

Synthesis and utilization of functionalized polystyrene resins

Gemma L. Thomas,^a Christine Böhner,^a Mark Ladlow^b and David R. Spring^{a,*}

^a*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK*

^b*GSK Cambridge Technology Centre, University of Cambridge, Lensfield Road, Cambridge, UK*

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Abstract—Co-polymerised 4-bromopolystyrene has been converted to a range of polymer-supported reagents and scavengers by bromine–magnesium exchange using Oshima’s trialkylmagnesium complex followed by quenching with a variety of electrophiles. Mitsunobu, halogenation and Wittig reactions, were explored to assess the utility of the resins for target oriented and diversity oriented synthesis.
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1. Introduction

The use of solid-supported reagents and scavengers have become increasingly popular in organic chemistry as their use bypasses the purification difficulties associated with traditional solution-phase reactions whilst retaining the beneficial aspects, such as ease of reaction monitoring (TLC, LC–S, NMR, etc.). Solid-supported reagents also enable the use of excess reagents to drive the reaction to completion, without complicating the work up procedure. Simple filtration, washing and solvent removal is all that is required to work up the reactions, which is particularly beneficial to high throughput synthesis.¹ Attaching toxic or hazardous compounds to a solid support reduces the risks associated with the reagent. Simple filtration of solid-supported catalysts also means that the catalyst can be recovered, regenerated and reused, reducing the cost associated with these reagents. The simple work up techniques associated with polymer-supported reagents and scavengers also make the use of automation a real possibility. Robots can carry out all the manipulations required and large libraries can be generated quickly and efficiently.

Perhaps the most important insoluble support for organic synthesis is cross-linked polystyrene. Derivatized polystyrene can be made either by *co*-polymerisation of styrene, divinylbenzene² and functionalized styrene, or in a more divergent fashion by functionalizing a polystyrene starting material. The functionalization of polystyrene has been

achieved by two methods with relatively small diameter (<75 µm) polystyrene beads: (1) by direct lithiation of the polystyrene³ and (2) by halogen–metal exchange.⁴ These procedures are not applicable nor optimized for relatively large diameter (>150 µm) cross-linked polystyrene functionalization.

Beads with diameters greater than 150 µm possess optimal handling properties. Larger diameter resins (>150 µm) are free flowing, greatly reducing the problem of static often associated with smaller diameter resins, which makes these smaller resins more difficult to manipulate. The rate of filtration of the larger diameter beads is faster, with none of the polymer support passing through the filter. This is often a problem with the smaller diameter beads requiring the reaction mixture to be re-filtered. Although smaller diameter beads often have increased chemical reaction rates, this needs to be balanced by the improved handling and increased functionality per bead associated with larger beads.

In this paper we report on the development of a cost effective method of derivatizing 4-bromopolystyrene, in one step, to generate a range of functionalized resins. Moreover, this methodology can be used on small and large diameter (up to at least 600 µm) beads of polystyrene. These reagents can be used as polymer-supported reagents, scavengers or supports for target oriented and diversity oriented synthesis.

Triphenylphosphine polystyrene (**1**) is one of the most successful polymer-supported reagents developed, as it avoids the need for troublesome purification to remove triphenylphosphine oxide. Triphenylphosphine is used in a wide range of reactions, including Mitsunobu,⁵ halogenation⁶ and Wittig^{7,8} reactions. Furthermore, it is commonly

Keywords: Polystyrene; Triphenylphosphine; Polymer-supported synthesis; Metallation.

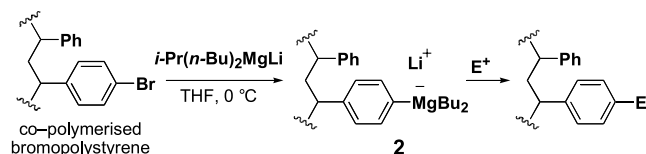
* Corresponding author. Tel.: +44 1223 336498; fax: +44 1223 336362;
e-mail: drspring@ch.cam.ac.uk

used as a ligand for metal catalysed reactions, such as the Suzuki reaction.⁹ Polymer-supported triphenylphosphine, on cross-linked polystyrene, is usually synthesised by bromination followed by lithiation of the polystyrene. The lack of complete selectivity in this process results in less chemically defined resin (**1b**). Higher quality polymer-supported triphenylphosphine has been synthesised by many different methods such as ring opening methathesis polymerization of norbornadiene structures,^{10–12} and radical *co*-polymerisation² of diphenyl-(4-vinylphenyl)phosphane, styrene and cross-linkers; however, these resins are either expensive or not commercially available.

