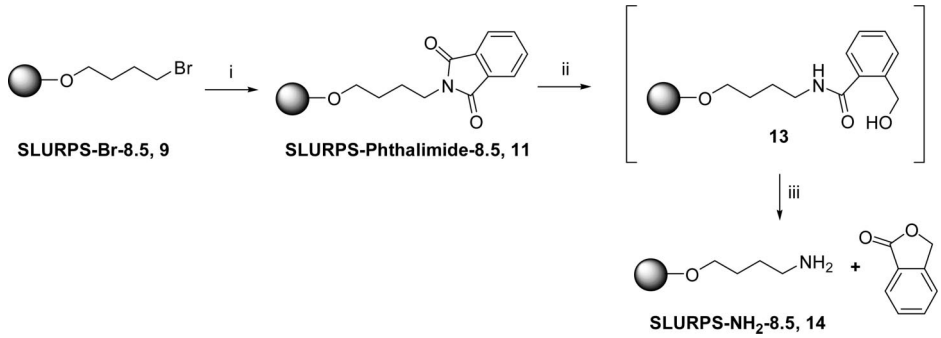
We set out to compare SLURPS under solid-phase peptide synthesis (SPPS) conditions with poly(dimethyl acrylamide) supports (PDMA or Sheppard's resin), an industry standard considered to be among the best supports for SPPS.[20–23] We will discuss the synthesis of the aminofunctional SLURPS first, followed by linker conjugation, as this has not been reported before, followed by our SPPS of Leu-enkephalin.

Functionalization of SLURPS Resins. SLURPS-Br-1.5, **7**, (1.5 mmol/g) was synthesized as reported earlier.[1] Following a similar route, copolymerization of acetate **5** with 2 mol % of cross-linker **3** and subsequent hydrolysis under basic conditions gave SLURPS-OH-8.5 (8.5 mmol/g), **8** with quantitative conversion.[1] Bromination of this resin with Br_2/PPh_3/imidazole in DCM produced SLURPS-Br-8.5, **9**, (5.5 mmol/g) with complete conversion of –OH to bromide groups.[1] Brominated resins, **7** and **9**, were both treated with excess potassium phthalimide in DMF at 80 °C to afford complete conversion to SLURPS-Phthalimide-1.5, **10**, and SLURPS-Phthalimide-8.5, **11** (Scheme 3) with quantitative conversion. SLURPS-Phthalimide-1.5, **10**, was deprotected using traditional hydrazinolysis to give SLURPS-NH_2-1.5, **12** (1.5 mmol/g). However, to explore alternative reaction conditions at the same time SLURPS-Phthalimide-8.5, **11**, was treated as reported by Osby et. al.[24] Reduction with

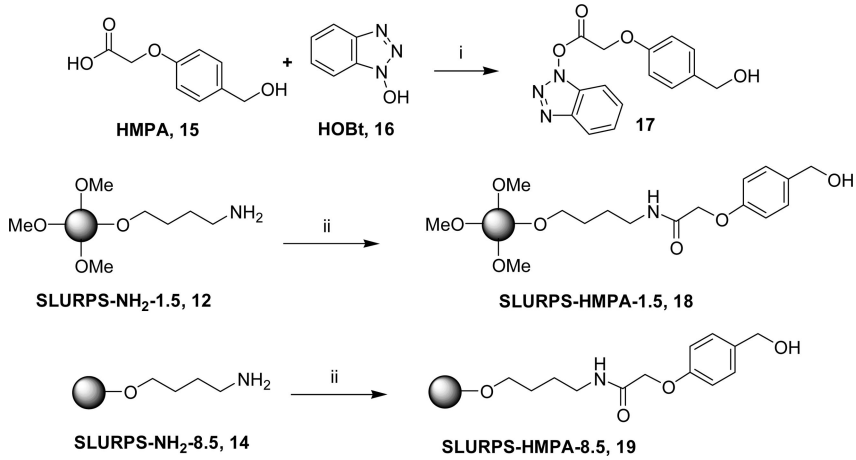
Scheme 3. (i) Potassium phthalimide, KI, DMF, 80 °C, overnight, 100%; (ii) NH_2NH_2-H_2O, ethanol, reflux, overnight, 100%



Scheme 4. (i) Potassium phthalimide, KI, DMF, 80 °C, overnight, 100 %; (ii) $NaBH_4$, 2-propanol, H_2O, r.t., 3 days, 100%; (iii) addition of AcOH, 80 °C, 2 h, 100%



Scheme 5. (i) DIPCDI, DMF, r.t., 5 min, 100%; (ii) **17**, DMF, r.t., 1 h, 100%

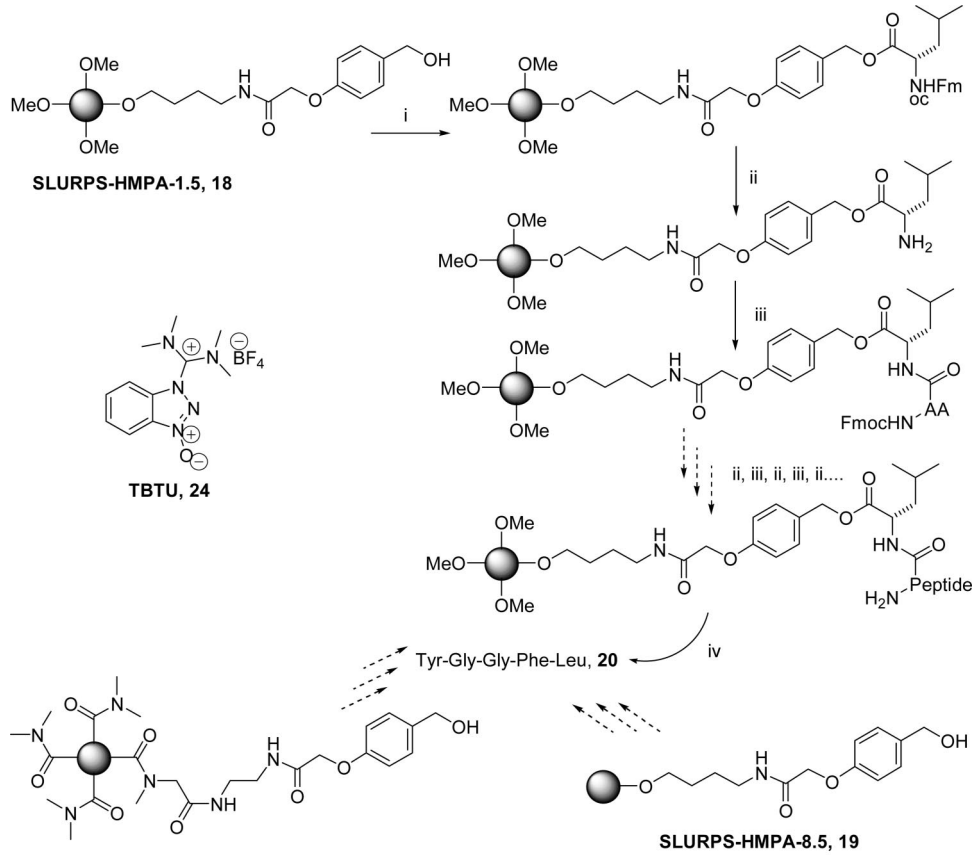


$NaBH_4$ gave amido-alcohol gel **13** followed by acid cleavage producing SLURPS-NH_2-8.5, **14** (8.6 mmol/g), as shown in Scheme 4. Phthalimide deprotection of **14** has the advantage of avoiding toxic hydrazine while still requiring the use of protic solvents, challenging the suitability of SLURPS in polar media.

Finally, we incorporated (4′-hydroxymethyl)-2-phenoxyacetic acid (HMPA, **15**) as linker into the SLURPS as it is employed routinely in SPPS and is also incorporated generally as amide into an amino support. We selected carbodiimide-mediated coupling in the presence of HOBt (*N*-hydroxybenzotriazole, **16**) to form an activated ester (**17**) in situ to synthesize SLURPS-HMPA-1.5, **18** (1.2 mmol/g), and SLURPS-HMPA-8.5, **19** (3.6 mmol/g) (Scheme 5). All reactions reached completion as monitored by FTIR and NMR (see below).

SPPS Using SLURPS Resins. To evaluate the suitability of SLURPS resins for SPPS we selected a pentapeptide (Leucine-Enkephalin, Leu-Enkephalin, Tyr-Gly-Gly-Phe-Leu or YGGFL, **20**) as synthetic target. Leu-Enkephalin has been extensively used to test the suitability of supports in SPPS, therefore providing a useful comparison with available data in the field.[25–29] Both SLURPS-HMPA-1.5 (**18**) and SLURPS-HMPA-8.5 (**19**) carrying the routine HMPA linker[30] were tested together with a standard SPPS PDMA resin also functionalized with an HMPA linker but with a lower loading level of 0.75 mmol/g (PDMA-HMPA-0.75, **21**). Apart from the PDMA resin belonging to the best performing supports in SPPS, our choice was also influenced by the availability of an already established and optimized SPPS method for PDMA support routinely carried out at Avecia Ltd., where these experiments were performed.[23] We followed the established Fmoc protocol in which C-terminal N-Fmoc-protected aminoacid is loaded as HMPA ester through a *N*,*N*′-diisopropylcarbodiimide (DIPCDI, **22**)-mediated coupling in the presence of catalytic DMAP (**23**) carried out twice.[23] Fmoc deprotection of the bound amino groups was induced with piperidine.[23] All subsequent N-Fmoc-protected aminoacids were incorporated by means of TBTU (**24**)-mediated couplings in the presence of DIPEA (**25**) followed by deprotection with piperidine, **26**. DMF was used as solvent throughout these transformations. Finally, the peptide was cleaved with neat TFA using phenol as a protecting group scavenger (Scheme 6). The synthesis was carried out manually using a methodology previously described by Wellings and Atherton.[23] Following this method, attachment

Scheme 6. Solid-phase peptide synthesis: (i) N-Fmoc-Leu, **22**, **23**, DMF, r.t., 1 h (twice), 100%; (ii) **26**, DMF, r.t., 10 min, 100%; (iii) N-Fmoc amino acid, **24**, **25**, r.t., 20 min., 100%; (iv) phenol, TFA, r.t., 90 min, 100%



of Fmoc-Leu to SLURPS-HMPA-1.5 (**18**) resulted in 0.8 mmol/g support (93% esterification, equivalent to 1 mmol/g based on deprotected Leu resin; measured by Fmoc cleavage and UV analysis of piperidine adduct). The higher loaded resin (**19**) treated similarly gave a Fmoc-Leu loaded resin of 1.5 mmol/g (90% esterification, equivalent to 2.2 mmol/g resin based on deprotected Leu.

