Organic & Biomolecular Chemistry

PAPER

Polymer-supported syntheses of thiophene-containing compounds using a new type of traceless linker

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A new type of traceless linker is described for use in polymer-supported (PS) syntheses of thiophene-containing compounds. It is based on the cleavage of PS aryl 2-thienyl ketones by a mixture of potassium *t*-butoxide and water (typical mol ratio 10 : 3) in an ethereal solvent. Cleavage occurs to give the soluble thiophene-containing product. The method is used to prepare a range of eight thiophene-containing compounds including a terthiophene and a dialkylquaterthiophene. PS unsymmetrical diaryl ketones incorporating, for example, *ortho*-methoxyphenyl or pyrrole moieties could also serve as traceless linkers.

Introduction

Polymer-supported (PS) organic syntheses, that is PS syntheses other than those of natural oligomers or polymers, have been of great interest since the 1970s.[1–3] An important strategy with many of these syntheses is the use of traceless linkers.[4–6] With traceless linkers, when the target molecule is released from the support, the site by which it was originally attached to the support is not apparent. This can be achieved, for example, by the site of attachment on the target molecule being transformed into a C–H bond,[4,7–13] or by a combined cyclization-cleavage reaction.[4,14–19]
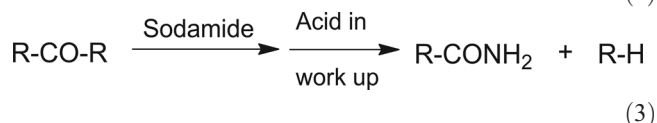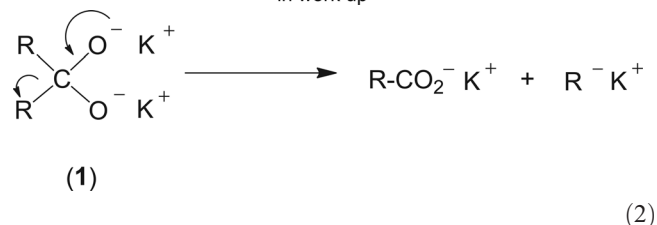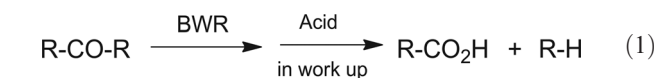
Small molecules or oligomers with conjugated π-electron systems are of interest because of their potential applications in molecular electronics.[7–9,10,13,20–30] They can also serve as valuable models for the corresponding polymers.[30,31] The purity of such compounds is often an issue, but their purification can be difficult. Because using insoluble supports in syntheses can assist with the purification of the products, this has prompted the investigation of PS syntheses of small molecules or oligomers with conjugated π-electron systems.[7–9,10,13,20–25] Some of these syntheses have used conventional linkers, such as ester linkages,[22,25] whilst others have used traceless linkers,[7–13] such as silicon-based,[7–9] germanium-based,[10,13] bismuth-based[32] or activated-sulfonate linkers.[11,12] The target products from many of these syntheses are oligothiophenes with unsubstituted and/or 3-substituted aromatic units.[7–10,13,21,22,25,28,29] Oligothiophenes have recently also found application as fluorescent ligands for the detection of protein aggregates and a library of oligothiophenes has been prepared.[33]

