Facile attachment of functional moieties to crosslinked polystyrene beads *via* robust linkages: Suzuki reactions using polymer-supported boronic acids

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Aryl bromides containing carboxylic acid, alcohol, phenol, amine, triphenylphosphine, sulfonamide, thiophene or furan moieties were linked directly to polystyrene beads containing boronic acid groups by Suzuki reactions. In all cases except that with 2-bromofuran, the coupling yields were greater than 50%. In several cases those boronic acid residues that did not take part in the Suzuki reaction were lost by hydrolysis of the B–C bond; in other cases the remaining residues could be removed easily by Suzuki reactions using an excess of bromobenzene. The Suzuki reaction therefore provides an easy means to attach functional moieties to polystyrene beads *via* robust linkages without the need for protecting groups and without leaving in the beads any of the reactive groups used in the linking reaction. It should be noted that using the polymer-supported boronic acid allows functionalised aryl halides to be attached, whereas the reverse type of Suzuki reaction would require functionalised arylboronic acids. Functionalised aryl halides are more accessible than functionalised arylboronic acids.

Introduction

Since Merrifield described his method of "solid phase" peptide synthesis in 1963,[1] innumerable organic compounds, both peptides and non-peptides, have been prepared by multi-stage syntheses where the organic substrate is covalently attached to crosslinked polystyrene beads,[2,3] especially recently in the context of combinatorial chemistry.[4–8] In the course of such work a great variety of *cleavable linking groups* has been developed. These allow the various polymer-supported (PS) syntheses to be carried out successfully on the beads, but then allow the final products to be detached cleanly and efficiently. It is, however, not always desirable to have a linking group of this general type. Indeed, for several other types of application a *readily formed non-cleavable linker* is desirable. Such linkers could, for example, be useful in the preparation of PS catalysts which are to be re-cycled many times,[9] used for extended periods in flow systems,[10] or used in membrane systems,[11] or could be useful in the preparation of PS reactants which are to be recycled repeatedly in achieving separations.[12] Ideally this different type of linker should meet the following criteria.

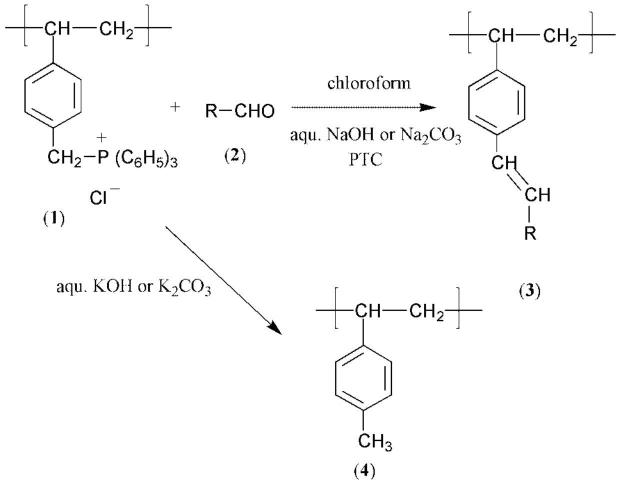
(i) The desired functional moieties are attached to the beads directly with a minimal recourse to functional group protection.

(ii) The attachment reactions proceed cleanly and in good yield.

(iii) The linkages formed are chemically very stable.

(iv) The attachment reactions do not leave in the beads any of the original functionalities used in the attachment reaction, or indeed any other functionalities which may interfere in subsequent reactions.

We have previously reported a method which meets most of these criteria. It involves phase transfer catalysed (PTC) Wittig reactions carried out between PS phosphonium residues **1**, readily available from chloromethylated polystyrene beads, and functional aldehydes **2**[13] (Scheme 1). Here the functional moiety becomes bound to the beads *via* an olefinic linkage, as in residues **3**. Carrying out the reaction under PTC conditions using sodium hydroxide or carbonate as the base, not only means that anhydrous conditions are not necessary, but also results in those phosphonium salt residues (**1**) which do not take part in the Wittig reaction being hydrolysed to methyl residues (**4**). The latter are unlikely to interfere in subsequent reactions on the beads. This linking method has been used successfully to prepare beads with, for example, triphenylphosphine,[13] thiophene,[13] ferrocene,[13] or crown ether[14] moieties. The catalytic properties of the supported crown ethers were investigated.[14]



R = triphenylphosphine-, thiophene-, ferrocene- or crown ether-containing moieties

Scheme 1

In the present paper we report a linking procedure which meets the above criteria more satisfactorily. It is based on the Suzuki reaction[15] and involves reactions between PS boronic acids **5** and functional aryl halides **6** (Scheme 2). The following features of this method are noteworthy.