2. Results and discussion

2.1. Functionalisation of bromopolystyrene

Previously we have reported a reproducible method of derivatising bromopolystyrene using Oshima's trialkylmagnesium complex¹³ *i*-Pr(*n*-Bu)₂MgLi to form a Grignard-like polymer (**2**) quantitatively, which was then intercepted with a variety of electrophiles to form the derivatised polymer beads (Scheme 1).¹⁴



Scheme 1. Functionalization of 4-bromopolystyrene resin.

Polymer-supported triphenylphosphine **1a** was prepared using this methodology with chlorodiphenylphosphine as the electrophile (Table 1). Combustion analysis revealed that the commercially available co-polymerised bromopolystyrene starting material contained 16% bromine. When isopropylmagnesium chloride or butyllithium was used to metalate the polymer a significant percentage of bromine in the polymer still remained after the reaction. While this was expected for isopropylmagnesium, 4-bromobenzene reacts completely using butyllithium at -78°C to form phenyllithium. This indicated that diffusion of butyllithium throughout the resin is a problem. In contrast, the magnesium–ate complex reacts with all the aryl bromides throughout the beads.

Table 1. Synthesis of triphenylphosphine resin (**1a**)

Bead size (μm)	Reagent	Time (h)	% Br ^a	% P ^a	mequiv/g
150–300	<i>i</i> -PrMgCl	5	10.6	0.45	0.15
150–300	<i>n</i> -BuLi	5	6.7	2.80	0.90
150–300	<i>i</i> -Pr(<i>n</i> -Bu) ₂ MgLi	5	0.0	4.20	1.36
400–500	<i>i</i> -Pr(<i>n</i> -Bu) ₂ MgLi	12	0.0	4.60	1.49
500–600	<i>i</i> -Pr(<i>n</i> -Bu) ₂ MgLi	12	0.0	4.15	1.34

^a Starting bromopolystyrene = 16.0% Br; 0% P. The theoretical maximum phosphorous content in product polymer = 5.1%.

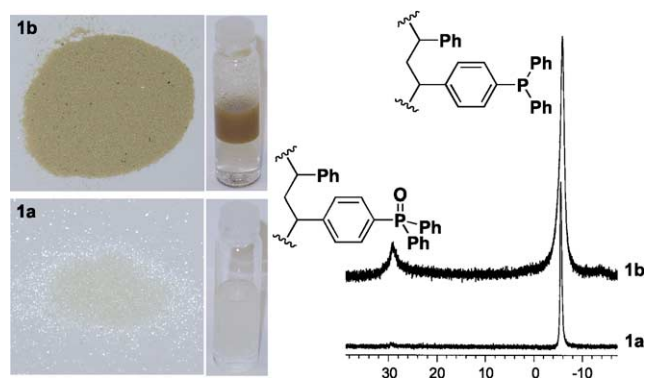


Figure 1. ³¹P NMR and photographs of triphenylphosphine polystyrene resin **1a** (synthesized using methodology described in this paper) and **1b** (commercially available). Each polymer is photographed dry and suspended in solvent (200 mg beads in 2 ml CH₂Cl₂).

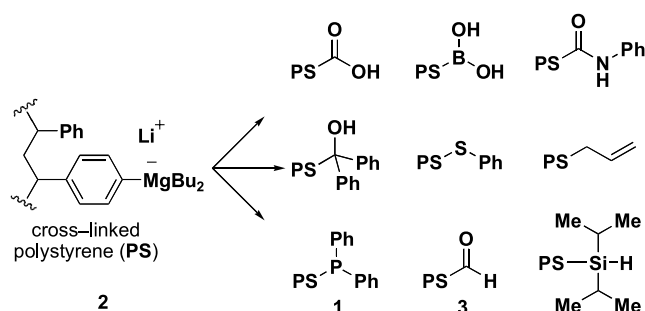
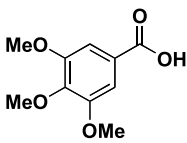
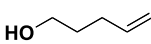
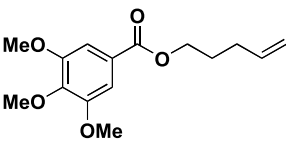
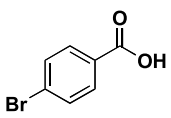
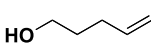
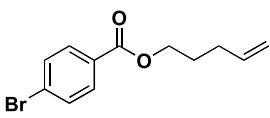
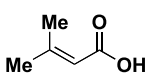
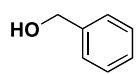
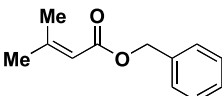


Figure 2.

Longer reaction times were required for larger diameter beads, with 12 h being necessary to ensure complete functionalization. This method of functionalizing polystyrene gave high purity products, with only trace amounts of phosphine oxide being detected by gel-phase ³¹P NMR. A higher proportion of phosphine oxide was present in commercially available resin **1b** (Fig. 1).