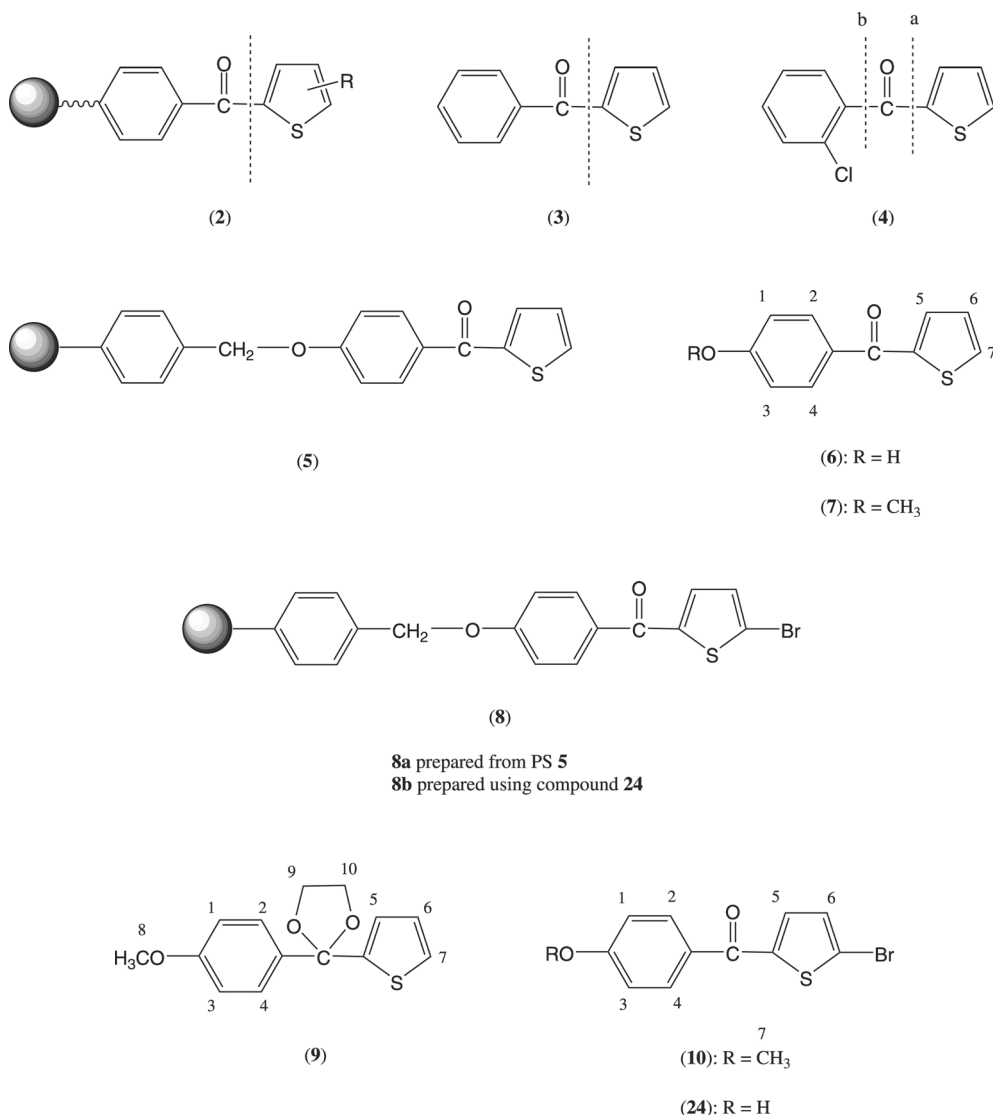We now report a new type of traceless linker, a linker that can be used for the synthesis of molecules containing thiophene moieties. We exemplify its use by the synthesis of a range of eight thiophene-containing compounds with conjugated π-electron systems.

Results and Discussion

The present traceless linker is based on the cleavage of non-enolizable ketones, see Reaction 1, by treatment with the *heterogeneous* mixture formed by adding small amounts of water to potassium *t*-butoxide (typical mol ratio 3 : 10) in an ethereal solvent such as 1,2-dimethoxyethane or tetrahydrofuran (THF): the so-called butoxide–water reagent (BWR).[34–36] It is believed that in these reactions initially the carbonyl group of the ketone is attacked by the hydroxide anion and then the tetrahedral intermediate formed is deprotonated by *t*-butoxide to give dianion **1**.[35] The latter cleaves to give a carboxylate anion and a carbanion: Reaction 2.[35] This cleavage reaction is clearly closely related to the classical Haller–Bauer reaction which typically uses a suspension of sodamide in a high boiling hydrocarbon solvent to cleave non-enolizable ketones: Reaction 3.[37] The BWR cleaves diaryl ketones cleanly and in high yields under much milder conditions.