(i) The Suzuki reaction is relatively tolerant of functional groups[15] so that protection of functional groups is generally not necessary.

(ii) The functional moieties become attached *via* aryl–aryl bonds: see residues **7**. These are clearly very stable linkages.

(iii) The "extra" aryl ring introduced serves as a small rigid spacer.

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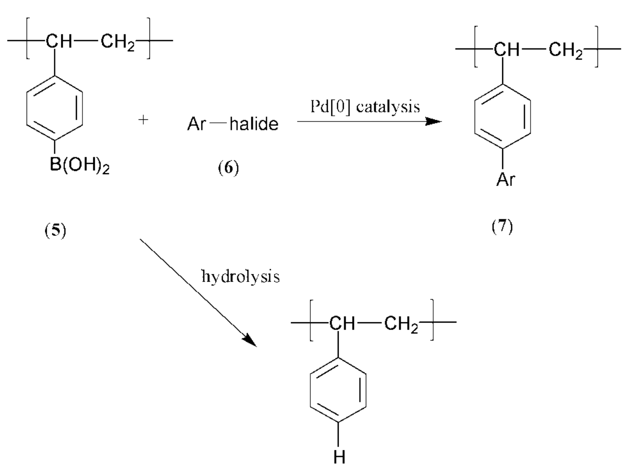


Scheme 2

(iv) Suzuki reactions tend to be accompanied by hydrolysis of the B–C bonds.[15–18] In the present case this removes unreacted boronic acid residues **5** from the beads and simply leaves unsubstituted phenyl residues.

Numerous Suzuki reactions involving *PS aryl halides* have been reported before. They generally involve a *p*-bromo- or iodo-benzoic acid derivative bound to polystyrene beads *via* ester[19,20] or amide linkages.[21–23] The present work is concerned with the reverse type of Suzuki reaction, *i.e.* those where the aryl halide is in solution and a *PS boronic acid* is used. Relatively few Suzuki reactions using this latter approach have been reported before.[19,21] It should be noted that using the polymer-supported boronic acid allows functionalised aryl halides to be attached whereas using the reverse type of Suzuki reaction requires functionalised arylboronic acids. Functionalised aryl halides are more readily accessible than functionalised arylboronic acids. It has been noted that Suzuki reactions using PS boronic acids tend to proceed more slowly than those involving PS aryl halides.[19] The optimum reaction conditions for the former type of reaction may, however, differ significantly from the optimum conditions for the latter. Thus, the polarity of the functionalities on the beads differs and hence the swelling properties will differ.[24] Also, some neighbouring boronic acid residues may condense to form, in effect, crosslinks. These will need to be cleaved to maximise access.[24]

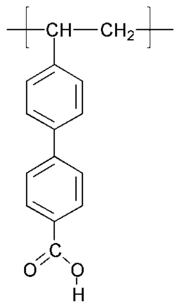
Results and discussion

Preparation of PS boronic acids 5

Polystyrene beads, 1% crosslinked, were brominated and then reacted with *n*-butyllithium to give, by a bromine–lithium exchange, lithiated polystyrene.[25] Reaction of the latter with trimethyl borate followed by hydrolysis gave beads bearing 1.90 mmol per g of boronic acid residues **5**.[25] By elemental analysis these beads no longer contained any of the original bromo groups, an important consideration when the beads are to be used in Suzuki reactions. In an alternative preparation, which avoids altogether the possibility of bromo groups being present in the beads, lithiated polystyrene beads were prepared directly from 1% crosslinked polystyrene by a hydrogen–lithium exchange.[25] Subsequent treatment of the lithiated polymer as before gave beads with 2.21 mmol per g of boronic acid residues. Using this approach the boronic acid residues are expected to be introduced partly *para* to the backbone and partly *meta*.[25,26] For simplicity derivatives synthesised from the boronic acid prepared in this way are simply shown as the *para* isomer.