Leu-Enkephalin was first synthesized on the PDMA-HMPA resin (**21**). The same method was then used for SLURPS-HMPA-1.5 (**18**) and in a move to exploit the high loading levels of SLURPS with SLURPS-HMPA-8.5 (**19**). After cleavage with TFA/phenol and removal of solvent the crude peptides were washed with diethyl ether and analyzed by HPLC (H_2O/MeCN gradient; reverse-phase HPLC). The identity of the samples was confirmed by coelution with a Leu-Enkephalin standard, MS (MALDI-Tof and FAB).

Figure 1 shows the HPLC traces corresponding to crude Leu-Enkephalin synthesized on PDMA-HMPA (**21**), SLURPS-HMPA-1.5 (**18**), and SLURPS-HMPA-8.5 (**19**), respectively. Leu-Enkephalin was successfully synthesized in high yields on all resins as confirmed by HPLC. Crude yields were in all cases above 85%. Our analysis focused on the purity of the peptide. Overall, the SLURPS resins (Figure 1b and c) performed as well as the PDMA resin (Figure 1a) in the synthesis of Leu-Enkephalin both in terms of yield and purity, a most promising result considering that SLURPS had not been optimized for this task.

The purity of crude Leu-Enkephalin synthesized on the PDMA-HMPA (**21**) resin was 95% (Figure 1a) with the major impurity being 2.6% of phenol (coelution with pure sample) The purity of the sample synthesized with SLURPS-HMPA-1.5 (**18**) was almost identical with 94.5% (Figure 1b) and in this case no major impurities were observed. At higher loading levels, using SLURPS-HMPA-8.5 (**19**), the purity of the crude Leu-Enkephalin decreased to 79% (Figure 1c). Major impurities, which were not characterized, were present at concentrations ranging from 1% to 6%.

Comparing our experimental results with those reported in the literature on different supports was not as straightforward as it may appear. Even if Leu-Enkephalin has been a widely used pentapeptide for resin and peptide chemistry development, most solid-phase synthesis of this compound had varied in some form from the method used by us: such as protecting groups (Boc instead of Fmoc chemistry)[27,29,31] or coupling methods (for example, the use of carbodiimides instead of TBTU).[25–33] A valid comparison in terms of synthetic methodology could be made with CPG as support, although a rigid material, showing a much poorer performance to yield Leu-Enkephalin in 35–70% purity (the purity improved when a flexible spacer arm is used) using the same synthetic chemistry.[5] Loading levels of CPG are extremely low (even as low as μmol/g) which should minimize peptide–peptide interactions detrimental to amino acid coupling efficiencies. However, even our ultrahigh SLURPS-HMPA-8.5 (**19**) performed better than the best report on CPG.[5]

Leu-Enkephalin was also synthesized as part of the development of highly cross-linked CLEAR resins.[6] The

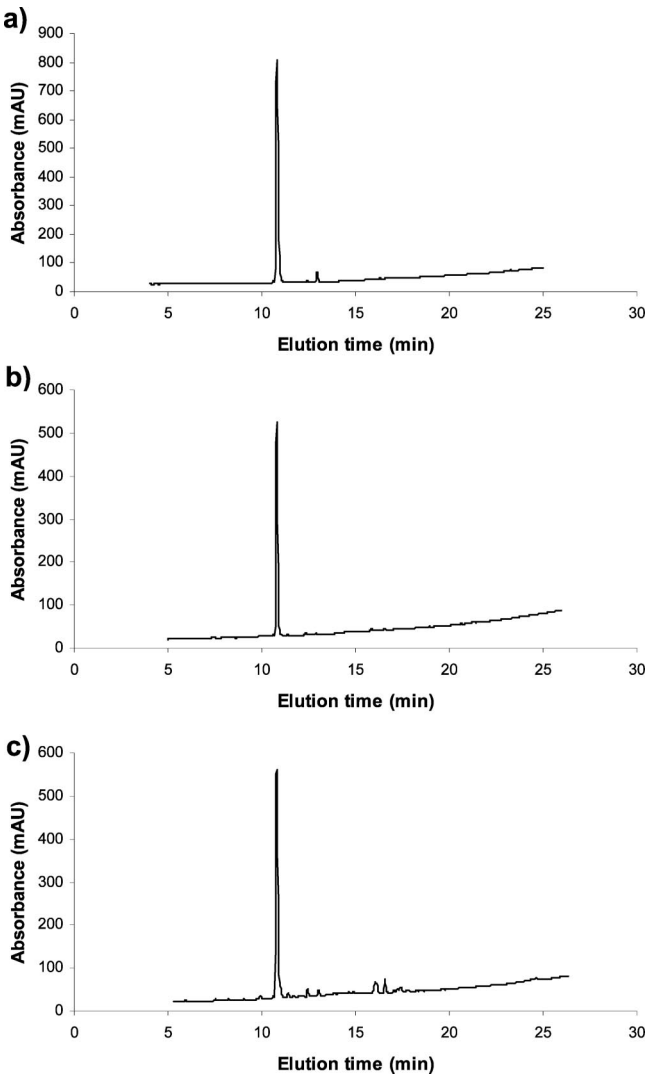
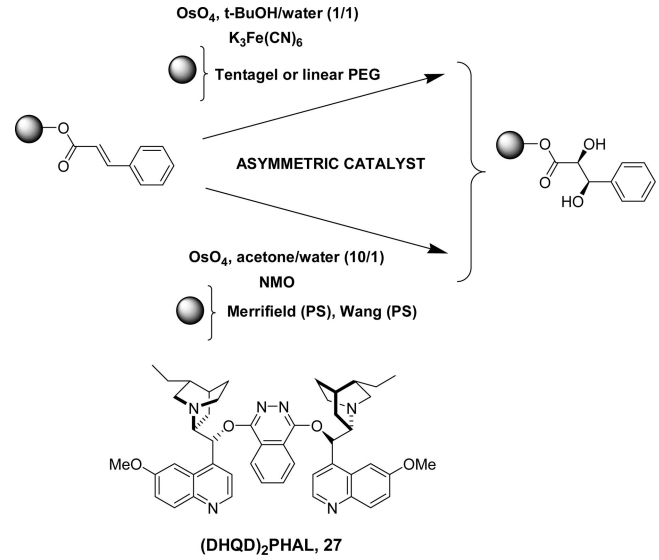


Figure 1. HPLC trace of crude Leu-Enkephalin (**20**): (a) synthesized on PDMA-HMPA (**21**); (b) synthesized on SLURPS-HMPA-1.5 (**18**); (c) synthesized on SLURPS-HMPA-8.5 (**19**).

purity of the peptide varied, depending on the type of CLEAR resin, from 86% to 99%. The purity of crude Leu-Enkephalin synthesized on Tentagel resins has been quoted as 90–94%. In both cases one can conclude that SLURPS-HMPA-1.5 (**18**) performed equally well despite its much higher loading level (Tentagel: 0.5 mmol/g and CLEAR: less than 0.30 mmol/g) Leu-Enkephalin has also been synthesized on PS supports but the synthetic methodology was too different from ours to allow a comparison to be made. Merrifield's model tetrapeptide (Leu-Ala-Gly-Val),[34] was synthesized on a 1,4-butanediol dimethylacrylate cross-linked PS following the same chemistry we carried out for the synthesis of Leu-Enkephalin.[7] The purity of the crude tetrapeptide was 91% as analyzed by HPLC and only 68% on a standard Merrifield resin.[7] These results cannot be compared directly but they provide an indication on how well the same chemistry has taken place. Even in its nonoptimized form SLURPS resin performed at the same level as dedicated SPPS supports, and, relatively speaking, better when one takes into account the higher loading levels employed.

Scheme 7. Studies by Janda on the solid-phase asymmetric dihydroxylation of alkenes on TentagelTM, linear PEG and PS[4]



Solid-Phase Organic Synthesis Using SLURPS Resins. Based on the fact that solid-phase organic synthesis (SPOS) has been dominated by two "universal" supports, PS-DVB and PEG-grafted PS (Tentagel and related matrices), with the former offering higher loadings and the latter offering wider solvent compatibility, our goal was to design a single resin combining both features as a further indication of the favorable performance characteristics established so far. The functionalization of SLURPS and subsequent SPPS carried out on them has demonstrated the suitability of poly(vinyl ethers) to produce supports with excellent control over loading levels and with loading levels as high as 8.5 mmol/g, thus improving performance over both Tentagel and PS loading features. Furthermore, swelling studies using poly(vinyl ether) model gels showed that they exhibited very good swelling over a wide range of solvents from lowly polar to highly polar and even protic solvents, but with the exception of water.[1] This suggests that SLURPS are better suited for more diverse sets of synthetic transformations in a wider range of solvents than is possible with PS supports. We needed, then, to demonstrate that these features could be translated to a substantial benefit, on actual chemical transformations. SLURPS can be used with protic solvents and solvent mixtures such as ethanol, ethanol/water, isopropanol, and isopropanol/acetic acid under which gel PS supports are known to collapse and perform poorly.[1,5,9,10,12,13,35] We identified additional synthetic transformations to contrast and compare with the synthetic utility of SLURPS. Dihydroxylation of alkenes was selected (cat. OsO_4 plus stoichiometric oxidants), which is usually performed in its asymmetric version to produce chiral diols (Sharpless dihydroxylation).[14] A key feature of this method is that homogeneous conditions (e.g., acetone/water using NMO as oxidant) lead to lower enantiomeric excess (ee) due to competing reaction pathways, whereas the use of heterogeneous conditions (notably *t*-BuOH/water and $K_3Fe(CN)_6$), results in a single mechanistic pathway leading to higher ees.

Table 1. Catalytic Dihydroxylation of SLURPS-VBA, **28**

entry	support	mol % OsO_4[a]	solvent mixture (vol. ratio)	external oxidant (mol %)[a]	yield of diol 31 (%)[b]	observations
1	SLURPS	1	acetone–water (1:1)	NMO (150)		no reaction occurred
2	SLURPS	1	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (300)	7	remainder starting material
3	SLURPS	10	acetone–water (1:1)	NMO (150)	65	remainder starting material
4	SLURPS	10	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (300)	100	
5	Merrifield[c]	1	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)		
6	Merrifield[c]	1	acetone–water (10:1)	NMO (150)	100	
7	PS-Wang[c]	1	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)		
8	PS-Wang[c]	1	acetone–water (10:1)	NMO (150)	100	
9	Tentagel[c]	1	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)	3	
10	Tentagel[c]	2	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)	63	
11	Tentagel[c]	10	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)	100	
12	linear PEG[c]	8	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)	80	
13	linear PEG[c]	10	*t*-BuOH–water (1:1)	$Ke_3Fe(CN)_6$ (600)	100	

[a] Relative to supported olefin. [b] Determined from ^{1}H-NMR spectra of the cleaved product. [c] Taken from Janda's work.[4]

The solid-phase dihydroxylation of alkenes has been investigated before.[4,7] In particular, Janda et al. have carried out the asymmetric dihydroxylation of bound cinammic acid on various polymer supports using $(DHQD)_2PHAL$ (**27**) as asymmetric catalyst (Scheme 7, Table 1).[4] They investigated the use of PS supports (Merrifield and Wang), Tentagel resin, and soluble linear PEG. They noted that the use of biphasic *t*-BuOH/water was only suitable for Tentagel and PEG supports since the PS supports were unable to swell well in the solvent mixture so that the reaction could not proceed at all on these supports.[4] Tentagel and PEG, on the other hand, required undesirably high quantities of OsO_4 to proceed to high conversions of diol (10 mol % relative to bound alkene instead of the typical 1 mol %) to overcome the sequestering effect of the chelating nature of PEG for osmium species.[4] PS-supported dihydroxylations only proceeded in acetone/water (10/1 v/v) and NMO (with expected lower ees) as *t*-BuOH/water and $K_3Fe(CN)_6$ failed as reagents.[4] The proportion of acetone required was very high and in our experience a higher water content is needed to dissolve NMO completely.