$$R\text{-CO-}R \xrightarrow{\text{BWR}} \xrightarrow[\text{in work up}]{\text{Acid}} R\text{-CO}_2H \ + \ R\text{-H} \quad (1)$$

$$\begin{array}{c} R \\ R \end{array} C \begin{array}{c} O^- \ K^+ \\ O^- \ K^+ \end{array} \longrightarrow R\text{-CO}_2^- \ K^+ \ + \ R^- \ K^+$$

(1)

$$\quad (2)$$

$$R\text{-CO-}R \xrightarrow{\text{Sodamide}} \xrightarrow[\text{work up}]{\text{Acid in}} R\text{-CONH}_2 \ + \ R\text{-H}$$

$$\quad (3)$$

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(2)

(3)

(4)

(5)

(6): R = H

(7): R = CH₃

(8)

8a prepared from PS **5**
8b prepared using compound **24**

(9)

(10): R = CH₃

(24): R = H

The cleavage of unsymmetrical diaryl ketones is a key part of the present work. They can cleave in two directions, the favoured direction being that which produces the most stable aryl carbanion and/or relieves steric congestion resulting from the presence of an *ortho*-substitutent.[35] The unsymmetrical ketones of interest in the present work are PS aryl 2-thienyl ketones **2** and these must cleave mainly, if not entirely, at the bond neighbouring the 2-thienyl moiety as shown in **2**. Two results from previous work indicate that this will be the case.[38,39] First, 2-benzoylthiophene (**3**), when treated with the BWR in ether at 21 °C for 5 min, cleaves in high yield and gives benzoic acid as the only isolated acid, *i.e.* cleavage occurs exclusively as shown in **3**.[38] Second, ketone **4** cleaves 90% at 'a' and 10% at 'b'.[38] This latter result is of particular interest because in most cases 2-chlorophenyl aryl ketones cleave almost entirely at the bond neighbouring the 2-chlorophenyl moiety. Indeed, 2-chlorobenzoylation followed by cleavage using the BWR is a convenient method to introduce carboxylic acid groups into aromatic compounds.[39] The result with ketone **4** indicates that the 2-thienyl group promotes cleavage of the neighbouring bond even more effectively than the 2-chlorophenyl group.

Initially in the present work aryl 2-thienyl ketone moieties (**5**) were created on 1% crosslinked polystyrene beads by reacting chloromethylated beads with 4-hydroxyphenyl 2-thienyl ketone (**6**), potassium carbonate and potassium iodide in *N*-methylpyrrolidone (NMP) at 140 °C for 48 h. The required phenol **6** was readily obtained by demethylating the commercially available ketone **7**. The loading of moieties **5**, as estimated by the weight gain, was 2.14 mmol g⁻¹. Cleavage of ketone **7** gave 4-methoxybenzoic acid in an isolated yield of >95%, so indicating that the presence of the 4-alkoxy group does not significantly affect the direction of cleavage.[35]