Establishment of a standard Suzuki coupling procedure

Initially two types of Suzuki reactions, one involving a relatively π-poor aryl halide and one a relatively π-rich halide, were selected for study in some detail with a view to identifying reaction conditions that would allow the aryl halides to be coupled to the beads efficiently whilst at the same time leaving the final beads as free as possible of unreacted boronic acid residues **5**. One type of reaction studied was that using either 4-bromo- or iodo-benzoic acid as the aryl halide. This gave beads with residues **8**. The other type studied was that involving 2-bromo- or iodo-thiophene. This gave beads with residues **9**. In these initial experiments the effects of using either bromides or iodides, different excesses of these halides, and different base–solvent combinations were investigated. All the reactions used 5 mol% of tetrakis(triphenylphosphine)palladium as the catalyst. The results are summarised in Table 1.



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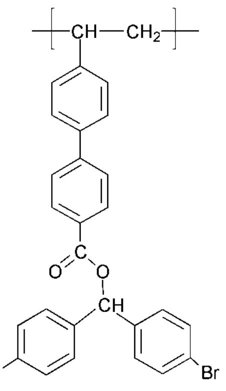

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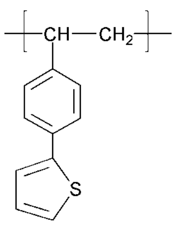

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The introduction of the carboxylic acid groups was easily detected by FT-IR spectroscopy. To estimate the content of residues **8** the beads were treated with 4,4′-dibromodiphenyldiazomethane.[27] This facile esterification, to give residues **10**, permits two methods of analysis. First, there is a measurable increase in the weight of the beads and secondly the content of bromo groups can be determined by elemental analysis. The two methods of analysis generally gave results that were reproducible and in good agreement. The contents of residues **9** were estimated by analyses for sulfur. For both types of coupling, the presence of unreacted boronic acid groups **5** was estimated by analysis for boron.

Several points from the results presented in Table 1 merit comment.

(i) In general neither the results obtained with the aryl bromides and iodides nor those obtained using a 10 or 100% excess of the aryl halides were very different: compare entries 1 and 3, 2 and 4, 6 and 10; and entries 1 and 2, and 3 and 4. Accordingly it was decided to use only aryl bromides in subsequent experiments, as these are usually more readily available than the iodides, and to use them in an excess of just 10%.

(ii) Sodium carbonate (2 M) in 1,2-dimethoxyethane was the best base–solvent combination of those investigated: compare entries 6–9. Accordingly this combination was used in all subsequent experiments.

(iii) Under the best conditions noted above, a reaction time of 24 h resulted in good coupling yields but the excess boronic acid residues **5** were not always completely removed, *i.e.* reduced below the limits of detection (*ca.* 0.05 mmol g^{-1}).

(iv) The observation noted in (iii) prompted the use of a longer reaction time. A reaction time of 72 h was considered to be appropriate. It is clear from entries 1 and 5, and 6 and 11 that this gave significantly better results, though sometimes (see below and Table 2), some boronic acid residues **5** still remained. Indeed in an experiment where no aryl halide was present (Table 1, entry 12), the boronic acid content of the beads fell only to 40% of the original value in 72 h.

(v) It was demonstrated (Table 1, entry 13 and several entries in Table 2) that when necessary the content of boronic acid

Table 1 Suzuki couplings of 4-halogenobenzoic acids or 2-halogenothiophenes with PS boronic acids **5** at 70 °C under various reaction conditions[a]