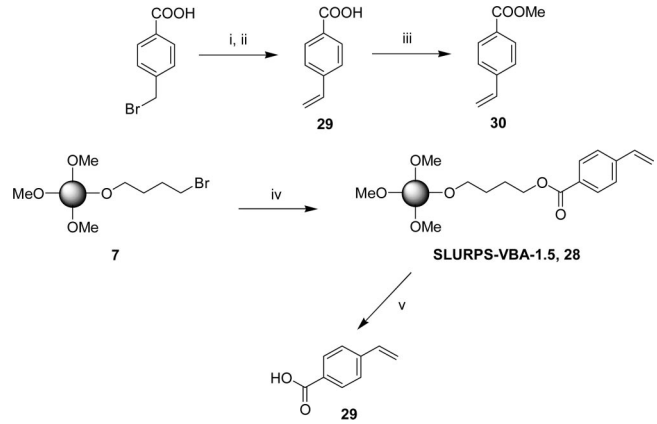
Tappe, Berkessel, et al.[7] also opted for PS-Wang and Tentagel resins though they had to resort to a 1:1 (v/v) mixture of water/THF as both *t*-BuOH/water and acetone/water mixed solvent systems failed with $K_3Fe(CN)_6$ as external oxidant. Yields varied from 8 to 96% percent with low ees depending on substrate (0–97%),[7] due to homogeneous reaction conditions.[7,14]

SLURPS resins could be advantageous here as their ability to chelate should be less and they show better swelling in mixed organic/aqueous solvents. As both Janda's and Tappe's work showed, the main problem associated with this solid-phase transformation in *t*-BuOH/water is low conversion and not low enantioselectivity, so we concentrated our efforts on the former.[4,7]

We decided to prepare a SLURPS-bound 4-vinyl benzoic ester **28**. Wittig chemistry led from 4-bromomethyl benzoic acid to 4-vinyl benzoic acid (**29**) in high yields (90%), which was converted to its methyl ester **30** as solution-phase equivalent of **28** via in situ formation of the corresponding acyl chloride and subsequent methanolysis. again in high yields (93%).

4-Vinyl benzoic acid **29** was conjugated to SLURPS-Br-1.5 (**7**) following a procedure by Janda et al. for Merrifield and macroporous PS supports via the Cs carboxylate

Scheme 8. (i) PPh_3, acetone, reflux, 45 min, 100%; (ii) CH_2O, H_2O, NaOH, r.t., 45 min, 90%; (iii) $SOCl_2$, methanol, reflux, 90 min, 93%; (iv) **32**, Cs_2CO_3, DMF, 50 °C, overnight, 100%; (v) K_2CO_3, methanol, reflux, 5 h, 90%

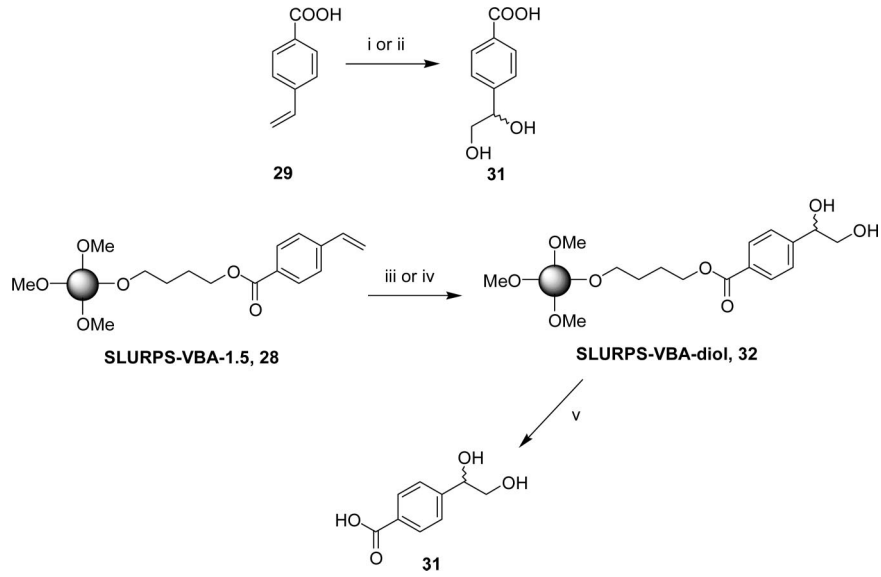


(Scheme 8).[36] They had noted that, though reactions were quantitative on Merrifield resin and the resin managed to swell well, macroporous supports reacted faster due to site accessibility being less affected by solvent effects.[36] The reaction on SLURPS-Br-1.5 proceeded smoothly to completion yielding SLURPS-VBA (**28**). Prior to dihydroxylation we performed a test hydrolytic cleavage on **28** using MeOH/K_2CO_3 as shown in Scheme 8 as Janda et al. [36] had reported that a similar resin cleavage, using NaOH/dioxane/H_2O, had not been successful on a PS support. Although we failed to obtain the sought corresponding methyl ester, we succeeded in recovering 4-vinyl benzoic acid in 90% yield.

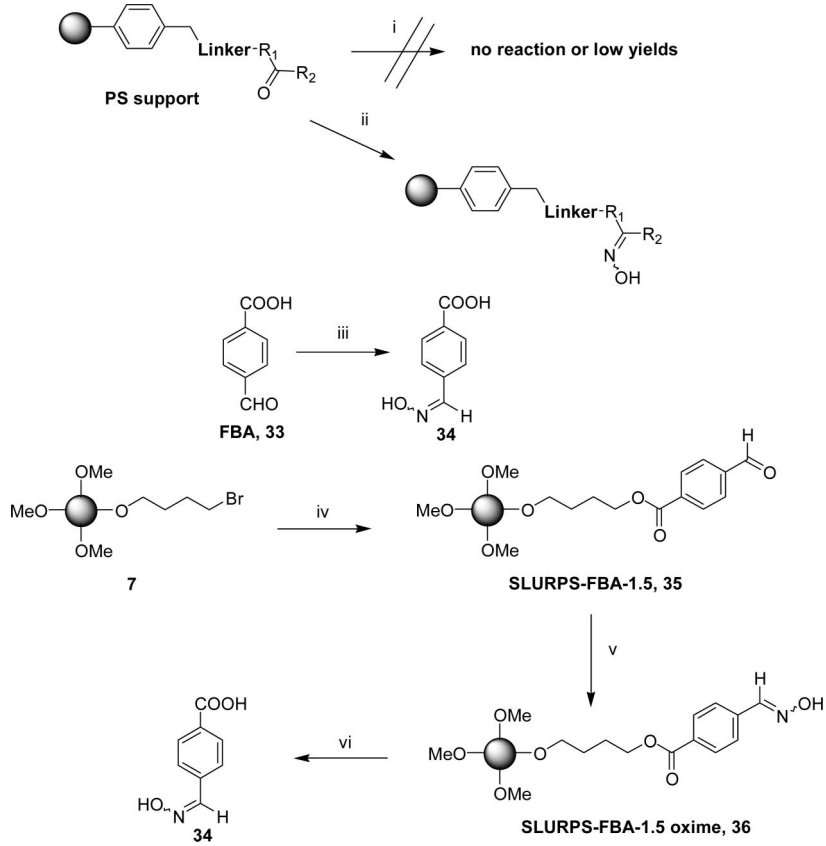
This was followed by the catalytic dihydroxylation of SLURPS-VBA using the before-mentioned heterogeneous reaction conditions, *t*-BuOH/water mixture and $K_3Fe(CN)_6$, and as an example for homogeneous conditions employed acetone/water (1:1, v/v) with NMO as stoichiometric oxidant. Although exhibiting intrinsically lower stereoselectivity than the heterogeneous system, our interest in the homogeneous system was that it would allow us to establish if SLURPS could perform at much higher water content than previously reported by Janda who had to resort to 10:1 (v/v) acetone/water mixtures for PS supports.[14]

After oxidation of **28** the products were cleaved as shown in Scheme 9 and the crude products were analyzed by ^{1}H-NMR to determine reaction yields and to compare them to the standards obtained by solution-phase chemistry (diols **32**

Scheme 9. (i) OsO_4, NMO, acetone/H_2O (1/1), r.t., 5 h, 90%; (ii) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1/1), r.t., 24 h, 100%; (iii) OsO_4, NMO, acetone/H_2O (1/1), r.t., overnight, see Table 1; (iv) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1/1), r.t., 24 h, see Table 1; (v) K_2CO_3, methanol, reflux, 5 h, 90%



Scheme 10. (i) $(H_3N^+–OH)Cl^–$, NaOAc, H_2O/ethanol (3/1), heat; (ii) $(H_3N^+–OH)Cl^–$, Py, heat; (iii) $(H_3N^+–OH)Cl^–$, NaOAc, ethanol/H_2O (3/1), reflux, 6 h, 100%; (iv) **39**, Cs_2CO_3, DMF, 50 °C, overnight, 100%; (v) $(H_3N^+–OH)Cl^–$, NaOAc, ethanol/H_2O (3/1), r.t., 3 h, 100%; (vi) K_2CO_3, methanol, reflux, 5 h, 90%



and **31**). The results are summarized in Table 1 with added literature data for benchmarking.[4]

For SLURPS, the use of 1 mol % OsO_4 (Table 1, entries 1 and 2) resulted in negligible conversion for the homogeneous-NMO system (Table 1, entry 1) and very little diol **31** in the case of the heterogeneous $K_3Fe(CN)_6$ method (Table 1, entry 2). This was similar to Janda's results using Tentagel supports which had required larger molar ratios of OsO_4.[4] We repeated the reaction with 10 mol % of OsO_4 (see Table 1, entries 3 and 4) and observed complete conversion with $K_3Fe(CN)_6$ but only 65% of diol **31** with NMO. Despite the undesirably large amounts of OsO_4 these are still among the best results (for the given conditions) showing that SLURPS are well suited as a potential high loading support for solid-phase dihydroxylation reactions, with the proviso that sequestration of the catalyst still takes