This methodology can be used with a wide range of electrophiles, including CO₂, trimethylborate, DMF, diisopropylchlorosilane¹⁴ and allyl bromide, to generate a variety of resins (Fig. 2), which could be used as polymer-supported reagents and scavengers, and as supports for solid phase synthesis.

Table 2. Mitsunobu reactions^a comparing triphenylphosphine polystyrene resins **1a** and **1b**

Acid	Alcohol	Product	Polymer reagent	Time (h)	Yield (%)
		 4	1a	12	78
			1b	12	68
		 5	1a	12	91
			1b	12	61
		 6	1a	12	87
			1b	12	45

^a **1** (1.5 equiv), di-*tert*-butyl azodicarboxylate (1.5 equiv), THF.

2.2. Mitsunobu reaction

Initial work using Mitsunobu reactions showed an increased yield when using resin **1a** compared to the commercial resin **1b**. Di-*tert*-butyl azodicarboxylate (DBAD) was added to the acid, alcohol and triphenylphosphine polystyrene in THF at 0 °C under nitrogen and the reactions were stirred overnight. At the end of the reaction any excess DBAD was scavenged out of the reaction using more triphenylphosphine resin.

Higher yields of **4**, **5** and **6** were obtained for each reaction when using resin **1a** compared to **1b**. One of the major disadvantages of the commercial resin **1b** was encountered during the filtering step. As the resin was so finely powdered occasionally it came through the filter so that re-filtering of the reaction was required. Also, drying the **1b** was problematic. The small diameter beads tended to stick together to form a gum, which was then difficult to dry; no such problems were encountered with resin **1a**. Table 2 shows a summary of the results obtained.

The increased yields obtained using resin **1a**, compared to the **1b** in Mitsunobu reactions led to investigation of other reactions using polymer-supported triphenylphosphine.

2.3. Amide bond formation reactions

The importance of methodology for the efficient formation of amide bonds cannot be overstated. Solid-supported reagents and scavengers can be used to eliminate the necessity for product purification, which can be problematic using standard coupling reagents. A two step strategy was adopted via acid bromide intermediates to synthesize the amides. Cycloheptanecarbonyl bromide was prepared from the corresponding acid using carbon tetrachloride, and polymer-bound triphenylphosphine **1** in dichloromethane. The acid bromide was subsequently used in amide coupling reactions under Schotten–Baumann conditions to give **7** to

10. The yields for these amide syntheses were comparable when side by side reactions were carried out with **1a** and the commercially available equivalent **1b**. Non-volatile amines, such as cyclohexylamine, required the use of a polymer-bound aldehyde **3** to scavenge out excess amine. This aldehyde resin can be used also as a scavenger to remove excess amines,⁷ 1,3-diols and hydride reducing agents.¹ Using cyclohexylamine under standard coupling conditions resulted in a 46% yield of **7**; however, the addition of scavenger resin **3** gave significantly higher yields (>95% purity by ¹H NMR). Importantly, the only purification necessary in these reactions was filtration and removal of solvent. The results are summarised in Table 3.

The stability of the resins should also be mentioned. The activity of both the polymer-supported triphenylphosphine **1a** and aldehyde **3** remained the same whether using freshly prepared resin or resin that had been prepared up to a year earlier.

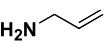
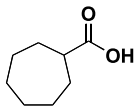
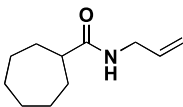
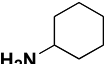
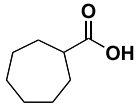
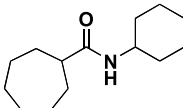
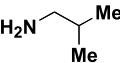
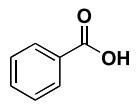
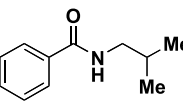
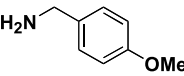
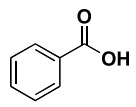
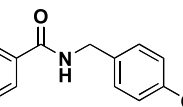
2.4. Wittig reaction

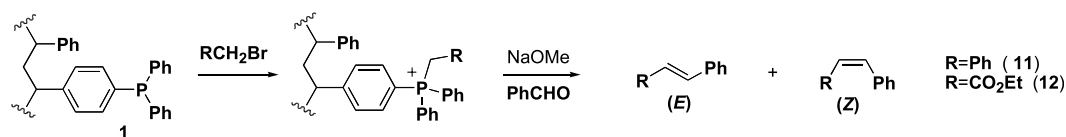
The Wittig reaction is an important reaction in the synthesis of alkenes and one of the most commonly employed reactions using triphenylphosphine. The solution-phase synthesis of stilbene (**11**) via the Wittig reaction results in a 7:3 *E/Z* product mixture.¹⁵ In contrast, using solid-supported triphenylphosphine **1b** in the same reaction gives **9** as a 1:1 *E/Z* product mixture.¹⁶ Resin **1a** was investigated in this reaction to determine its *E/Z* selectivity.