Entry	Boronic acid[b]	Initial DS[c] of boronic acid residues[b]	Aryl halide	Excess of Ar (%)	Reaction conditions[a]			Loading of Ar residues		Loading of boronic acid residues	
					Base[d]	Solvent[e]	Time/h	mmol g^{-1}[f]	DS[c]	mmol g^{-1}[g]	DS[c]
1	A	0.22	4-Bromobenzoic acid	10	SC	DME	24	1.31	0.16	0.08	0.01
2	A	0.22	4-Bromobenzoic acid	100	SC	DME	24	1.13	0.14	0.05	0.01
3	A	0.22	4-Iodobenzoic acid	10	SC	DME	24	1.04	0.13	0.20	0.02
4	A	0.22	4-Iodobenzoic acid	100	SC	DME	24	1.18	0.14	0.09	0.01
5	B	0.26	4-Bromobenzoic acid	10	SC	DME	72	1.37	0.17	<0.05	0.00
6	A	0.22	2-Bromothiophene	10	SC	DME	24	0.61	0.07	0.98	0.11
7	A	0.22	2-Bromothiophene	10	SC	DMF	24	0.23	0.03	1.10	0.12
8	A	0.22	2-Bromothiophene	10	TE	Tol	24	0	0	1.72	0.19
9	A	0.22	2-Bromothiophene	10	TE	DMF	24	0	0	1.69	0.19
10	A	0.22	2-Iodothiophene	10	SC	DME	24	0.52	0.06	0.63	0.07
11	B	0.26	2-Bromothiophene	10	SC	DME	72	1.53	0.18	0.25	0.03
12	A	0.22	None	—	SC	DME	72	—	—	0.78	0.08
13	A	0.22	Bromobenzene	500	SC	DME	72	—	—	<0.05	0.00

[a] See Experimental section for a typical reaction procedure. [b] "A" refers to the PS boronic acid **5** prepared *via* bromine–lithium exchange. It had 1.90 mmol g^{-1} of residues **5** corresponding to a degree of substitution of 0.22. "B" refers to the PS boronic acid **5** prepared *via* hydrogen–lithium exchange. It had 2.21 mmol g^{-1} of residues **5** corresponding to a DS of 0.26. [c] DS = degree of substitution. [d] SC = sodium carbonate; TE = triethylamine. [e] DME = 1,2-dimethoxyethane; DMF = *N*,*N*-dimethylformamide; Tol = toluene. [f] Determined as indicated in the text. [g] Determined by elemental analysis for boron.

Table 2 Attachment of various functional aryl bromides to polystyrene beads using Suzuki reactions[a]

Entry	Boronic acid[b]	Initial DS[c] of boronic acid residues[b]	Aryl bromide	Product	Loading of Ar		Yield of Suzuki coupling (%)[e]	Loading of boronic acid residues		Loading of boronic acid residues after "capping"	
					mmol g^{-1}[d]	DS[c]		mmol g^{-1}[f]	DS[c]	mmol g^{-1}[f]	DS[c]
1[g]	B	0.26	4-Bromobenzoic acid	**8**	1.37	0.17	65	<0.05	0.00	—	—
2	A	0.22	4-Bromobenzyl alcohol	**11**	1.51	0.19	86	0.01	0.00	—	—
3	B	0.26	4-Bromophenol	**12**	1.38	0.16	62	0.62	0.06	<0.05	0.00
4	A	0.22	6-Bromo-2-naphthol	**13**	1.34	0.18	81	<0.05	0.00	—	—
5	A	0.22	4-Bromobenzylamine	**14**	1.33[h]	0.16	73	0.01	0.00	—	—
6	A	0.22	4-Bromotriphenylphosphine	**15**	0.85[h]	0.11	50	0.60	0.08	<0.05	0.00
7	B	0.26	4-Bromobenzenesulfonamide	**16**	1.10[h]	0.14	54	0.03	<0.03	<0.09	<0.01
8[i]	B	0.26	2-Bromothiophene	**9**	1.53[h]	0.18	69	0.25	0.03	<0.09	<0.01
9	B	0.26	2-Bromofuran	**17**	0.46	0.06	23	0.20	0.02	—	—

[a] All reactions were carried out by treating the polymer beads bearing boronic acid residues **5** with a 10% excess of the aryl bromide and 2 M sodium carbonate in 1,2-dimethoxyethane at 70 °C for 72 hours. [b] See footnote *b* in Table 1. [c] DS = degree of substitution. [d] See text for methods of estimating the contents of functionalised aryl groups in the products. [e] DS of aryl residues as a percentage of the DS of the initial boronic acid residues. [f] By elemental analysis. [g] Reaction summarised in Table 1, entry 5. [h] Directly by elemental analysis for N, P or S on the Suzuki product. [i] Reaction summarised in Table 1, entry 11.

residues could be reduced to an insignificant level by simply retreating the beads with a 5-fold excess of bromobenzene under the standard Suzuki coupling conditions.