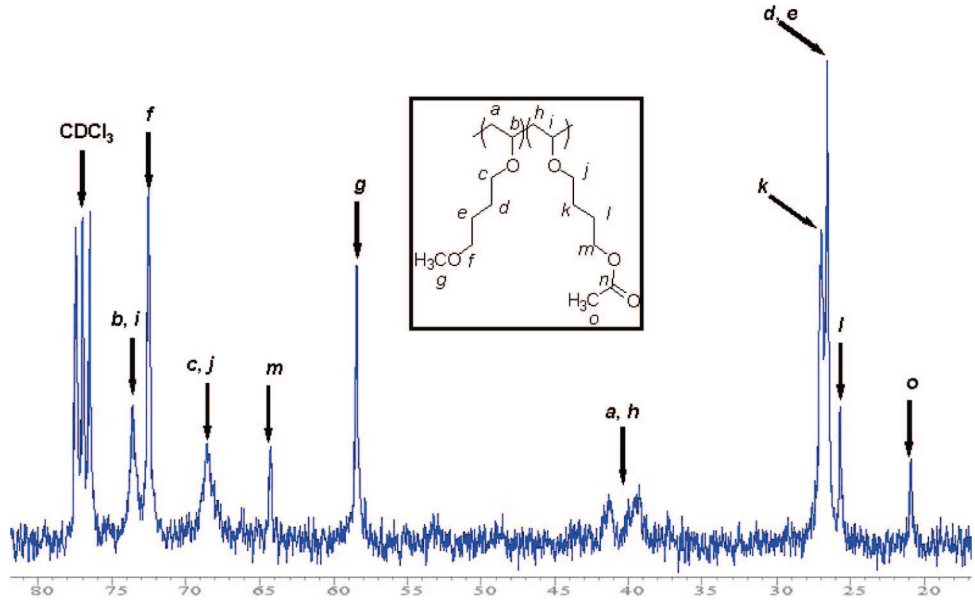


Figure 2. Gel-phase ^{13}C-NMR spectrum of SLURPS-Ac (**5**).

place. Further work will evaluate asymmetric dihydroxylation processes.[4,7,14]

Looking at the pattern of results of these experiments one cannot help but muse that the properties of SLURPS are in some form the consequence of being kind of isomeric to Tentagel-like supports; both because of structural similarities as well as performance features in SPOS.[4] However, the increased loading levels with respect to PEG-grafted PS resins set SLURPS apart from these established supports and presents a clear and intrinsic advantage that these commercially available matrices will never achieve. When compared to PS supports with comparable loading levels, SLURPS outperform them, exhibiting suitability to be employed in reaction conditions with a high water content leading to asymmetric natural product synthesis under which PS resins have shown to perform poorly.[4]

In the SPS of oximes, our interest lay in the fact that they are key intermediates for the synthesis of heterocycles, such as isoxazolines.[16,17,19,37,38] Their solution-phase synthesis is straightforward and typically requires a carbonyl compound and hydroxylamine hydrochloride in a mixture of ethanol/water and sodium acetate. The polar solvent conditions are challenging and provide another instructive test scenario for SLURPS. We have found in earlier work that in the synthesis of oximes on PS supports for the SPOS of isoxazolines via 1–3 dipolar cycloadditions, pyridine had to be used instead of ethanol/water mixtures due to the low swelling and concomitant low efficiency of oxime formation (Scheme 10).[39]

4-Formyl-benzoic acid (FBA, **33**) was chosen as carbonyl component to synthesize the corresponding aldoxime (**34**) as the additional carboxyl group could be linked to SLURPS-1.5-Br in a similar manner as already demonstrated for SLURPS-VBA, **28**. The synthesis of **34** proceeded quantitatively in a water/ethanol mixture (1:3 v/v) with hydroxylamine hydrochloride and sodium acetate. For the solid-phase transformation 4-formyl-benzoic acid was attached to SLURPS-1.5-Br, **7**, via in situ formation of its Cs salt. We observed complete conversion to the SLURPS-bound ester-aldehyde, SLURPS-FBA (**35**) as monitored by gel-phase ^{13}C-NMR and FTIR (Scheme 10).

SLURPS-FBA (**35**) was treated under the same conditions as 4-formyl benzoic acid (**33**) to form SLURPS-bound oxime **36**. Cleavage of **36** upon treatment with methanol/K_2CO_3 under reflux afforded 4-formyl benzoic acid oxime, **34**, in 90% yield corresponding to the calculated loading levels.

These examples of SPPS and SPOS with SLURPS clearly indicate their potential as high-loading support, with finely adjustable loading levels, for challenging transformations in particular in situations where good compatibility with polar and protic solvents is prescribed by established solution phase procedures. With little or no effort we were able to translate solution conditions to the solid phase. Further improvements are possible and needed if SLURPS are to be developed into genuinely "universal" solid-phase support, which is the focus of our ongoing investigations.

Suitability of SLURPS for On-Resin Spectroscopic Analysis. In the course of our experiments we found that SLURPS are very well suited for on-resin analysis of bound products using standard NMR and FTIR equipment and experiments, without the need to resort to expensive or not easily available techniques such as solid-state NMR, MAS–NMR or single-bead FTIR.

For NMR experiments we only had to swell the dry resin, placed in a NMR tube, with an appropriate deuterated solvent (usually $CDCl_3$) and use routine NMR experimental settings. For FTIR we swelled the resin with an "IR-transparent" solvent (again usually $CHCl_3$) and pressed the sample between NaCl plates before recording the FTIR spectra. In comparison to similarly functionalized PS resins spectra resolution was always better for the equivalent SLURPS.

As the corresponding ^{1}H-NMR spectrum only showed broad resonances of no analytical use, (in fact this seems to be a general feature of ^{1}H-NMR spectra of SLURPS regardless of functionalization) the first example of a SLURPS NMR is a gel-phase ^{13}C-spectrum of **5** (Figure 2) The spectrum exhibits sharp peaks which allows the complete and unambiguous characterization of **5**. Similarly clearly resolved resonances

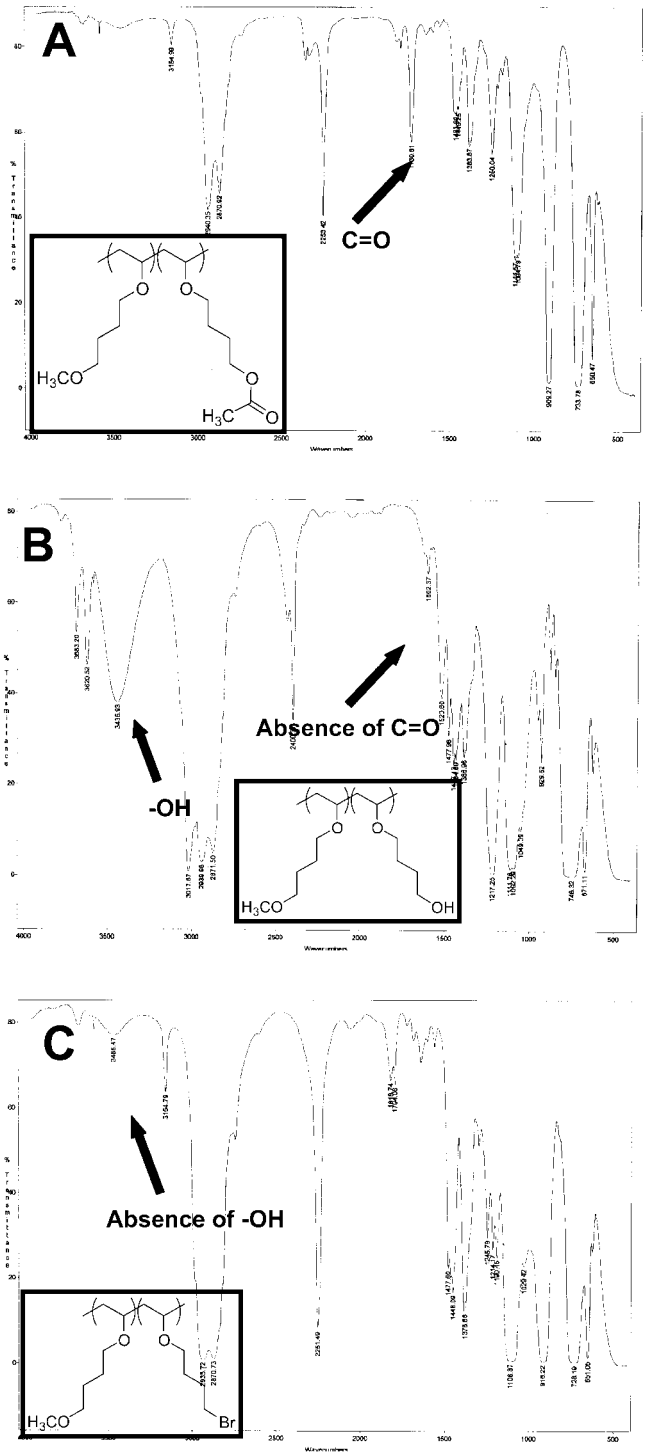


Figure 3. Gel-phase FTIR spectra: (A) SLURPS-Ac (**5**); (B) SLURPS-OH (**6**); (C) SLURPS-Br (**7**).

were observed for the whole series of SLURPS discussed here. ^{13}C NMR in conjunction with "gel-phase" FTIR (Figure 3) provided us with a strong tool for reaction monitoring further supported by spectroscopic information collected from cleaved products. In comparison, spectra of similar Merrifield resins were of no analytical value as the ^{1}H NMR was almost entirely dominated by broad resonances of the polymer backbone and although polymer backbone resonances were generally less broad in the corresponding ^{13}C spectra, linker and substrate resonances were still obscured by it (not shown).

Other examples illustrating the suitability of SLURPS for gel-phase ^{13}C-NMR monitoring are shown below in Figures 4–7 (SLURPS-OH-1.5, **6**, SLURPS-Br-1.5, **7**, SLURPS-Phthalimide-1.5, **10** ,and SLURPS-VBA-1.5, **28**).

An instructive set of examples for the utility of FTIR for SLURPS characterization is the sequence SLURPS-Ac (**5**) to SLURPS-OH (**6**) followed by bromination yielding SLURPS-Br (**7**) as shown in Figure 3. Linking an ester group to SLURPS-Br (**7**) to produce SLURPS-VBA (**28**) was equally revealing (Figure 8).