Treatment of the polymer-supported triphenylphosphine **1a** with benzyl bromide generated the phosphonium salt, which was reacted with a stoichiometric quantity of base (NaOMe), followed by 1 equiv of aldehyde (Scheme 2). Filtration of the reaction through a pad of silica generated stilbene **11** in a 48% yield. ¹H NMR showed **11** was synthesised in a 51:49 *E/Z* product mixture. This result indicates that the selectivity difference between supported

Table 3. Amide bond formation reactions comparing triphenylphosphine polystyrene resins **1a** and **1b**

$\text{PS} = \text{polystyrene}$
 $\text{PS}-\text{P}(\text{Ph})_3 \text{ (1)} + \text{R}-\text{C}(=\text{O})\text{OH} \xrightarrow{\text{CBr}_4} \text{R}-\text{C}(=\text{O})\text{Br} \xrightarrow{\text{R}'\text{NH}_2, \text{Na}_2\text{CO}_3, \text{PS}-\text{CHO (3)}} \text{R}-\text{C}(=\text{O})\text{NH}_2\text{R}'$

Amine	Acid	Product		Reagent (1)	Scavenger (3)	Yield (%)
			7	1a	No	55
			7	1b	No	52
			8	1a	No	46
			8	1a	Yes	79
			9	1a	Yes	68
			10	1a	Yes	80

**Scheme 2.** Witting reaction using solid-supported triphenylphosphine (**1b**).

and unsupported triphenylphosphine (**1a** and **1b** versus Ph_3P) is a general observation and not dependent on the polymer used. A difference between supported and unsupported triphenylphosphine is not observed in the synthesis of **12**, which gives only the *E*-isomer in both cases.

3. Conclusion

We have developed an operationally simple, reliable and cost effective method of metallating throughout small and large diameter co-polymerised 4-bromopolystyrene using Oshima's trialkylmagnesiato complex. These polymeric Grignard-like reagents can be quenched with a variety of electrophiles to synthesis a wide range of easy to handle, high purity and stable polymer-supported reagents and scavengers that can be used in target oriented and diversity oriented synthesis.

4. Experimental

4.1. Experimental techniques and apparatus

Experimental techniques and apparatus are standard except as otherwise indicated, reactions were carried out under nitrogen with dry, freshly distilled solvents. Dichloromethane was distilled from calcium hydride. *n*-BuLi in hexane (Aldrich) was titrated with benzyl-biphenyl-4-ylmethylene-amine¹⁷ and anhydrous menthol before use. All other reagents were purified in accordance with the instructions in 'Purification of Laboratory Chemicals'¹⁸ or

used as obtained from commercial sources. Yields refer to spectroscopically pure compounds. All reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with Merck silica gel 60 F₂₅₄ or aluminium oxide 60 F₂₅₄. Visualization was by the quenching of UV fluorescence ($\lambda_{\text{max}} = 254 \text{ nm}$) or by staining with ceric ammonium molybdate, potassium permanganate or Dragendorff's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3 M aq. AcOH). Retention factors (R_f) are quoted to 0.01. Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected. Infrared spectra were recorded neat on a Perkin–Elmer Spectrum One spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500. Proton assignments are supported by ^1H – ^1H spectra where necessary. Chemical shifts (δ_{H}) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (e.g. dd, dt, etc.)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X', where the ' indicates the higher field proton. Carbon magnetic resonance spectra were recorded on Bruker Ultrashield 500 spectrometers. Carbon spectra assignments are supported by DEPT editing and where necessary ^{13}C – ^1H (HMQC) correlations. Chemical

shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent. Phosphorous magnetic resonance spectra (^{31}P) were recorded on a DPX 400 MHz spectrometer. Chemical shifts (δ_P) are quoted in ppm to the nearest 0.01 ppm and are referenced to H_3PO_4 (external). LCMS spectra were recorded on an HP/Agilent MSD LC–S APCI 120–1000 full gradient ACq $T=1$ min 1 μl . High resolution mass measurements were made by the EPSRC mass spectrometry service (Swansea) and reported mass values are within the error limits of ± 5 ppm mass units. Microanalyses were performed by the University of Cambridge Microanalytical Laboratory in the Department of Chemistry, and are quoted to the nearest 0.1% for all elements except for hydrogen, which is quoted to the nearest 0.05%. Reported atomic percentages are within the error limits of $\pm 0.4\%$.