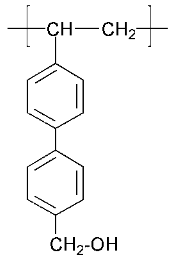
Reactions with other aryl bromides using the standard procedure

Since many catalysts contain alcohol, phenol, amine or phosphine groups, it was of interest to attempt Suzuki couplings with aryl bromides containing such groups using the standard reaction conditions established as described above. Accordingly, Suzuki reactions were carried out using 4-bromobenzyl alcohol, 4-bromophenol, 6-bromonaphthol, 4-bromobenzylamine and 4-bromotriphenylphosphine.[28] The results are summarised in Table 2, entries 2–6. The contents of the alcohol residues **11** and phenolic residues **12** and **13** in the products were estimated by esterification with thiophene-2-carbonyl chloride (entries 2 and 3) or 4-bromobenzoyl chloride (entry 4) followed by elemental analysis for sulfur or bromine as appropriate. The contents of the amine residues **14** and phosphine residues **15** were estimated by analyses for nitrogen and phosphorus respectively. It is evident that all the above moieties can be introduced in yields of 50% or more and that in four of the cases the final content of unreacted boronic acid residues in the beads was so low there was no need for "capping".

PS benzenesulfonamide residues have been used as "safety catch" linkers for reactive moieties attached through acyl groups.[29,30] By using *p*-bromobenzenesulfonamide as the aryl halide, residues **16** were introduced satisfactorily (Table 2, entry 7). The content of residues **16**, corresponding to a yield of 54%, was estimated by analysis for sulfur.

As discussed above, the coupling with 2-bromothiophene using the standard procedure afforded (Table 2, entry 8) beads containing 1.53 mmol g^{-1} of residues **9**, corresponding to a coupling yield of 69%. Residues **9** are of interest because it is known that the thiophene residues in closely related polymers are more reactive to electrophilic aromatic substitution[31] and are more easily metallated at the α-position than the phenyl residues in polystyrene.[32,33]

Finally the Suzuki coupling with 2-bromofuran[34] to give beads containing residues **17** was investigated. The latter were estimated by reaction with *N*-(4-bromophenyl)maleimide. The reaction is expected to give the Diels–Alder adduct residues **18**. Consistent with this the infrared spectrum of the beads showed a strong carbonyl band at 1717 cm^{-1}. Analysis for bromine



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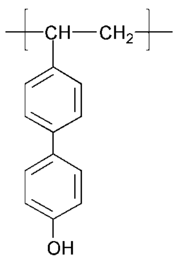

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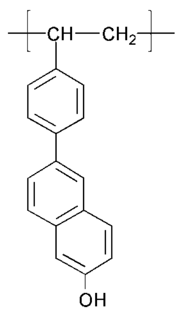

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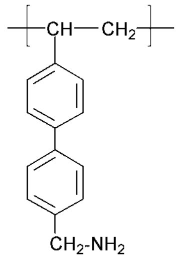

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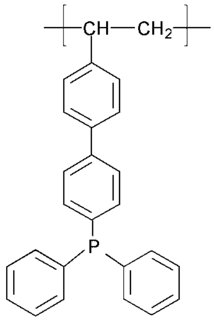

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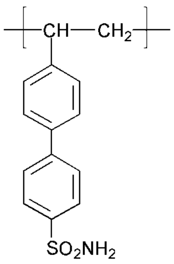
indicated that the loading of the adduct residues was 0.46 mmol g^{-1}, corresponding to an *overall* efficiency of only 23%. If the efficiency of the process could be improved, Diels–Alder reactions might provide a simple thermal method to attach groups to beads reversibly in the same manner that linear polymers containing pendant furan residues may be crosslinked by reaction with a bismaleimide and then the process reversed by treatment with an excess of 2-methylfuran.[35]



