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Complete functionalisation of small and large diameter bromopolystyrene beads; applications for solid-supported reagents, scavengers and diversity-oriented synthesis†

Gemma L. Thomas,[a] **Mark Ladlow**[b] **and David R. Spring***[a]
[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK. E-mail: drspring@ch.cam.ac.uk*
[b] *GSK Cambridge Technology Centre, University of Cambridge, Lensfield Road, Cambridge, UK*

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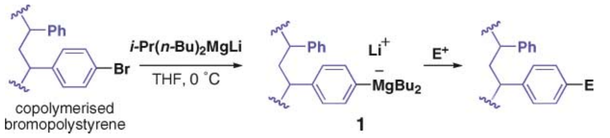
Bromopolystyrene beads with diameters of up to 600 μm have been derivatized completely, *via* bromine–magnesium exchange and interception with electrophiles, to yield high quality solid-supported reagents, scavengers and solid supports for use in diversity-oriented synthesis.

The operational efficiency of parallel, combinatorial and diversity-oriented syntheses[1] is greatly improved by the use of insoluble solid supports.[2] The functionalization of solid supports, such as cross-linked polystyrene, is therefore of enormous importance.[3] We and others have found that bead diameters greater than 150 μm possess optimum handling properties.[4] However, existing methodology used to generate a polystyrene aryl carbanion, which could be intercepted by a variety of electrophiles, is only applicable to smaller-sized beads.[5] This is presumably due to insufficient penetration by the reagent. Metallation of cross-linked polystyrene has been performed by the direct lithiation of polystyrene[6] or by halogen (usually bromine)–metal exchange.[7] We set out to develop a metallation approach using copolymerized bromopolystyrene beads of various sizes as the starting material that results in substitution of all metal–halogen sites (Scheme 1).[8]



Scheme 1 Strategy to derivatize bromopolystyrene.

We describe herein a reproducible method of derivatising bromopolystyrene using Oshima's trialkylmagnesate complex[9] i-Pr(n-Bu)$_2$MgLi to form quantitatively a Grignard-like polymer (**1**), which can be intercepted with electrophiles to form derivatized polymer beads of any size up to at least 600 μm diameter beads.[10] Oshima and coworkers have used their magnesium ate complexes to metallate aryl bromides, but have not reported their use on polymeric starting materials.

Triphenylphosphine polystyrene (aka diphenylphosphino polystyrene), which can be used as a replacement for triphenylphosphine, but avoids the need for troublesome post-synthesis purification to remove phosphine-derived products such as triphenylphosphine oxide, is a huge commercial success. Use of Ph_2PCl as an electrophile generates high quality triphenylphosphine polystyrene (**2**) beads of any size (150–600 μm). Treatment with i-PrMgCl or n-BuLi alone fails to functionalize completely the beads (Table 1).

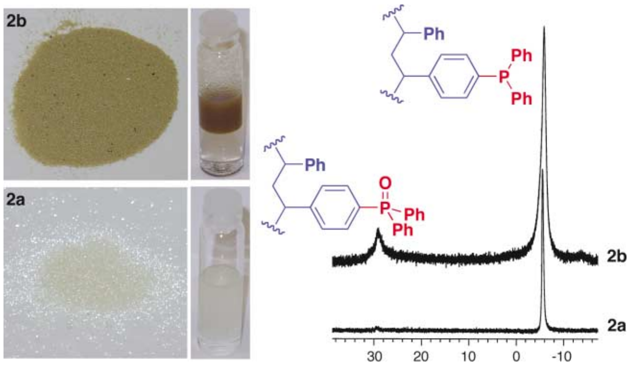
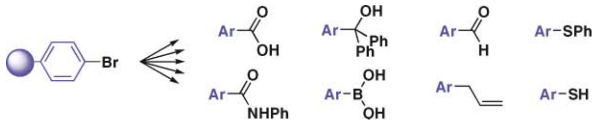


Fig. 1 Triphenylphosphine polymers are photographed dry and suspended in solvent (200 mg beads in 2 ml CH_2Cl_2); also, the gel-phase ^{31}P NMR spectrum is shown.