4.2. General procedure for functionalizing resins

i-Pr(*n*-Bu) $_2$ MgLi was prepared by stirring *i*-PrMgCl (2 equiv, 2.0 M in THF) in anhydrous THF (quantity to result in a 0.2 M solution of *i*-Pr(*n*-Bu) $_2$ MgLi) at 0 °C under a nitrogen atmosphere and adding *n*-BuLi (4 equiv, 2.5 M solution in hexanes). The resulting solution was stirred for a further 30 min to leave a clear yellow solution. Dry, white *co*-polymerized (74% styrene; 1% divinylbenzene; 25% 4-bromostyrene) 4-bromopolystyrene beads (1 equiv, 2.0 mmol/g, 150–300 μm) were swollen in anhydrous THF (10–30 ml of THF per gram of beads) for 15 min at 0 °C under a nitrogen atmosphere and then the preformed *i*-Pr(*n*-Bu) $_2$ MgLi was added and the resultant mixture stirred slowly. After 5 h (the beads were a golden yellow colour) the electrophile (6 equiv, freshly purified) was added and the mixture was agitated and allowed to warm to room temperature (22 °C) over 2 h. The beads were then filtered and washed with THF (3 $\times$ 5 min), CH_2Cl_2 :MeOH 1:1 (3 $\times$ 5 min), CH_2Cl_2 (5 $\times$ 5 min), and dried under reduced pressure to give free-flowing, white beads. Larger beads (400–500 or 500–600 μm) require 12 h to metallate completely throughout the beads

Electrophile	IR absorbance	Elemental analysis
<i>i</i> -Pr $_2$ SiHCl	2099 Si–H	Si 4.62%
Ph_2PCI	1433 P–C	P 4.60%
4-Iodophenyl isocyanate	1654 (Amide)	N 1.17%

Electrophile	IR absorbance
Carbon dioxide	3372 O–H 1687 C=O
Benzophenone	3414 O–H 1497–1450 C=C
DMF	1700 C=O
Allyl bromide	3026, 1638, 993, 911 RCH=CH $_2$
Trimethyl borate	3358 O–H 1340 B–O
S $_8$	3300 S–H
PhSSPh	2857 C–S

4.3. General Mitsunobu reaction procedure

To a mixture of carboxylic acid (1 equiv), alcohol (1.5 equiv) and polymer-bound triphenylphosphine (0.9 mmol/g, 1.5 equiv) in THF (ca. 0.1 M) under nitrogen at 0 °C was added di-*tert*-butyl azodicarboxylate (1.5 equiv)

in THF (1 ml). The reaction was warmed to room temperature and stirred overnight. The reaction was filtered and the resins washed with CH_2Cl_2 . The organic filtrate was washed with 3 M HCl ($\times 2$), brine ($\times 2$) dried (MgSO_4), filtered through a pad of silica and concentrated in vacuo to yield a colourless oil.

4.3.1. 3,4,5-Trimethoxy-benzoic acid pent-4-enyl ester (4).

Yield 78%; R_f 0.29 (SiO_2 ; CH_2Cl_2); ν_{max} (neat)/ cm^{-1} 1712s (C=O), 1124s (C–H); δ_{H} (500 MHz; CDCl_3) 7.32 (2H, s, aryl CH), 5.86 (1H, ddt, $J=16.0, 15.0, 10.0$ Hz, CHCH_2), 5.09 (1H, d, $J=16.0$ Hz, CH=CH'H), 5.03 (1H, d, $J=10.0$ Hz, CH=CH'H), 4.35 (2H, t, $J=6.5$ Hz, OCH_2CH_2), 3.92 (9H s, OCH_3), 2.22 (2H, dt, $J=15.0, 6.5$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.88 (2H, tt, $J=6.5, 6.0$ Hz, OCH_2CH_2); δ_{C} (125 MHz; CDCl_3) 166.21 (C), 152.95 (C), 142.24 (C), 137.47 (CH), 125.45 (C), 115.35 (CH_2), 106.85 (CH), 64.56 (CH_2), 60.91 (CH_3), 56.25 (CH_3), 30.18 (CH_2), 27.96 (CH_2); LCMS (MeCN) 281 (MH^+); HRMS (EI) found 281.1385 $\text{C}_{15}\text{H}_{21}\text{O}_5$ (MH^+) required 281.1384.

4.3.2. 4-Bromo-benzoic acid pent-4-enyl ester (5).