As it was intended to elaborate the 2-thienyl moiety of PS **5** using Suzuki couplings, it was necessary to introduce a 5-bromo substituent into the thiophene ring, *i.e.* prepare PS **8**. Model reactions were carried out to help to identify a suitable bromination procedure. Initially an attempt was made to *selectively* and efficiently brominate ketone **7** with one equivalent of *N*-bromosuccinimide (NBS) in dry *N,N*-dimethylformamide (DMF) at 153 °C. This was not successful: a mixture of products was obtained. Compound **7** was therefore treated with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic
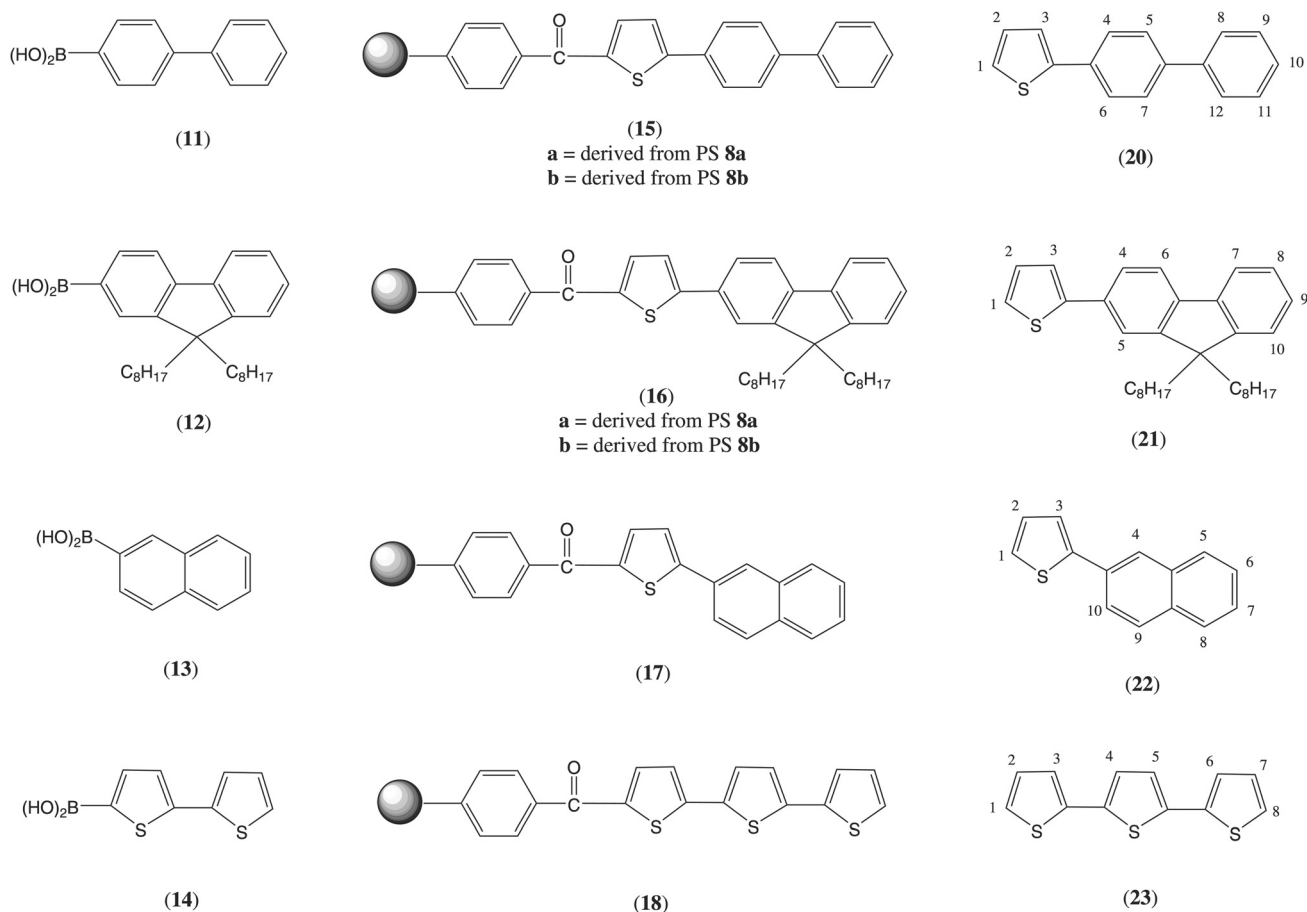
(11)

(15)
a = derived from PS **8a**
b = derived from PS **8b**

(20)

(12)

(16)
a = derived from PS **8a**
b = derived from PS **8b**

(21)

(13)

(17)

(22)

(14)

(18)

(23)

Chart 1

Table 1 Summary of PS syntheses of thiophenes **20–23**, **29** and **30**[a]