Bead sizes over 150 μm are more convenient to handle, and our resulting white beads (Fig. 1) react favourably as compared with commercial products (Table 2). In side-by-side Mitsunobu reactions the use of our triphenylphosphine polystyrene beads (**2a**; 150–300 μm) gave reproducibly a higher yield and purer product *versus* a popular polymer-supported triphenylphosphine available commercially (**2b**; 38–75 μm); however, the rate of both reactions was essentially the same. The differences in yield and purity are likely to be due to (i) the higher purity of **2a**; and, more significantly, (ii) its ease of separation by filtration. Presumably some product is not being washed out of the small beads, even though they were thoroughly washed and filtered over several hours. Gel-phase ^{31}P NMR of our beads detects triphenylphosphine, but only a trace of phosphine oxide, unlike the beads purchased (Fig. 1). At the end of the reaction any excess azodicarboxylate was scavenged by adding more triphenylphosphine polystyrene.

Our procedure works successfully with many other electrophiles such as CO_2, isocyanates, ketones, trimethyl borate, dimethylformamide (to give aldehyde derivatized polystyrene), thioisocyanates, allyl bromide, S_8, or PhSSPh (Scheme 2).[6,7,10] The derivatised products can be used as reagents, scavengers and for solid-supported organic synthesis.



Scheme 2 Synthesis of functionalized polystyrene, which can be used as reagents, scavengers and for solid-supported synthesis.

Of particular interest to our efforts in solid-phase, diversity-oriented synthesis is the efficient formation of a novel diisopropylsilane-derivatized polystyrene (**3**),[11] which could not be

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† Electronic supplementary information (ESI) available: experimental techniques, apparatus, characterisation and spectroscopic data. See http://www.rsc.org/suppdata/ob/b4/b406488g/

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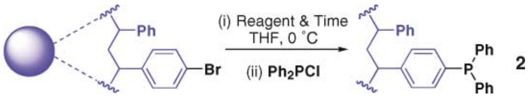
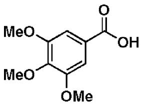
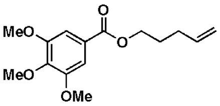
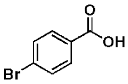
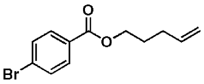
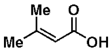
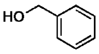
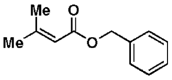
Table 1 Synthesis of triphenylphosphine polystyrene



Bead size	Reagent	Time	% Br[a]	% P[a]	mequiv g^{-1}
150–300 μm	*i*-PrMgCl	5 h	10.6	0.45	0.15
150–300 μm	*n*-BuLi	5 h	6.7	2.80	0.90
150–300 μm	*i*-Pr(*n*-Bu)$_2$MgLi	5 h	0.0	4.20	1.36
400–500 μm	*i*-Pr(*n*-Bu)$_2$MgLi	12 h	0.0	4.60	1.49
500–600 μm	*i*-Pr(*n*-Bu)$_2$MgLi	12 h	0.0	4.15	1.34

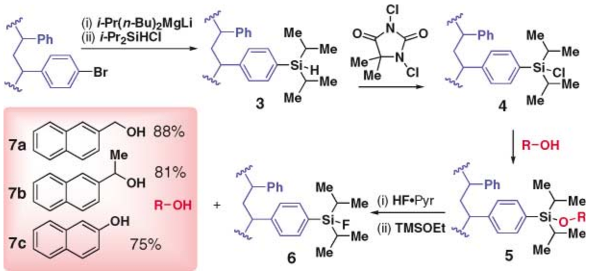
[a] Starting bromopolystyrene = 16.0% Br; 0% P. The theoretical maximum phosphorous content in product polymer = 5.1%.