Yield 91%; R_f 0.81 (SiO_2 ; CH_2Cl_2); ν_{max} (neat)/ cm^{-1} 1717s (C=O); δ_{H} (500 MHz; CDCl_3) 7.89 (2H, d, $J=8.5$ Hz, aryl CH), 7.58 (2H, d, $J=8.5$ Hz, aryl CH), 5.88–5.78 (1H, m, CH=CH_2), 5.10–5.03 (1H, br dt, $J=17.0$ Hz, CH=CH'H), 5.02–5.00 (1H, br dt, $J=10.0$ Hz, CH=CH'H), 4.32 (2H, t, $J=6.5$ Hz, OCH_2), 2.21 (2H, dt, $J=14.0, 6.5$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.87 (2H, tt, $J=7.0, 6.5$ Hz, OCH_2CH_2); δ_{C} (125 MHz; CDCl_3) 165.86 (C), 137.35 (CH), 131.70 (CH), 131.09 (CH), 129.35 (C), 127.96 (C), 110.00 (CH_2), 64.65 (CH_2), 30.13 (CH_2), 27.88 (CH_2); LCMS (MeCN) 271 (MH^+); HRMS (ES) found 291.0001 $\text{C}_{12}\text{H}_{13}\text{BrNaO}_2$ (MNa^+) required 290.9997.

4.3.3. 3-Methyl-but-2-enoic acid benzyl ester (6).

Yield 87%; R_f 0.88 (SiO_2 ; CH_2Cl_2); ν_{max} (neat)/ cm^{-1} 1715s (C=O), 1648m (C=C); δ_{H} (500 MHz; CDCl_3) 7.53–7.22 (5H, m, aryl CH), 5.75 (1H, s, CHCO_2Bn), 5.12 (2H, s, CH_2), 2.18 (3H, s, CH_3), 1.88 (3H, s, CH_3); δ_{C} (125 MHz; CDCl_3) 166.41 (C), 157.23 (C), 136.51 (C), 128.51 (CH), 128.11 (C), 128.01 (CH), 115.82 (CH), 65.36 (CH_2), 27.42 (CH_3), 20.28 (CH_3); LCMS (MeCN) 191 (MH^+); HRMS (ES) found 213.0890 $\text{C}_{12}\text{H}_{14}\text{NaO}_2$ (MNa^+) required 213.0891.

4.4. Amide formation

4.4.1. Cycloheptanecarboxyl allylamide (7).

A mixture of cycloheptane carboxylic acid (0.14 ml, 1.03 mmol), polymer-bound triphenylphosphine (2.2 mmol) and carbon tetrabromide (365 mg, 1.1 mmol) in dry CH_2Cl_2 (8 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of allylamine (0.11 ml, 0.11 mmol) in sodium carbonate solution (2 M, 8 ml) was added the bromide in dry CH_2Cl_2 (8 ml). The mixture was stirred over night at room temperature. The organic layer was separated and washed with sodium bicarbonate solution ($\times 2$), brine ($\times 2$), dried (MgSO_4), filtered through a pad of silica and concentrated in vacuo to give the title compound as a white solid (95 mg, 55%). R_f : 0.29 (SiO_2 ; Hexane/Ethyl acetate; 10:4); ν_{max} (neat)/ cm^{-1} 3299 (N–H), 2922 (C–H), 1637 (C=O); δ_{H}

(500 MHz, CDCl_3) 5.85–5.76 (1H, m, $\text{CH}=\text{CH}_2$), 5.65 (1H, s, NH), 5.14 (1H, dd, $J=17.0$, 1.5 Hz, $\text{CH}=\text{CHH}'$), 5.09 (1H, dd, $J=10.0$, 1.0 Hz, $\text{CH}=\text{CHH}'$), 3.83 (2H, t, $J=5.5$ Hz, HNCH_2), 2.26–2.23 (1H, m, CHCO), 1.90–1.83 (2H, m, cycloheptane ring) 1.80–1.46 (10H, m, cycloheptane ring); δ_{C} (125 MHz, CDCl_3) 176.09 (C), 133.57 (CH), 115.06 (CH_2), 46.52 (CH), 40.70 (CH_2), 30.75 (CH_2), 27.12 (CH_2), 25.62 (CH_2); LCMS (MeCN): 182.1 (MH^+); mp 44–46 °C; HRMS (ES) found 204.1428 $\text{C}_{11}\text{H}_{19}\text{NONa}$ (MNa^+) required 204.1436.