Entry	PS Linker after purification	Suzuki reactions			Cleavage reactions		
		Boronic acid	Product	Yield	Crude Yield	Yield	Product
1	**8a**	**11**	**15a**	80%	78%	65%	**20**
2	**8a**	**12**	**16a**	89%	59%	—	**21**
3	**8a**	**13**	**17**	86%	79%	67%	**22**
4	**8a**	**14**	**18**	86%	81%	72%	**23**
5	**8b**	**11**	**15b**	81%	92%	74%	**20**
6	**8b**	**12**	**16b**	79%	79%	—	**21**
7	**8b**	**25**	**27**	71%	96%	88%	**29**
8	**8b**	**26**[b]	**28**	83%	84%	—	**30**

[a] Full details of the reaction conditions are given in the Experimental Section. [b] Compound **26** is a boronate ester.

acid (PTSA) in refluxing toluene to give the ketal **9** (93% isolated yield). Bromination of the latter with NBS in dry DMF followed by deketalization gave the desired bromo compound **10** in an isolated yield of 90%. Repetition of the reactions with the PS ketone **5** gave PS **8a** in an overall yield of 74%, as estimated by weight changes and elemental analyses for S and Br. The loading of residues **8** was 1.59 mmol g^{-1}. It is labeled **8a** to distinguish it from a similar sample of PS **8** prepared by another route which is described below.

To elaborate PS **8a** prior to cleavage it was treated separately with boronic acids **11** to **14** in THF and potassium carbonate in the presence of tetrakis(triphenylphosphine)palladium(0) at 60 °C for 72 h: see Chart 1. As judged by weight gains the Suzuki couplings occurred to give PS **15** to **18** in yields of 80 to 89%: see Table 1 entries 1 to 4.

Cleavage of the target molecules from the support is complicated by the fact that both the BWR and PS reactions are heterogeneous. This has been negotiated successfully before in a
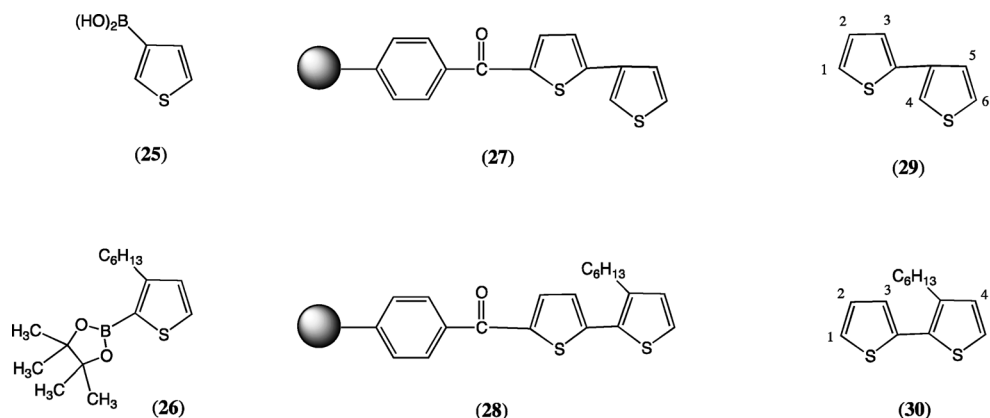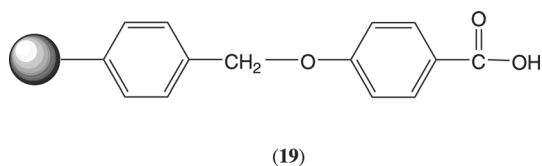
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Chart 2

procedure for introducing carboxylic acid groups into cross-linked polystyrene beads.[40] In this the beads were first 2-chlorobenzoylated in a Friedel–Crafts reaction then the unsymmetrical diaryl ketone moieties were cleaved by treatment with the BWR generated *in situ* in the beads. The latter was achieved by treating the acylated beads with a solution of potassium *t*-butoxide in 1,2-dimethoxyethane for 1 h, then the appropriate amount of water was added to the bead suspension. As the water diffused into the beads the heterogeneous BWR was formed within the beads. Cleavage was then achieved by allowing the PS acyl groups to react with the BWR at 85 °C for 4–10 h. Cleavage yields were essentially quantitative though with the more highly loaded beads it was sometimes necessary to retreat the beads with the BWR. In an extension of this earlier work it was found that under very similar reaction conditions the cleavage yield, based on elemental analyses for chlorine, was 75% in 8h, and >90% in 24 h.[41] In the present work the reaction time was standardised at 72 h simply in order to obtain maximum yields in all cases. Applying these conditions to the cleavage of PS **5** gave polymer beads containing 0.15% of sulfur. This corresponds to a cleavage yield of 97% to give PS **19**.