Table 2 Mitsunobu reactions comparing **2a** with **2b**[a]

Acid	Alcohol	Product	Polymer reagent	Time (h)	Average yield (%)
			**2a** **2b**	12 12	78 68
			**2a** **2b**	12 12	91 61
			**2a** **2b**	12 12	87 45

[a] **2** (1.5 equiv.), di-*tert*-butyl azodicarboxylate (1.5 equiv.), THF.

generated by radical copolymerisation. Grignard-like polymer **1** was quenched with diisopropylchlorosilane (Gelest), which yielded colourless, air- and moisture-stable beads of any size (**3**; 150–300 μm, 400–500 μm & 500–600 μm have all been made successfully), which can be stored indefinitely (Scheme 3). Elemental analysis measured 4.5% silicon (indicating a loading of 1.6 mequiv g^{-1})[12] and 0% bromine present in **3**; also, on-bead FTIR detected a strong Si–H stretch at 2096 cm^{-1}. The silane polymer can be oxidized to the silyl chloride by the use of chlorinating agents such as 1,3-dichloro-5,5-dimethylhydantoin. Alternatively, the silyl triflate can be generated by treatment of **3** with triflic acid. The silyl chloride derivatized polystyrene (**4**) was used immediately to attach primary, secondary and phenolic alcohols onto the polystyrene solid support.[11] High yielding attachment of the secondary and phenolic alcohols required dimethylaminopyridine (DMAP). The alcohols could be cleaved from the polymer using 10% v/v solution of HF·pyridine in THF. Excess HF·pyridine was quenched using ethoxytrimethylsilane.[13] The yield over the 4 steps from bromopolystyrene to alcohol detachment is reported (**7a**: 70%, **7b**: 66% & **7c**: 59%). Chemical stability of **5** is comparable to a triisopropylsilyl (TIPS) protecting group: stable to anhydrous basic, neutral and strong Lewis acid conditions.



Scheme 3 Synthesis of diisopropylsilane-functionalized polystyrene (**3**) and its use for attaching primary, secondary and phenolic alcohols covalently onto the polystyrene solid-support. Overall yields from silane polystyrene **3** (three steps) were calculated by mass after cleavage of the alcohols from the polymer.

In summary, we have developed a reliable and operationally simple method to metallate completely bromopolystyrene beads with a diameter of up to 600 μm. Furthermore, the resulting polymeric Grignard-like reagent can be quenched with electrophiles to produce derivatized polystyrenes. High quality solid-supported reagents and scavengers were generated. Also, a novel diisopropylsilane polymer support for solid-phase organic synthesis was synthesized efficiently and employed for the covalent attachment, and release, of primary, secondary and phenolic alcohols to polystyrene beads. The use of these solid-supports for the diversity-oriented synthesis of structurally-diverse and structurally-complex collections of small molecules will be disclosed in due course.

Experimental

General procedure for polystyrene derivatisation

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 an argon atmosphere and adding *n*-BuLi (4 equiv., 2.5 M soln in hexanes). The resulting solution was stirred for a further 30 min to leave a clear yellow solution. Dry, white copolymerized (74% styrene; 1% divinylbenzene; 25% 4-bromostyrene) 4-bromopolystyrene beads (1 equiv., 2.0 mequiv g^{-1}, 150–300 μm; Stratospheres™ from Polymer Laboratories Ltd; PL-PBS resin) were swollen in anhydrous THF (10–30 ml of THF per gram of beads) for 15 min at 0 °C under an argon atmosphere and then the preformed *i*-Pr(*n*-Bu)$_2$MgLi was added and the resultant mixture agitated slowly on an orbital shaker (or stirred slowly with a magnetic stirring bar). 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 × 5 min), CH_2Cl_2 : MeOH 1 : 1 (3 × 5 min), CH_2Cl_2 (5 × 5 min), and dried under reduced pressure to give free-flowing, white beads. Larger beads (400–500 µm or 500–600 µm; Stratospheres (from Polymer Laboratories Ltd; PL-PBS resin) require 12 hours to metallate completely throughout the beads.