Critically, the IR transparency in the carbonyl region of SLURPS was also noticeable when comparing FTIR spectra corresponding to SLURPS-HMPA (**18**) to PDMA-HMPA (**21**) (Figures 9 and 10). These spectra were recorded on standard FTIR instrumentation fitted with a ZnSe microfocus beam condenser to improve the resolution of dry resin samples (routine monitoring at Avecia Ltd. for SPOS and SPPS). Surprisingly, the spectrum of SLURPS-HMPA-1.5 **18** shown in Figure 9 is by no means better resolved than those we had obtained with swollen gels pressed between NaCl plates (Figures 3 and 8). FTIR analysis of SLURPS therefore does not require sophisticated instrumentation to improve spectral resolution (compare Figures 3, 8, 9, and 10).

A final illustration of the utility of IR transparency of SLURPS is the coupling reaction of HMPA to SLURPS-NH_2 (repeated once) to ensure complete conversion of all amino groups (Scheme 5; Avecia Ltd., in-house recipe). The conditions used were those optimized for the PDMA solid support apparently producing only amide and no ester linkages. FTIR analysis of the SLURPS product **18**, showed the expected O–H stretch (3429 cm^{-1}) and amide bond (NHC=O; 1679 cm^{-1}). In addition, however, another strong band in the ester carbonyl stretch region was present (1756 cm^{-1}) (Figure 9) which was also found for SLURPS-NH_2-8.5, **19** (3307, 1753, 1650 cm^{-1}). We can only account for the "extra" carbonyl peak in the ester region through formation of oligomeric HMPA (Figure 9), which has been hitherto undetected. This would not have been detectable in a PDMA resin preparation due to the presence of overlapping amide bonds in the polymer backbone. Oligomer formation was also indicated through a 36% weight excess in the thoroughly dried resin assuming 100% conversion of all amine groups, and cleavage of **18** with TFA for 1.5 h removed all ester carbonyl signals but retained the amide functionality of the HMPA linker (1666 cm^{-1}). This leaves the question whether or not HMPA oligomer formation is taking place on PDMA supports and to what extent; what is clear is that the "IR-transparency" of SLURPS offers advantages in linker development and reaction monitoring.

Conclusions

We have successfully expanded the diverse functionalization of SLURPS from our original disclosure to include SLURPS-Br-8.5 (**9**, 5.5 mmol/g), amino supports SLURPS-NH_2 (**12** and **14**), and HMPA supports (SLURPS-HMPA, **18** and **19**). These novel functional supports include ultra-high-loading SLURPS-NH_2-8.5 (**14**, 8.6 mmol/g) and high-loading SLURPS-HMPA-8.5 (**19**, 3.6 mmol/g), which were employed successfully in the synthesis of a pentapeptide with

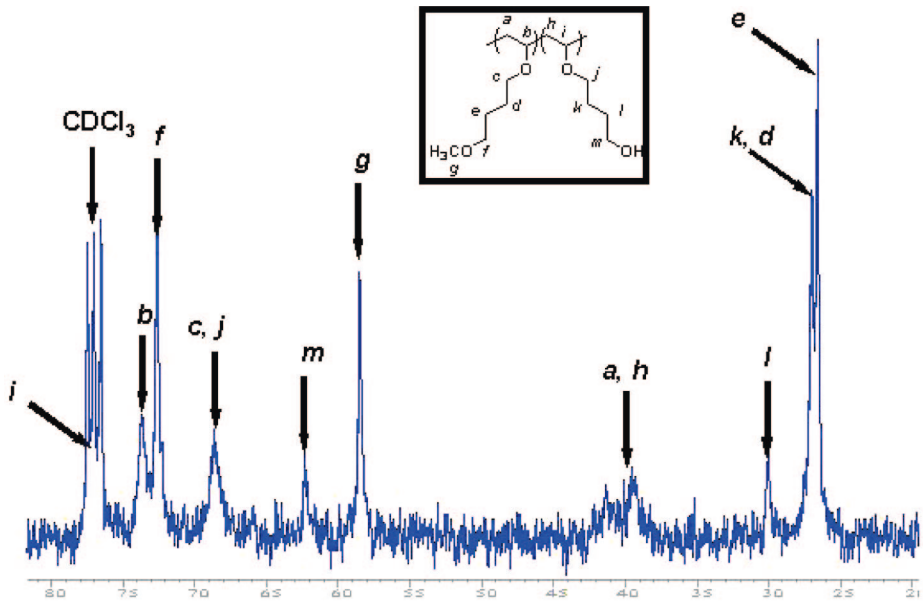


Figure 4. Gel-phase ^{13}C-NMR spectrum of SLURPS-OH (**6**).

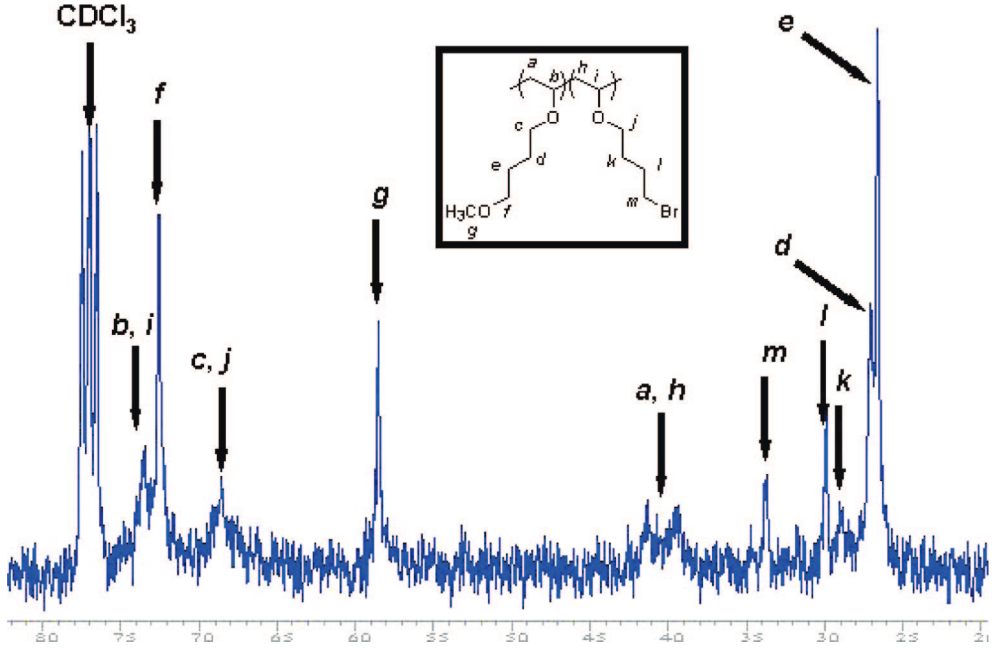


Figure 5. Gel-phase ^{13}C-NMR spectrum of SLURPS-Br (**7**).

results comparable to Sheppard's resin, PDMA-HMPA, even when the ultrahigh-loading resin **19** was used.

SLURPS gave excellent results in the heterogeneous dihydroxylation of alkenes, rivalling the performance of Tentagel supports, and with the advantage of higher loading levels (3–4 times). Compared to PS supports, reaction on SLURPS also gave higher yields under conditions in which Merrifield and related resins have been reported to fail.

Finally, SLURPS are superbly suited for on-resin monitoring using simple gel-phase NMR and FTIR techniques without the need to resort to more expensive or sophisticated instrumentation usually required for solid-phase synthesis.

Experimental Section

General. All manipulations of air- and moisture-sensitive compounds were performed under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker AC250 (250 MHz ^{1}H, 62.5 MHz ^{13}C), a Jeol GSX270 AC250 (270 MHz ^{1}H, 67.5 MHz ^{13}C), or a Bruker (400 MHz ^{1}H, 100 MHz ^{13}C) instrument. Chemical shifts were quoted as δ in ppm relative to the appropriate reference. Reference compounds for NMR and their chemical shifts were $CDCl_3$ (^{1}H 7.26 ppm), CD_3OD (^{1}H 3.35 ppm), and CD_3COCD_3 (^{1}H 2.03 ppm). NMR solvents were obtained commercially from Aldrich. Gel-phase FTIR spectra were obtained on a Perkin Elmer 1710 series FTIR using NaCl plates or on a Perkin Elmer 1605 series FTIR with a ZnSe microfocus beam condenser (Specac Ltd.) accessory. For the Perkin Elmer 1605 series FTIR machine, samples were analyzed using a Diasqueeze Plus diamond compression cell (Specac Ltd.).

For HPLC analysis dry peptides were dissolved in MeCN/H_2O (50/50% v/v) (1 mg/mL). Analytical HPLC (AKTA

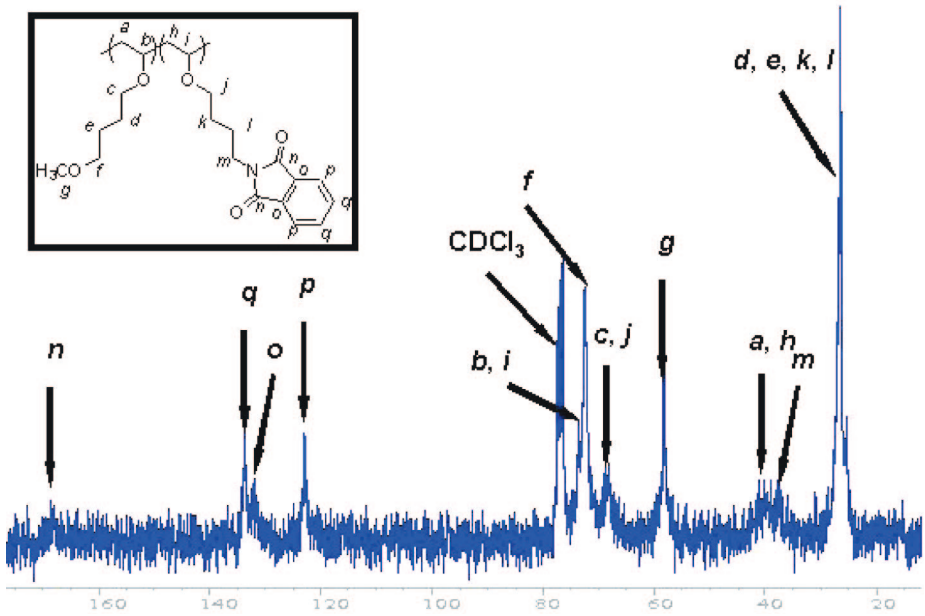


Figure 6. Gel-phase ^{13}C-NMR spectrum of SLURPS-Phthalimide-1.5 (**10**).