and 2 and Table 1 entries 5 to 8. Cleavage in the usual manner gave products **20**, **21**, **29** and **30** in 79–96% yields. It is evident that PS **8a** and PS **8b** behave similarly.

In the final part of the project compounds, **31** and **32**, each containing four conjugated aromatic rings, were prepared using the new linker PS **33**. The latter was prepared using standard reactions as outlined in Scheme 1. Thus, 2-bromo-3-hexylthiophene (**34**)[42] was treated with 4-methoxybenzoyl chloride under Friedel–Crafts conditions to give diaryl ketone **35**. Demethylation of this gave compound **36**. Reaction of compound **36** with chloromethylated 1% crosslinked polystyrene beads, potassium carbonate and potassium iodide in NMP at 140 °C for 2 days gave PS **33**. From the gain in weight and elemental analyses for bromine and sulfur the beads contained 1.86 mmol g^{-1} of residues **33**.

PS **33** was reacted in a Suzuki reaction with biphenyl-4-boronic acid (**11**) to give PS **37**: see Scheme 2. This was brominated by treatment with NBS in DMF to give PS **38**. Though it was possible that PS **37** could brominate at more than one site, the ^{1}H NMR spectrum of the final soluble product indicated that

(19)

Cleavage of PS **15** to **18** using the standard conditions gave products **20** to **23**, see Chart 1, in crude yields of 59–81% and, in most cases, in yields of 65% to 72% after recrystallisation. The products were identified by ^{1}H NMR spectroscopy and melting point or elemental analyses.
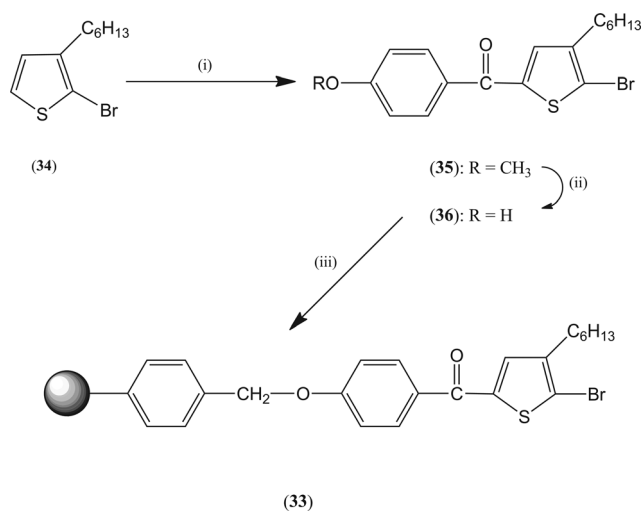
In an alternative and shorter procedure to obtain PS **8**, ether **10** was demethylated to give phenol **24** and the latter was directly attached to the chloromethylated 1% crosslinked polystyrene beads to give PS **8b**. Based on the gain in weight of the beads and elemental analyses for S and Br, the loading of residues **8** was 1.89 mmol g^{-1}, *i.e.* slightly higher than in PS **8a**.

Using PS **8b** Suzuki reactions were carried out as before with boronic acids **11**, **12**, and also with **25** and boronate **26**,[42,43] to give PS ketones **15b**, **16b**, **27** and **28** respectively: see Charts 1

Scheme 1 (i) 4-Methoxybenzoyl chloride/SnCl$_4$/dichloromethane, 59% yield. (ii) BBr$_3$ in dichloromethane, 93% yield. (iii) Potassium carbonate/potassium iodide/NMP.