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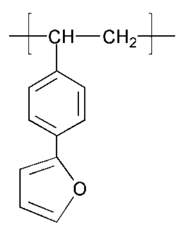

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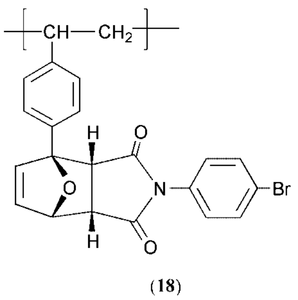

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Conclusions

It has been shown that aryl bromides containing carboxylic acid, alcohol, phenol, amine, triarylphosphine, sulfonamide, thiophene or furan moieties can be linked easily and directly to polystyrene beads containing boronic acid groups **5** by Suzuki reactions. In all cases except that with 2-bromofuran, the coupling yields were >50%. In several cases the boronic acid residues **5** that did not take part in the Suzuki reaction were simply lost by hydrolysis; in other cases the remaining residues could be removed easily by Suzuki reactions using an excess of bromobenzene. The reactions therefore provide an easy means for cleanly attaching a variety of functional moieties directly to polystyrene beads without the need for protecting groups. It should be noted that using the PS boronic acid allows functionalised aryl halides to be attached, whereas the reverse type of Suzuki reaction would require functionalised arylboronic acids. Functionalised aryl halides are more accessible than functionalised arylboronic acids. Future work will involve the preparation of various PS catalysts using the above approach and studies of their reactions.

Experimental

The polystyrene beads (1% crosslinked) were purchased from Phase Separations Ltd and before use were washed repeatedly and successively with (i) 1 M sodium hydroxide solution at 60 °C, (ii) 1 M hydrochloric acid at 60 °C, (iii) water at 60 °C, (iv) *N*,*N*-dimethylformamide at 40 °C, (v) 1 M hydrochloric acid at 60 °C, (vi) water at 60 °C, (vii) dichloromethane–methanol (3 : 1 v/v) at 40 °C, and (viii) dichloromethane at 20 °C. They were then dried to constant weight in a vacuum oven at 50 °C and 2 mmHg. Melting points were determined using a Gallenkamp Melting Point Apparatus and are uncorrected. Organic solutions were dried over magnesium sulfate. Solid samples were dried in a vacuum oven (20 mmHg) at 40 °C to constant weight. Infrared spectra were obtained with a Perkin Elmer 1710 Infrared Fourier Transform Spectrometer. Nuclear magnetic resonance spectra were obtained on a Unity Inova 300 (300 MHz) or Varian Unity 500 (500 MHz) machine. Elemental analyses for carbon, hydrogen, nitrogen and sulfur were carried out using a Carlo Erba 1108 elemental analyser. Halogen analyses were carried out by silver nitrate titration using a Metrolim 686 Titroprocessor. Boron analyses were made on a Horizon ICP Elemental Analyser.

Polystyrene beads with boronic acid residues 5 *via* bromination

(a) Bromination.[25] Thallium(III) acetate (1.20 g, 3.15 mmol) was agitated for 30 min with 1% crosslinked polystyrene beads (20.00 g, 192.3 mmol) suspended in carbon tetrachloride (300 ml) in a three-necked round-bottomed flask (500 ml) fitted with a condenser and protected from light with aluminium foil. Bromine (15.22 g, 95.2 mmol) in carbon tetrachloride (20 ml) was then added dropwise over 10 min at 20 °C. The reaction mixture was kept at this temperature for 1 h before the mixture was raised to reflux temperature. After 90 min at this temperature the evolution of hydrogen bromide had ceased and the bromine colour faded. The mixture was cooled and the beads filtered off and washed successively with carbon tetrachloride (200 ml), acetone (150 ml), benzene (150 ml), and methanol (150 ml), and then dried. The product (26.43 g) had, by elemental analysis, 25.7% Br, corresponding to 3.21 mmol g^{-1}.