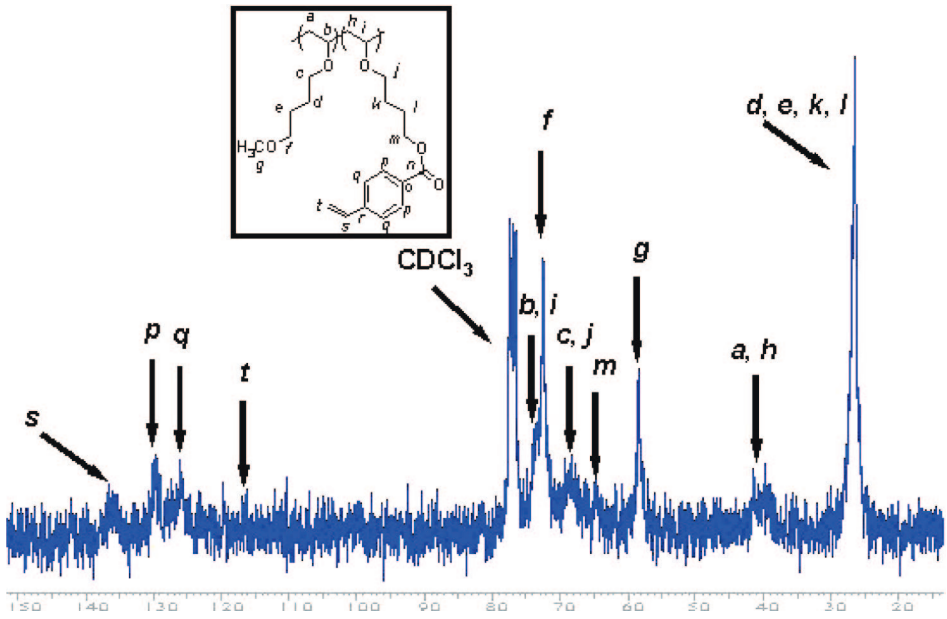


Figure 7. Gel-phase ^{13}C-NMR spectrum of SLURPS-VBA (**28**).

Explorer, Pharmacia Biotech) was monitored at 230 nm, using a Vydac 218TP54, C18 column (250 × 4.6 mm, 5 μm, 300 Å). Gradient = 10–90% B in A gradient over 30 min at 1.5 mL/min, where A = 0.1% TFA/water and B = 0.1% TFA/acetonitrile. Injection = 20 μL. Software used = Unicorn v 3.00.10 (APBiotech).

Reagents were obtained commercially from Aldrich, Avocado, or Acros at their highest purity available and used as received unless stated otherwise. Solution-phase organic reactions were monitored by TLC (Merck TLC aluminum sheets, Silica 60 F_{254}).

Synthesis of Supports and Synthesis of Bromo Resins 7 and 9.[1] The synthesis of compounds **2** and **4**–**9** has been published in detail elsewhere.[1]

General Procedure for Cationic Polymerization.[1] In a dried 50-mL round-bottomed flask under nitrogen at −78 °C, dried CH_2Cl_2 (10 mL), an appropriate monomer (68.60 mmol total), and cross-linker **3** (1.40 mmol, 2 mol %) were added. BF_3-OEt_2 (0.05 mL, 57 mg, 0.40 mmol) was added, and the mixture was allowed to warm slowly standing under nitrogen until gelation occurred. Afterward, the mixture was allowed to stand for 2 h, slowly warming. Then chilled NH_3 (0.50 mL, 35% in H_2O, 0.88 g/mL) in MeOH (4 mL) was added. The mixture was allowed to warm to room temperature, more MeOH (30 mL) was added, and then the gel was filtered and washed several times with dichloromethane, tetrahydrofuran, ethanol, acetone, ethyl acetate, and diethyl ether (3 × 30 mL each). The gel was smashed to small particles (0.1 – 0.5 mm) while swollen.

The final gel was dried under vacuum at room temperature until constant weight was reached. In all cases, the final product was an off-white sticky solid that adhered to glass and plastics but not to metals. In all cases, when swollen, the gel was very easy to handle and filter. Conversion: 100%

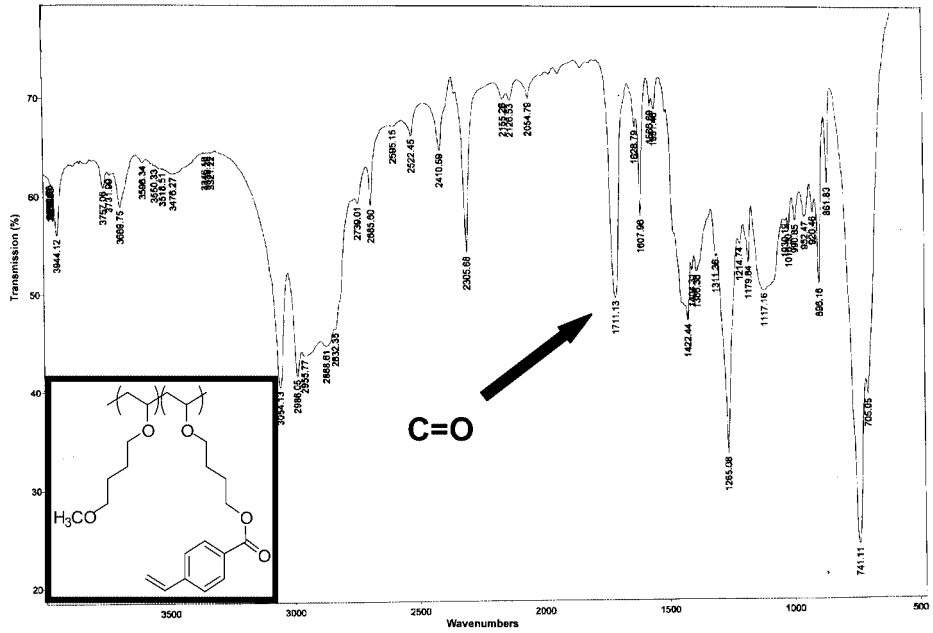


Figure 8. Gel-phase FTIR spectrum of SLURPS-VBA (**28**).

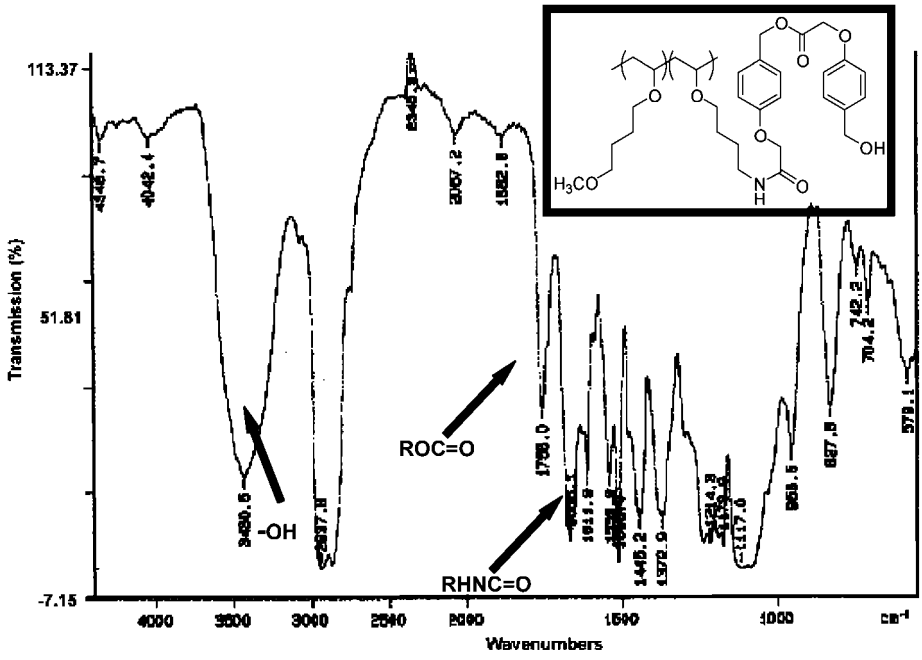


Figure 9. FTIR spectrum of SLURPS-HMPA (**18**) recorded using a beam condenser.

of starting material converted to polymeric structures as monitored by NMR and GC analysis of the crude filtrate.[1]

To synthesize resin **5**, monomer **4** (7.108 g, 55.00 mmol) and **2** (2.215 g, 14.00 mmol) were copolymerized cationically with **3** (200 mg, 1.40 mmol) as cross-linker. The procedure above was followed.

Resin **5**. Conversion: 100%. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 4.02 (broad shoulder, 0.15 H); 3.29 (broad s, 0.69 H); 2.00 (broad shoulder, 0.35 H); 1.56 (broad s, 0.44 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 170.0; 73.7; 72.6; 68.7; 64.4; 58.6; 41.5; 39.5; 27.1; 26.7; 25.7; 21.0. FTIR: νmax (cm^{-1}) 1730 (C=O), 1111 (C–O).[1]

Copolymerization of monomer **2** (68.60 mmol) with cross-linker **3** (1.40 mmol, 2 mol %) following the method described above produced an acetate resin in 100 % conversion. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 4.07 (broad s); 3.51 (broad s); 2.04 (broad s); 1.67 (broad s). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 171.1; 73.8; 68.3; 64.3; 40.4; 26.9; 25.8; 21.0.[1]

General Procedure for the Hydrolysis of Acetate Resins.[1] The corresponding gel (8.0 g) was swollen with a mixture of EtOH/H_2O (70/30 vol %, 20 mL/g resin), and the mixture was refluxed for 24 h in the presence of KOH (6.0 equiv/acetate group). Afterward, the mixture was cooled to room temperature, and the gel was filtered and washed with EtOH/ H_2O (66/34 vol %, 150 mL each) until the pH of the filtrates was neutral. Then the gel was washed with EtOH (3 × 100 mL), THF (3 × 100 mL), and Et_2O (3 ×

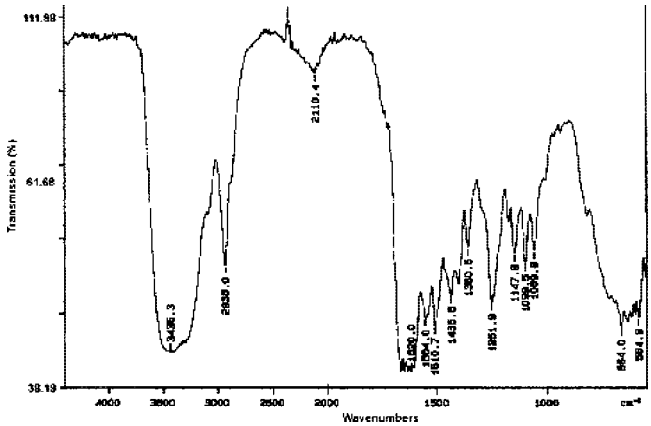


Figure 10. FTIR spectrum of PDMA-HMPA (**21**) recorded using a beam condenser.

100 mL), and the gel was dried under vacuum at room temperature until constant weight was reached.