4.4.2. Cycloheptanecarboxyl cyclohexylamide (8).¹⁹ A mixture of cycloheptane carboxylic acid (0.03 ml, 0.26 mmol), polymer-bound triphenylphosphine (644 mg, 0.58 mmol) and carbon tetrabromide (96 mg, 0.29 mmol) in dry CH_2Cl_2 (5 ml) was stirred under nitrogen at room temperature for 3 h. The beads were removed by filtration and the solvent removed in vacuo. To a solution of cyclohexylamine (0.045 ml, 0.39 mmol) in sodium carbonate solution (2 M, 5 ml) was added the bromide in dry CH_2Cl_2 (5 ml). The mixture was stirred over night at room temperature. The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution ($\times 2$), brine ($\times 2$), dried (MgSO_4) and the solvent was removed in vacuo to yield the title compound as a light yellow solid (46 mg, 79%). R_{f} : 0.23 (SiO_2 ; Hexane/Ethyl acetate; 10:4); ν_{max} (neat) cm^{-1} 3296 (N–H), 2923 (C–H), 1635 (C=O); δ_{H} (400 MHz, CDCl_3) 5.32–5.01 (1H, br s, NH), 3.79–3.70 (1H, m, HNCH), 2.16–2.15 (1H, m, CHCO), 1.89–1.84 (4H, m), 1.79–1.35 (15H, m), 1.12–1.11 (3H, m); δ_{C} (125 MHz, CDCl_3) 175.29 (C), 47.75 (CH), 47.71 (CH), 32.27 (CH_2), 30.81 (CH_2), 27.12 (CH_2), 25.69 (CH_2), 24.61 (CH_2), 23.89 (CH_2); mp 153–157 °C; HRMS (ES) found 246.1848 $\text{C}_{14}\text{H}_{25}\text{NONa}$ (MNa^+) required 246.1858.

4.4.3. *N*-Isobutyl-benzamide (9).²⁰ A mixture of benzoic acid (30 mg, 0.25 mmol), polymer-bound triphenylphosphine (0.5 mmol) and carbon tetrabromide (97 mg, 0.29 mmol) in dry CH_2Cl_2 (3 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of isobutylamine (0.04 ml, 0.39 mmol) in sodium carbonate solution (2 M, 3 ml) was added the bromide in dry CH_2Cl_2 (3 ml). The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution ($\times 2$), brine ($\times 2$), dried (MgSO_4) and the solvent was removed in vacuo to yield the title compound as a white solid (30 mg, 68%). R_{f} : 0.28 (SiO_2 ; Hexane/Ethyl acetate; 2:1); ν_{max} (neat) cm^{-1} 3321 (N–H), 2960 (C–H), 1639 (C=O), 1541 (C=C); δ_{H} (500 MHz, CDCl_3) 7.77 (2H, d, $J=7.0$ Hz, ArH), 7.53–7.50 (1H, m, ArH), 7.43 (2H, t, $J=7.5$ Hz, ArH), 6.18 (1H, br s, NH), 3.31 (2H, t, $J=6.5$ Hz, NHCH_2), 1.92 (1H, sept, $J=6.5$ Hz, NHCH_2CH), 1.00 (6H, d, $J=6.5$ Hz, CH_3); δ_{C} (125 MHz, CDCl_3) 167.62 (C), 134.97 (C), 131.32 (CH), 128.58 (CH), 126.81 (CH), 47.36 (CH_2), 28.65 (CH), 20.18 (CH_3); LCMS (MeCN): 178 (MH^+); mp 52–54 °C, lit. 55 °C.²⁰

4.4.4. *N*-(4-Methoxy-benzyl)-benzamide (10).^{20,21} A mixture of benzoic acid (30 mg, 0.25 mmol), polymer-bound

triphenylphosphine (0.5 mmol) and carbon tetrabromide (97 mg, 0.29 mmol) in dry CH_2Cl_2 (3 ml) was stirred under nitrogen at room temperature for 3 h. The beads were filtered and the solvent removed in vacuo. To a solution of 4-methoxy-benzylamine (0.05 ml, 0.39 mmol) in sodium carbonate solution (2 M, 3 ml) was added the bromide in dry CH_2Cl_2 (3 ml). The polymer-bound aldehyde (**3**) was added and the reaction stirred overnight. The beads were removed by filtration and the organic layer was separated and washed with sodium bicarbonate solution ($\times 2$), brine ($\times 2$), dried (MgSO_4) and the solvent was removed in vacuo to yield the title compound as a pale yellow solid (48 mg, 80%). R_{f} : 0.26 (SiO_2 ; Hexane/Ethyl acetate; 2:1); ν_{max} (neat) cm^{-1} 3315 (N–H), 2934 (C–H), 1636 (C=O), 1509 (C=C), 1244 (C–H); δ_{H} (500 MHz, CDCl_3) 7.79 (2H, dd, $J=7.5$, 1.0 Hz, ArH), 7.52–7.50 (1H, m, ArH), 7.44 (2H, t, $J=7.5$ Hz, ArH), 7.28 (2H, d, $J=8.0$ Hz, ArH), 6.90 (2H, d, $J=8.0$ Hz, ArH), 6.52 (1H, br s, NH), 4.57 (2H, d, $J=5.5$ Hz, NHCH_2), 3.81 (3H, s, OCH_3); δ_{C} (125 MHz, CDCl_3) 167.28 (C), 159.13 (C), 134.49 (C), 131.48 (CH), 130.33 (C), 129.30 (CH), 128.55 (CH), 126.97 (CH), 114.17 (CH), 55.32 (CH_3), 43.63 (CH_2); LCMS (MeCN): 241 (MH^+); mp 91–94 °C, lit. 87–88 °C.^{20,21}