General procedure for alcohol attachment

Dry silane polystyrene **3** (1.6 mequiv g^{-1}) was added to a dry, fritted polypropylene column (Bruker) fitted with a Teflon stopcock and capped with a suba seal. The vessel was evacuated and purged with Ar. The beads were swollen with CH_2Cl_2 (10 ml per gram of beads) and TMSCl (6 equiv.) and occasionally agitated over 30 min, at room temperature, under Ar. The solution was then drained under positive Ar pressure, and washed/drained three times with anhydrous CH_2Cl_2. The beads were then suspended in a CH_2Cl_2 solution of 1,3-dichloro-5,5-dimethylhydantoin (3 equiv.) and agitated occasionally over 2 h, at room temperature, under Ar. The solution was then drained under positive Ar pressure, and washed/drained two times with anhydrous CH_2Cl_2 to give **4**. The silyl chloride beads were suspended in a CH_2Cl_2 solution of 2,6-lutidine (4 equiv.), DMAP (0.1 equiv.) and anhydrous alcohol (3 equiv.; 1.5 equiv. can be used if the alcohol is valuable), the mixture was agitated then left to stand overnight, at room temperature, under Ar. The solution was then drained under positive Ar pressure (excess alcohol can be recovered), and washed/drained as in ref. 10. The beads were air-dried under suction for 2 h with occasional agitation, and then placed under high vacuum.

General procedure for alcohol cleavage

The beads (100 mg) were swollen in THF (0.5 ml) and HF•Pyr (50 µl, 1.77 mmol) was added. The vials were sealed and agitated for 2.5 h, then quenched using trimethylethoxysilane. The vials were agitated for a further 30 min to ensure complete quenching. Then the solvent was filtered through a plug of silica gel and the resin washed with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by column chromatography.

General Mitsunobu reaction procedure

To a mixture of carboxylic acid (1 equiv.), alcohol (1.5 equiv.) and polymer bound triphenylphosphine (0.9 mequiv g^{-1}, 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. Extra polymer bound triphenylphosphine (0.5 equiv.) was added to scavenge remaining *tert*-butyl azodicarboxylate and the mixture stirred for a further 30 min. The reaction was filtered and the resins washed with CH_2Cl_2. The organic filtrate was washed with 3 M HCl (× 2), brine (× 2) dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using CH_2Cl_2 as the eluent to yield a colourless oil.

Acknowledgements

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Notes and references

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3 Derivatized polystyrene can be synthesized either by copolymerization (styrene, divinylbenzene & functionalized styrene) or, more divergently, by functionalization of a polystyrene starting material.

4 Beads smaller than 75 µm have the advantage that chemical reaction rates on polymer-supported substrates are faster relative to larger beads; however, they have the major disadvantages that they are more difficult to handle (filtration, flow characteristics, relative avoidance of the effects of static, ease of compartmentalization into porous capsules and cartridges) and have a much lower capacity of functionality per bead.

5 G. Thomas and D. R. Spring, unpublished results. Bead sizes for previous metallation procedures are given in refs. 6 and 7. Suzuki–Miyaura cross-coupling is successful with large beads (see ref. 10).

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8 The use of copolymerized bromopolystyrene (styrene, divinylbenzene & 4-bromostyrene) ensures that the bromine functionalisation occurs uniformly throughout the polymer bead. Commercially available polymers are available in a range of bead sizes, from 38–75 µm (400–200 mesh) to 500–600 µm (35–30 mesh).

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10 The metallated polymer could be transmetallated also, *e.g.* with copper (CuCN•2LiBr) or zinc ($ZnCl_2$), before addition of the electrophile. In Scheme 2 the cuprate was made before addition of allyl bromide.

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12 The theoretical maximum silicon content in product polymer = 5.2%.

13 Ethoxytrimethylsilane (bp = 75 °C), ethanol (bp = 79 °C), pyridine (bp = 115 °C) and trimethylsilyl fluoride (bp = 16 °C) can all be removed under reduced pressure.