(b) Lithiation *via* bromine–lithium exchange.[25] The brominated polystyrene beads (10.00 g), prepared as above, were swelled over 30 min in dry toluene (250 ml) in a three-necked round-bottomed flask (250 ml) fitted with a condenser, septum and nitrogen purge. *n*-Butyllithium (50 ml of 1.6 M solution in hexane, 80 mmol) was added using a syringe. The temperature of the reaction mixture was raised to 65 °C and held at that temperature for 5 h. The reaction mixture was then cooled to ambient temperature, the beads allowed to settle over 30 min and the liquor removed by syringe. The beads were washed in the flask three times with dry toluene (80 ml) and on each occasion the washings were removed by syringe.

(c) Reaction of lithiated beads with trimethyl borate.[25] The lithiated beads, prepared in (b) above, were treated with trimethyl borate (10.98 g, 105.7 mmol) in tetrahydrofuran (80 ml) and the mixture was stirred at ambient temperature for 18 h. The beads were then allowed to settle over 30 min and the liquor removed by syringe. To hydrolyse the boronate ester the beads were treated with dioxane–water–6 M hydrochloric acid (10 : 1 : 4 v/v; 100 ml) and the mixture was stirred for 2 h at 60 °C. The beads were collected by filtration and washed in a Soxhlet apparatus for 24 h successively with dioxane–water (1 : 1 v/v) and dioxane. The beads were dried. By elemental analysis the product (7.50 g) contained 0.00% Br and 2.05% B. The latter corresponds to 1.90 mmol g^{-1} of boronic acid residues **5** and a degree of substitution of 0.22.

Polystyrene beads with boronic acid residues 5 *via* direct lithiation

(a) Direct lithiation.[25] 1% Crosslinked polystyrene beads (28.00 g, 269.2 mmol) were swelled over 30 min in a mixture of dry cyclohexane (250 ml) and tetramethylethylenediamine (37.7 ml, 250 mmol) in a three-necked round-bottomed flask (250 ml) fitted with a condenser, septum and nitrogen purge. The mixture was then stirred and *n*-butyllithium (135 ml of 2.5 M solution in hexane, 338 mmol) was added using a syringe. The temperature of the reaction mixture (which became red) was raised slowly to 65 °C and held at that temperature for 5 h. The reaction mixture was then cooled to ambient temperature, the beads allowed to settle over 30 min and the liquor removed by syringe. The beads were washed in the flask three times with dry cyclohexane (80 ml) and on each occasion the washings were removed by syringe.

(b) Reaction of lithiated beads with trimethyl borate.[25] The lithiated beads, prepared in (a) above, were treated with trimethyl borate (27.45 g, 260.3 mmol) in tetrahydrofuran (80 ml) and the mixture was stirred at ambient temperature for 18 h. The beads were allowed to settle over 30 min and the liquor removed by syringe. The beads were then treated with dioxane–water–6 M hydrochloric acid (10 : 1 : 4 v/v; 100 ml) and the mixture stirred for 2 h at 60 °C. The beads were collected by filtration and washed in a Soxhlet apparatus for 24 h successively with dioxane–water (1 : 1 v/v) and dioxane. The beads were dried. By elemental analysis the product (26.50 g) contained 2.39% of B, corresponding to 2.21 mmol g^{-1} of boronic acid residues **5** and a degree of substitution of 0.26.

Standard procedure for Suzuki reactions

The following procedure is typical of that used for the Suzuki reactions summarised in Tables 1 and 2. The other reactions differed only either in the aryl halide, the excess of the aryl halide, the reaction solvent, the base and/or the reaction time used.

Table 1, entry 11: coupling of 2-bromothiophene. A mixture of polystyrene beads bearing boronic acid residues **5** (1.84 g, 4.06 mmol), 2-bromothiophene (0.77 g, 4.48 mmol), 2 M sodium carbonate (3.80 ml, 7.60 mmol) and 1,2-dimethoxyethane (25 ml) was stirred under argon for 15 min. Tetrakis(triphenylphosphine)palladium(0) (0.202 g, 0.175 mmol) was then added and the mixture stirred and heated at 70 °C for 72 h. At the end of this period the polymer beads were filtered off, washed successively on the filter with 1,2-dimethoxyethane (30 ml), 1,2-dimethoxyethane–water (30 ml, 1 : 1), hydrochloric acid (20 ml of 0.5 M) and finally 1,2-dimethoxyethane (10 ml). The beads were dried. The product had B = 0.27%, corresponding to 0.25 mmol of boronic acid residues per g, and S = 4.90%, corresponding to 1.53 mmol of thienyl residues **9** per g and a degree of substitution of 0.18.