Resin **6**. Yield: 100%. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.34 (broad s, 0.74 H); 2.62 (broad, 0.60 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ(ppm): 73.8; 72.7; 68.8; 62.5; 58.6; 39.6; 30.1; 27.1; 26.7; 25.7. FTIR: νmax (cm^{-1}) 3437 (broad, O–H), 1111 (C–O).[1]

Resin **8**. Yield: 100%. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.98 (shoulder); 3.35 (broad s); 1.40 (broad s). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 78.7–78.0; 74.0–67.0; 62.1, 41.5–39.0; 29.8; 27.3.

General Procedure for the Bromination of Alcohol Resins. SLURPS-OH-1.5 (**6**) (2.0 g, 3.3 mmol) was suspended in DCM (60 mL) and treated with triphenylphosphine (4.0 g, 15 mmol) and imidazole (1.0 g, 15 mmol). After the reagents were dissolved, the suspension was cooled to 10 °C in a water bath and treated dropwise with Br_2 (0.80 mL, 2.4 g, 15 mmol). The reaction was left stirring overnight at room temperature. The resin was filtered and washed with DMF, H_2O, DMF, acetone, THF, and DCM (3 × 60 mL each) and then dried under vacuum at room temperature until constant weight was reached. Conversion 100%. Yield of SLURPS-Br-1.5 (**7**): 2.3 g (>95%). ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 3.33 (broad s, 0.65 H); 1.60 (broad, 0.62 H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 73.8; 72.7; 69.0–67.8; 58.6; 41.5–39.5; 33.9; 30.0; 29.1; 27.1; 26.7. FTIR: νmax (cm^{-1}) 1092 (C–O); 665 (C–Br). Elemental microanalysis: 12.0 (0.2% Br (1.50 (0.02 Br/g resin).[1]

Synthesis of SLURPS-Phthalimide Resins (General Procedure). Dry SLURPS-Br (1.5 mmol based on Br), was swollen in DMF (30 mL per g of resin) and potassium phthalimide (8.4 g, 45 mmol) was added followed by KI (0.48 g, 2.4 mmol). The mixture was heated to 80 °C and stirred gently at this temperature for 24 h under N_2 atmosphere. Finally, the resin was filtered and washed consecutively with DMF (3 × 10 mL per gram of resin), ethanol (3 × 10 mL per gram of resin), DMF (3 × 10 mL per gram of resin), ethanol (3 × 10 mL per gram of resin), THF (3 × 10 mL per gram of resin), and diethyl ether (3 × 10 mL per gram of resin), and then dried under vacuum to constant weight.

SLURPS-Phthalimide-1.5, 10. 99% Yield. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 7.70 (broad s); 3.26 (broad s); 1.54 (broad). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 168.7; 133.7; 132.2; 123.1; 73.7; 72.5; 68.9; 58.4; 40.3; 39.1; 37.6; 26.7. FTIR: ν_{max} (cm^{-1}): 1773 and 1711 (O=CNC=O); 1114 (C–O–C).

SLURPS-Phthalimide-8.5, 11. 99% Yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.46 (broad s); 3.30 (broad s); 1.30 (broad). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 168.1; 133.7; 132.1; 123.0; 37.8; 27.6; 25.6. FTIR: ν_{max} (cm^{-1}): 1771 and 1701 (O=CNC=O); 1120 (C–O–C).

Synthesis of SLURPS-NH_2-1.5, 12. Dry SLURPS-Phtalimide-1.5 resin, **10** (10.0 g, 1.36 mmol), was swollen in ethanol (250 mL) and hydrazine monohydrate was added (2.2 mL, 45 mmol). The mixture was refluxed overnight and then cooled to room temperature. Finally, the resin was filtered and washed consecutively with ethanol (3 × 100 mL), THF (3 × 100 mL), ethanol (3 × 100 mL), THF (3 × 100 mL), and diethyl ether (3 × 100 mL), and dried under vacuum to constant weight. Yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 3.28 (broad s); 1.56 (broad). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 72.8; 58.6; 26.7. FTIR: ν_{max} (cm^{-1}): 3400–3500 (stretch N–H); 1650 (N–H bending), 1120 (C–O–C).

Synthesis of SLURPS-NH_2-8.5, 14. SLURPS-Phtalimide-8.5, **11**, (2.0 g, 8.1 mmol) was stirred for 3 days at room temperature in a mixture of $NaBH_4$ (1.53 g, 40.5 mmol), 2-propanol (73 mL), and water (13 mL). Acetic acid (8.5 mL) was added carefully (evolution of gas was observed) and when the foaming stopped the mixture was heated at 80 °C for 2 h. The resin was washed consecutively with ethanol (3 × 40 mL), ethanol–ammonia (3 × 40 mL, 5% NH_3 v/v), ethanol (3 × 40 mL), THF (3 × 40 mL), and diethyl ether (3 × 40 mL), and dried overnight under vacuum at 40 °C. FTIRν_{max} (cm^{-1}): 3266 (N–H stretch), 1650 (N–H bending), 1085 (broad, C–O–C).

Synthesis of SLURPS-HMPA and PDMA-HMPA Resins (General Procedure). The reaction was carried out as described elsewhere by Wellings and Atherton.[23] Dry SLURPS-NH_2, (8.3 mmol) was placed in a 200 mL sintered funnel. The resin was washed with DMF (30 mL) three times, allowing the resin to swell. A mixture of HMPA (3.80 g, 24.9 mmol), HOBt (3.20 g, 23.3 mmol), and DIPCDI (2.70 g, 3.40 mL, 21.0 mmol) was prepared by dissolving all components in DMF (18 mL), and then left standing for 3–5 min before it was added to the filtered resin. The mixture was left standing for 1 h. Ninhydrin (Kaiser) test of a small sample of resin resulted negative at this stage.[23] Finally, the resin was washed consecutively with DMF (10 × 30 mL) and diethyl ether (10 × 30 mL) and dried overnight at 40 °C under vacuum.

SLURPS-HMPA-1.5, 18. FTIR: ν_{max} (cm^{-1}): 3429 (O–H), 1756 (O–C=O), 1679 (NH–C=O), 1117 (C–O–C).

SLURPS-HMPA-8.5, 19. FTIR: ν_{max} (cm^{-1}): 3307 (O–H), 1753 (O–C=O), 1650 (NH–C=O), 1073 (broad C–O–C).

Cleavage of oligo-HMPA Esters from SLURPS-HMPA (General Procedure). Dry SLURPS-HMPA-1.5 resin, **18**, was mixed with TFA (25 mL per g of resin). The mixture was left standing for 1.5 h. Finally, the resin was filtered under vacuum and washed consecutively with DMF (10 ×

20 mL) and diethyl ether (10 × 20 mL) and dried under vacuum overnight at 40 °C.

Cleaved SLURPS-HMPA-1.5, 18. FTIR: ν_{max} (cm^{-1}): 3430 (O–H), 1666 (NH–C=O), 1137 (broad C–O–C).

Solid-Phase Synthesis of Peptides (Leu-Enkephalin) (General Procedure). We followed a procedure described elsewhere by Atherton and Wellings.[23] (Exact quantities given below). The resin was washed with DMF (3 × 30 mL). For the first coupling the Fmoc-protected aminoacid and DMAP were dissolved in DMF (15 mL). DIPCDI was added and the mixture was poured onto the resin. A stream of N_2 was bubbled through the mixture, which was left standing at room temperature with occasional swirling for 1 h.[23] The resin was washed with DMF (3 × 20 mL). The procedure was repeated and the resin was washed with DMF (10 × 20 mL). The resin was treated with piperidine solution (20% v/v in DMF, 20 mL) for 3 min, filtered, and treated again with piperidine solution (20% v/v in DMF, 20 mL) for 7 min. The resin was washed with DMF (10 × 20 mL) and a qualitative test for $–NH_2$ groups was carried out on a small sample of resin (5–8 mg) (usually Kaiser test, but also TNBS; see below).

For subsequent aminoacids the resin was treated for 20 min with a preformed mixture of Fmoc-protected aminoacid, TBTU, and DIPEA (see exact quantities below). The Kaiser test (or TNBS) was performed on a small sample of resin (5–8 mg). If the test resulted positive the coupling was repeated. The resin was washed with DMF (10 × 20 mL) and treated with piperidine solution (20% in DMF, 20 mL) for 3 min, filtered, and treated again with piperidine solution (20% in DMF, 20 mL) for 7 min. The resin was washed with DMF (10 × 20 mL).

Finally, the resin was washed with diethyl ether (7 × 20 mL) and dried overnight under vacuum at 40 °C. The peptide was cleaved from the resin by treating the resin for 90 min with a solution of TFA and phenol (97.5/2.5%, v/w), 25 mL per g of resin. The resin was filtered and washed with TFA (3 × 10 mL). The combined TFA filtrates were evaporated to yield an oil which was triturated by treatment with diethyl ether. The solids were further washed with diethyl ether (3 × 10 mL) and dried under vacuum overnight at 40 °C.

Kaiser Test.[23] The following three solutions were prepared: (a) ninhydrin (5 g) in ethanol (100 mL); (b) liquefied phenol (80 g) in ethanol (20 mL), and (c) aqueous solution of potassium cyanide 0.001 M (2 mL) in pyridine (98 mL). Prewashed resin beads were shrunk with diethyl ether and treated with 3 drops of each of the previous solutions. The mixture was homogenized and heated to 100 °C for 4 min. A positive test was indicated by deep blue resin beads (the supernatant was also deep blue).

TNBS Test.[23] Prewashed resin beads (DMF) were placed in a small sample tube and DMF was added (2 mL). A droplet of DIPEA was added followed by a droplet of 2,4,6-trinitrobenzenesulphonic acid (TNBS). The suspension was left for 10 min at room temperature. The supernatant turned orange upon addition of the reagents. A positive test was indicated by red beads.

Reaction Scale. For the synthesis on PDMA the following quantities were used: PDMA-HMPA resin 0.75 mmol/g (2.0 g, 1.5 mmol). First aminoacid attachment: Fmoc-Leu-OH (1.59 g), DIPCDI (0.94 mL), and DMAP (20 mg). (This coupling was performed twice). Subsequent aminoacids: Fmoc-Phe-OH (1.45 g), Fmoc-Gly OH (1.12 g), Fmoc-Gly OH (1.12 g), and Fmoc-Tyr(^{t}But)-OH (1.72 g). TBTU (1.13 g each time) and DIPEA (0.77 mL each time).

Leu-Enkephalin synthesized on PDMA-HMPA resin: MS (MALDI Tof), m/z: 556.13 (M^+), 557.14 ($M + 1^+$), 578.17 ($M + Na^+$), 579.12 ($M + 1 + Na^+$), 594.10 ($M + K^+$), 595.11 ($M + 1 + K^+$). MS (FAB) m/z (%): 556 (98, $M + 1^+$), 578 (18, $M + Na^+$), 594 (12, $M + K^+$).