4.5. Wittig reaction²²

4.5.1. Stilbene (11). Benzyl bromide (0.22 ml, 1.8 mmol) was added dropwise with stirring to a suspension of a polymer-bound triphenylphosphine (1.0 g, 0.9 mmol) in *N,N*-dimethylformamide (15 ml). The mixture was stirred over 48 h at 70 °C, cooled, filtered, washed with toluene ($\times 10$), CH_2Cl_2 ($\times 10$), diethyl ether ($\times 10$) and dried to yield the phosphonium salt as white solid (954 mg).

To a suspension of polymer-bound phosphonium salt (533 mg, 0.375 mmol) in THF at -10 °C was added a suspension of sodium methoxide (54 mg, 1.02 mmol) in methanol dropwise. After 3 h of stirring at room temperature the reaction was cooled down to 10 °C, and benzaldehyde (0.11 ml, 1.03 mmol) was added dropwise. The mixture was stirred over night at room temperature, refluxed for 3 h, filtered and washed with THF ($\times 10$), CH_2Cl_2 ($\times 10$) and diethyl ether ($\times 10$). The combined organic layers were dried (MgSO_4), filtered through a pad of silica and concentrated in vacuo to give the title compound as a 49:51 ratio of *E/Z* isomers (32 mg, 48%).

4.5.2. (*Z*)-stilbene (*Z*)-11. Colourless oil; R_{f} : 0.28 (SiO_2 ; Hexane); δ_{H} (400 MHz, CDCl_3) 7.27–7.19 (10H, m, CH aryl), 6.61 (2H, s, CHPh).

4.5.3. (*E*)-stilbene (*E*)-11. White solid; R_{f} : 0.23 (SiO_2 ; Hexane); δ_{H} (400 MHz, CDCl_3): 7.53 (4H, d, $J=8.0$ Hz, CH aryl), 7.37 (4H, t, $J=8.0$ Hz, CH aryl), 7.27 (2H, t, $J=7.25$ Hz, CH aryl), 7.12 (2H, s, CHPh); mp 102–104 °C.²²

4.5.4. (*E*)-2-Methyl-3-phenyl-acrylic acid ethyl ester (12).²³ Ethyl-2-bromo-propionate (0.23 ml, 1.8 mmol) was added dropwise with stirring to a suspension of a polymer-bound triphenylphosphine (1.0 g, 0.9 mmol) in *N,N*-dimethylformamide (15 ml). The mixture was stirred over 48 h at 70 °C, cooled, filtered, washed with toluene ($\times 10$),

CH_2Cl_2 ($\times 10$), diethyl ether ($\times 10$) and dried to yield the phosphonium salt as white solid (983 mg).

To a suspension of polymer-bound phosphonium salt (400 mg, 0.3 mmol) in THF at -10°C was added a suspension of sodium methoxide (16.4 mg, 0.31 mmol) in methanol dropwise. After 3 h of stirring at room temperature the reaction was cooled down to -10°C , and benzaldehyde (0.03 ml, 0.30 mmol) was added dropwise. The mixture was stirred over night at room temperature, refluxed for 3 h, filtered and washed with THF ($\times 10$), CH_2Cl_2 ($\times 10$) and diethyl ether ($\times 10$). The combined organic layers were dried (MgSO_4), filtered through a pad of silica and concentrated in vacuo to give the title compound as a colourless oil (42 mg, 61%). ν_{max} (neat) cm^{-1} 2983 (C–), 1706 (C=O), 1253 (C–), 1111; δ_{H} (500 MHz, CDCl_3) 7.71 (1H, br s, $\text{CH}=\text{CCH}_3$), 7.44–7.32 (5H, m, ArH), 4.30 (2H, q, $J=7.25$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 2.14 (3H, d, $J=1.5$ Hz, CCH_3), 1.38 (3H, t, $J=7.25$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); δ_{C} (125 MHz, CDCl_3) 168.70 (C), 138.63 (CH), 136.01 (C), 129.62 (CH), 128.68 (C), 128.34 (CH), 128.26 (CH), 60.86 (CH_2), 14.33 (CH_3), 14.04 (CH_3); LCMS (MeCN): 191 (MH^+).

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