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

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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 syntheses1 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 polystyrene6 or by halogen–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.](image)

We describe herein a reproducible method of derivatising bromopolystyrene using Oshima’s trialkylmagnesate complex9 i-Pr(n-Bu)3MgLi 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 metalate 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 Ph3P 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).

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

Fig. 1 Triphenylphosphine polymers are photographed dry and suspended in solvent (200 mg beads in 2 ml CH2Cl2); also, the gel-phase 31P 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 31P 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 CO2, isocyanates, ketones, trimethyl borate, dimethylformamide (to give aldehyde derivatized polystyrene), thiocyanates, allyl bromide, S8, or PhSSPh (Scheme 2).5,7,10 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.](image)

Of particular interest to our efforts in solid-phase, diversity-oriented synthesis is the efficient formation of a novel disopropylsilane-derivatized polystyrene (3),11 which could not be...
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) 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 trflate 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. High yielding attachment of the secondary and phenolic alcohols required dimethylaminopyridine (DMAP). The silyl chloride derivatized 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**

\( i-\text{Pr}(n-\text{Bu})_2\text{MgCl} \) was prepared by stirring \( i-\text{PrMgCl} \) (2 equiv., 2.0 M in THF) in anhydrous THF (quantity to result in a 0.2 M solution of \( i-\text{Pr}(n-\text{Bu})_2\text{MgLi} \) at 0 °C under an argon atmosphere and adding \( n-\text{BuLi} \) (4 equiv., 2.5 M sohn 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-silanol (3) was 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 \( i-\text{Pr}(n-\text{Bu})_2\text{MgLi} \) 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.

**Table 1** Synthesis of triphenylphosphine polystyrene

<table>
<thead>
<tr>
<th>Bead size</th>
<th>Reagent</th>
<th>Time (h)</th>
<th>% Br</th>
<th>% P</th>
<th>mequiv g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–300 µm</td>
<td>( i-\text{PrMgCl} )</td>
<td>5</td>
<td>10.6</td>
<td>0.45</td>
<td>0.15</td>
</tr>
<tr>
<td>150–300 µm</td>
<td>( n-\text{BuLi} )</td>
<td>5</td>
<td>6.7</td>
<td>2.80</td>
<td>0.90</td>
</tr>
<tr>
<td>150–300 µm</td>
<td>( i-\text{Pr}(n-\text{Bu})_2\text{MgLi} )</td>
<td>5</td>
<td>0.0</td>
<td>4.20</td>
<td>1.36</td>
</tr>
<tr>
<td>400–500 µm</td>
<td>( i-\text{Pr}(n-\text{Bu})_2\text{MgLi} )</td>
<td>12</td>
<td>0.0</td>
<td>4.60</td>
<td>1.49</td>
</tr>
<tr>
<td>500–600 µm</td>
<td>( i-\text{Pr}(n-\text{Bu})_2\text{MgLi} )</td>
<td>12</td>
<td>0.0</td>
<td>4.15</td>
<td>1.34</td>
</tr>
</tbody>
</table>

*a* Starting bromopoly styrene = 16.0% Br; 0% P. The theoretical maximum phosphorous content in product polymer = 5.1%.

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

<table>
<thead>
<tr>
<th>Acid</th>
<th>Alcohol</th>
<th>Product</th>
<th>Reagent</th>
<th>Time (h)</th>
<th>Average yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td></td>
<td>2b</td>
<td></td>
<td>12</td>
<td>78</td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td>2b</td>
<td></td>
<td>12</td>
<td>68</td>
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<td>2a</td>
<td></td>
<td>2b</td>
<td></td>
<td>12</td>
<td>91</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>2b</td>
<td></td>
<td>12</td>
<td>61</td>
</tr>
<tr>
<td>2a</td>
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<td>2b</td>
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<td>12</td>
<td>87</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>2b</td>
<td></td>
<td>12</td>
<td>45</td>
</tr>
</tbody>
</table>

*a* 2 (1.5 equiv.), di-tert-butyl azodicarboxylate (1.5 equiv.), THF.
The beads were then filtered and washed with THF (3×5 min), CH₂Cl₂: MeOH 1:1 (3×5 min), CH₂Cl₂ (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 mettallate completely throughout the beads.

General procedure for alcohol attachment

Dry silane polystyrene (100 mg) was swollen in THF (0.5 ml) and HF/H₂O solution was then drained under positive Ar pressure, and the solution was then drained over 30 min, at room temperature, under Ar. The solution was then drained under positive Ar pressure, and washed/drained as in ref. 10. The beads were washed with 3 M HCl (10 ml per gram of beads) and TMSCl (6 equiv.) and occasion-ally 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 CH₂Cl₂. The beads were then suspended in a CH₂Cl₂ 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 CH₂Cl₂ to give 4. The silyl chloride beads were suspended in a CH₂Cl₂ 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, 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

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 over-night. 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 CH₂Cl₂. The organic filtrate was washed with 3 M HCl (×2), brine (×2) dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography using CH₂Cl₂ as the eluent to yield a colourless oil.

Acknowledgements

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Notes and references

3 Derivatized polystyrene can be synthesized either by copolymerization (styrene, divinylbenzene & functionalized styrene) or, more divergently, by functionalization of a polystyrene starting material.
4 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).
6 The metallated polymer could be transmetallated also, e.g. with copper (CuCN=2LiBr) or zinc (ZnCl₂), before addition of the electrophile. In Scheme 2 the cuprate was made before addition of allyl bromide.
8 The theoretical maximum silicon content in product polymer = 5.2%.
9 Ethoxytrimethylsilane (bp = 75 °C), ethanol (bp = 70 °C), pyridine (bp = 115 °C) and trimethylsilyl fluoride (bp = 16 °C) can all be removed under reduced pressure.

O r g . B i o m o l . C h e m . , 2 0 0 4 , 2 , 1 6 7 9 – 1 6 8 1 1 6 8 1