For the synthesis on SLURPS-HMPA-1.5 the following quantities were used: SLURPS-HMPA-1.5 (1.36 mmol/g) (1.2 g, 1.6 mmol). Firest aminoacid attachment: Fmoc-Leu-OH (1.73 g), DIPCDI (1.02 mL), and DMAP (20 mg). (This coupling was performed twice). Subsequent aminoacids: Fmoc-Phe-OH (1.58 g), Fmoc-Gly OH (1.21 g), Fmoc-Gly OH (1.21 g), and Fmoc-Tyr(^{t}But)-OH (1.88 g). TBTU (1.23 g each time) and DIPEA (0.84 mL each time).

Leu-Enkephalin synthesized on SLURPS-HMPA-8.5 resin: MS (MALDI Tof), m/z: 556.13 (M^+), 557.11 ($M + 1^+$), 578.14 ($M + Na^+$), 579.13 ($M + 1 + Na^+$), 594.13 ($M + K^+$), 595.10 ($M + 1 + K^+$). MS (FAB) m/z (%): 556 (100, $M + 1^+$), 578 (20, $M + Na^+$), 594 (18, $M + K^+$).

For the synthesis on SLURPS-HMPA-8.5 the following quantities were used: SLURPS-HMPA-8.5 (4.0 mmol/g) (0.50 g, 2.0 mmol). First aminoacid attachment: Fmoc-Leu-OH (2.12 g), DIPCDI (1.25 mL), and DMAP (25 mg). (This coupling was performed twice). Subsequent aminoacids: Fmoc-Phe-OH (1.94 g), Fmoc-Gly OH (1.49 g), Fmoc-Gly OH (1.49 g), and Fmoc-Tyr(^{t}But)-OH (2.30 g). TBTU (1.51 g each time) and DIPEA (1.03 mL each time).

Leu-Enkephalin synthesized on SLURPS-HMPA-8.5 resin: MS (MALDI Tof), m/z: 556.20 (M^+), 557.21 ($M + 1^+$), 578.22 ($M + Na^+$), 579.22 ($M + 1 + Na^+$), 594.17 ($M + K^+$), 595.19 ($M + 1 + K^+$). MS (FAB) m/z (%): 556 (10, $M + 1^+$), 578 (90, $M + Na^+$), 594 (20, $M + K^+$).

Synthesis of SLURPS-VBA-1.5, 28. Dry SLURPS-Br-1.5, **7** (0.50 g, 0.75 mmol), 4-vinylbenzoic acid (0.300 g, 2.00 mmol), and Cs_2CO_3 (0.500 g, 1.50 mmol) were mixed with dry DMF (10 mL) under N_2 and the mixture was warmed to 50 °C and gently stirred overnight. The reaction mixture was cooled to room temperature, the resin was filtered off and consecutively washed with water (3 × 30 mL), DMF (3 × 30 mL), water (3 × 30 mL), ethanol (3 × 30 mL), methanol (3 × 30 mL), THF (3 × 30 mL), DCM (3 × 30 mL), and diethyl ether (3 × 30 mL), and finally dried under vacuum to constant weight. Conversion: 100%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.00; 5.72 (shoulder); 3.07 (broad s); 1.34 (broad). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 136.0; 129.7; 126.5; 116.5; 73.4; 72.5; 68.4; 64.8; 58.4; 41.4; 39.6; 26.4. FTIR: ν_{max} (cm^{-1}): 1711 (C=O), 1608 (C=C), 1265 (C–O ester), 1117 (C–O–C).

Cleavage of SLURPS-VBA-1.5, 28 (General Procedure for Ester Cleavage). Dry SLURPS-VBA, **28** (0.50 g, 0.68 mmol) was swollen in methanol (15 mL) and K_2CO_3 (310 mg, 2.25 mmol) was added. The mixture was heated to reflux under N_2 for 5 h. The mixture was cooled to room temperature and the resin was filtered under suction and

washed consecutively with methanol (2 × 30 mL) and THF (3 × 30 mL). The combined filtrates were evaporated and the remaining residue was dissolved in brine (50 mL) and treated with excess 10% HCl (7 mL). Finally, the aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were washed with brine (5 × 50 mL), dried over $MgSO_4$, and evaporated. The residue (90 mg, 90% yield) was spectroscopically and chromatographically identical to 4-vinyl benzoic acid, **29**. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 12.00 (very broad s); 8.07 (d, J = 8.4 Hz, 2H); 7.49 (d, J = 8.2 Hz, 2H); 6.76 (dd, J = 17.6 Hz, J = 10.9 Hz, 1H); 5.89 (d, J = 17.6 Hz, 1H); 5.41 (d, J = 10.9 Hz, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 172.2; 142.9; 136.0; 130.6; 128.4; 126.3; 117.1. FTIR: ν_{max} (cm^{-1}): 1678 (C=O).

Solid-Phase Dihydroxylation Procedure Using Acetone/Water and NMO (General Procedure). Dry SLURPS-VBA, **28** (0.30 g, 0.41 mmol), was swollen in acetone/water (10 mL, 1/1 v/v), and OsO_4 2.5% in *t*-BuOH was added (see Table 1 for quantities). Then, NMO (0.10 g, 0.90 mmol) was added and the mixture was gently stirred overnight under N_2. The resin was filtered under suction and washed consecutively with acetone/water (1/1 v/v, 3 × 30 mL), acetone (3 × 30 mL), ethanol (3 × 30 mL), THF (3 × 30 mL), and diethyl ether (3 × 30 mL), and finally dried under vacuum to constant weight. The cleavage step was carried out as described above for the synthesis of **29** and the residue was analyzed. The products were spectroscopically (NMR) and chromatographically (TLC) identical to 4-vinyl benzoic acid, **29**, and its corresponding diol, **31**. The first run (1 mol % OsO_4) yielded nontransformed 4-vinyl benzoic acid. The second approach (10 mol % OsO_4) yielded a mixture of racemic diol **31** and alkene **29** (13:7 molar ratio, isolated in 90% yield) (see Table 1). Diol, **31**. ^{1}H NMR (270 MHz, $CDCl_3$), δ (ppm): 7.92 (d, J = 8.4 Hz, 2H); 7.34 (d, J = 8.4 Hz, 2H); 4.78 (dd, J = 8.2 Hz, J = 3.2 Hz, 1H); 3.69 (dd, J = 11.4 Hz, J = 3.2 Hz, 1H); 3.57 (dd, J = 11.4 Hz, J = 8.2 Hz, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$), δ (ppm): 167.1; 145.8; 129.8; 129.6; 126.1; 74.4; 67.8. FTIR: ν_{max} (cm^{-1}): 3414 (broad, O–H); 1680 (C=O).

Solid-Phase Dihydroxylation Procedure Using t-BuOH/Water and $K_3Fe(CN)_6$ (General Procedure). Dry SLURPS-VBA, **28** (0.30 g, 0.41 mmol) was swollen in *t*-BuOH/water (1/1 v/v, 10 mL), and OsO_4 2.5% in *t*-BuOH was added (see Table 1 for quantities). $K_3Fe(CN)_6$ (450 mg, 1.35 mmol) and K_2CO_3 (200 mg, 1.35 mmol) were added and the mixture was gently stirred overnight under N_2. The resin was filtered and washed consecutively with methanol/water (1/1, 3 × 30 mL), methanol (3 × 30 mL), ethanol (3 × 30 mL), THF (3 × 30 mL), and diethyl ether (3 × 30 mL), and finally dried under vacuum to constant weight.

SLURPS-VBA-diol, 31. FTIR: ν_{max} (cm^{-1}): 3410 (broad, O–H); 1712 (C=O ester). The product was cleaved as described above for the synthesis of **29** and the residue was analyzed. The products were spectroscopically (NMR) and chromatographically (TLC) identical to 4-vinyl benzoic acid, and its corresponding diol, **31**. The first run (1 mol % OsO_4) yielded 7% of diol, **31**, and 85% unreacted 4-vinyl benzoic acid, **29**. The second approach (10 mol % OsO_4) produced full conversion to diol, **31** (see Table 1) which was isolated in 90% yield after cleavage from the resin.

Synthesis of SLURPS-FBA-1.5, 35. Dry SLURPS-Br-1.5, **7** (1.0 g, 1.5 mmol), 4-formylbenzoic acid, **33** (680 mg, 4.50 mmol), and Cs_2CO_3 (980 mg, 3.00 mmol) were mixed with anhydrous DMF (15 mL) under N_2 and the mixture was warmed to 50 °C. The suspension was gently stirred at 50 °C overnight. The reaction mixture was cooled to room temperature and the resin was filtered under suction. The collected resin was washed consecutively with water (3 × 30 mL), DMF (3 × 30 mL), water (3 × 30 mL), ethanol (3 × 30 mL), methanol (3 × 30 mL), THF (3 × 30 mL), DCM (3 × 30 mL), and diethyl ether (3 × 30 mL), and dried under vacuum to constant weight. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 10.10; 8.14; 3.30 (broad s); 1.58 (broad). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 191.3; 130.0; 72.5; 68.3; 65.3; 58.3; 40.9; 26.5. FTIR: ν_{max} (cm^{-1}): 1711 (doublet, C=O, ester and aldehyde).

Synthesis of SLURPS-FBA-oxime-1.5, 36 and cleavage to product 34. Dry SLURPS-FBA, **35**, (0.50 g, 0.68 mmol) was swollen in ethanol (15 mL). Hydroxylamine hydrochloride (150 mg, 2.10 mmol) and sodium acetate (170 mg, 2.10 mmol) were dissolved in water (5 mL) and added to the swollen resin. The mixture was gently stirred at room temperature for 3 h before it was filtered. Finally, the resin was washed consecutively with ethanol/water (3/1 v/v, 3 × 20 mL), ethanol (3 × 30 mL), THF (3 × 30 mL), and diethyl ether (3 × 30 mL), and finally dried under vacuum to constant weight. (Full conversion to oxime as monitored by FTIR).

The resin was treated with K_2CO_3/methanol as described above for the synthesis of **29**. The final residue (100 mg, 90%) was spectroscopically (NMR) and chromatographically (TLC) identical to 4-formyl benzoic acid oxime, **34**.

SLURPS-FBA-oxime, 36. FTIR: ν_{max} (cm^{-1}): 3300 (broad, O–H), 1711 (C=O, ester, clean band free from shoulder observed in **35**).

Oxime 34. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 11.46 (broad s, 1.5H); 8.01 (s, 1H); 7.76 (d, J = 8.0 Hz, 2H); 7.49 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 167.1; 147.6; 137.2; 131.2; 129.8; 126.5. MS (EI) m/z (%): 165 (22, $[M]^+$), 148 (7, $[M - OH]^+$).

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