Preparation of bis(4-bromophenyl)diazomethane

A solution of bis(4-bromophenyl)diazomethane was prepared and assayed by the method of Zimmerman and Cotter.[27]

Derivatisation of carboxylic residues 8 by reaction with 4,4′-dibromodiphenyldiazomethane

The following reaction is typical of the derivatisation reactions reported in Table 1, entries 1–5.

The reaction product (0.400 g, from the experiment summarised in Table 1, entry 2) was stirred gently with a solution of 4,4′-dibromodiphenyldiazomethane in dichloromethane (8 ml of assayed solution containing at least 0.37 g of the diazomethane) in a loosely-capped sample tube for 22 h. The purple colour faded slightly. The polymer beads were then filtered off, washed successively on the filter with dichloromethane (50 ml), ethanol–water (50 ml; 1 : 1 v/v), and methanol (50 ml). After drying the product (0.570 g) had ν_{max} 1725 cm^{-1} and by elemental analysis contained 17.4% of bromine, corresponding to a degree of substitution of 0.14. The increase in weight of the beads corresponds to there being 1.23 mmol of carboxylic acid groups per g of the starting material, and a degree of substitution of 0.13.

Estimation of alcohol residues 11 and phenolic residues 12 and 13

The following procedure is typical of those used to derivatize alcohol and phenolic residues (Table 2, entries 2–4).

Reaction summarised in Table 2, entry 3. A portion of the reaction product (0.75 g) from the Suzuki coupling was stirred gently at 70 °C with a solution of thiophene-2-carbonyl chloride (0.52 g) in pyridine (8 ml). After 20 h the beads were filtered off and washed successively with water–tetrahydrofuran (15 ml; 2 : 1 v/v), water (15 ml), tetrahydrofuran (15 ml) and methanol (15 ml). The dry beads (0.95 g) had ν_{max} 1731 cm^{-1}. By elemental analysis they contained 3.39% sulfur corresponding to a degree of substitution of 0.16.

"Capping" of the excess of boronic acid residues 5

The functionalised beads were treated with an excess of bromobenzene (5 × the number of mmol of the aryl halide used in the initial coupling) using the standard Suzuki coupling procedure described above. The beads were recovered as before and the boron content determined by elemental analysis. The results of these experiments are presented in Table 2.

Preparation of 4-bromotriphenylphosphine

This compound, prepared as described by Schiemenz,[28] had mp 62–64 °C (lit.,[28] 64–71 °C), and satisfactory FT-IR and ^{1}H NMR spectroscopic data.

Preparation of 2-bromofuran

This compound was prepared as described by Clennan and Mehrsheikh-Mohammadi.[34] It had bp 87–93 °C/740 mmHg (lit.,[34] 92–93 °C/580 mmHg), and δ (300 MHz; $CDCl_3$) 7.46 (1H; dd, J 2.0 and 0.9 Hz; H-5), 6.42 (1H; dd, J 3.3 and 2.0 Hz; H-4) and 6.34 ppm (1H; dd, J 3.3 and 0.9 Hz; H-3).

Reaction of beads containing residues 17 with *N*-(4-bromophenyl)-maleimide

The polymer beads containing residues **17** (0.50 g), *N*-(4-bromophenyl)maleimide (2.78 g, 11.1 mmol) and toluene (10 ml) were placed in a flask and reacted together under reflux for 48 h. The reaction mixture was then cooled down and the beads filtered off and washed successively with dichloromethane (20 ml), 1,2-dimethoxyethane (20 ml), ethyl acetate (20 ml) and methanol (20 ml) and dried. This gave beads (0.50 g) which had ν_{max} 1717 cm^{-1} (strong) and, by elemental analysis, contained 3.67% bromine. This corresponds to an original content of residues **17** of at least 0.46 mmol g^{-1} and a degree of substitution of at least 0.06.

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