Boronic acid **11** + **PS 33**

Boronic acid **14** + **PS 33**
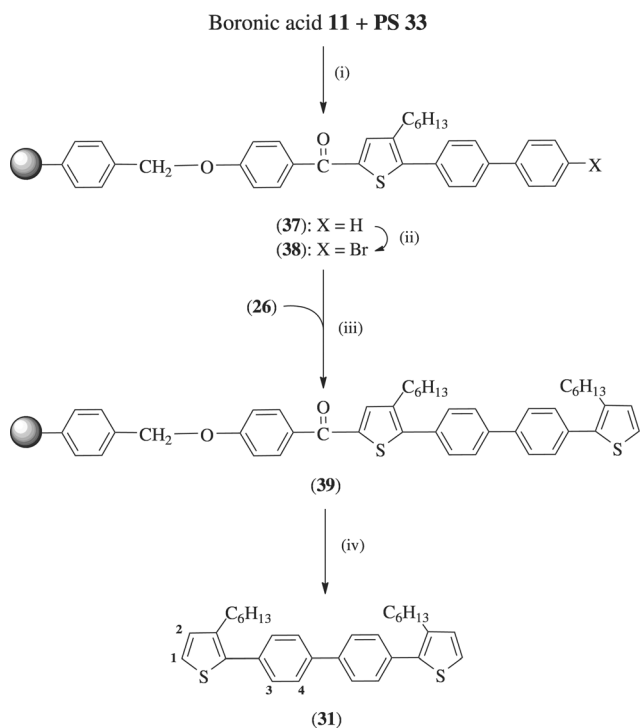
Scheme 2 (i) Suzuki coupling, 83% yield. (ii) Bromination, 85% yield. (iii) Suzuki coupling, 94% yield. (iv) Cleavage with BWR, 68% yield.

Scheme 3 (i) Suzuki coupling, 61% yield. (ii) Bromination, 90% yield. (iii) Suzuki coupling, 87% yield. (iv) Cleavage with BWR, 54% yield.

the main bromination product was PS **38**. As judged by elemental analyses the bromination yield was 85%. PS **38** was then reacted with boronate ester **26** in a further Suzuki reaction to give PS **40** in 94% yield. Cleavage from the support in the usual way gave, after column chromatography, compound **31** in 68% yield. The final product was characterized by ^{1}H NMR spectroscopy, mass spectroscopy and elemental analyses.
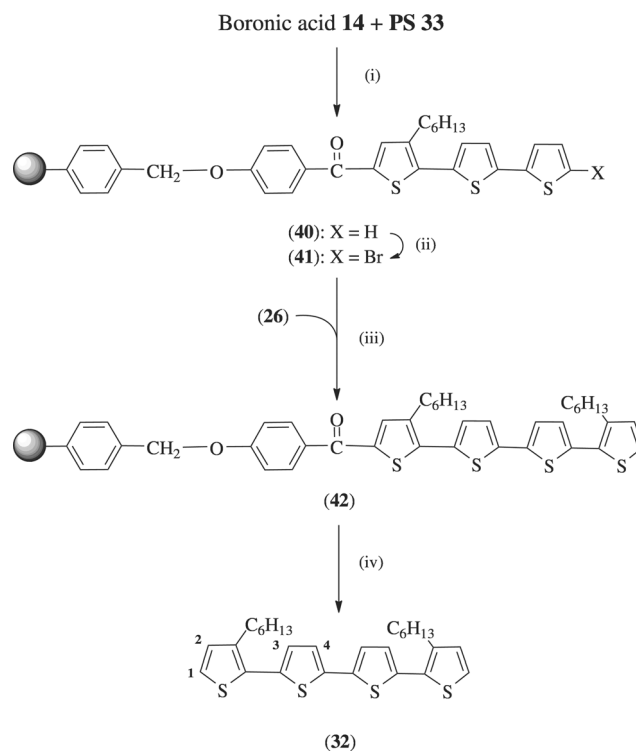
Using similar procedures, but replacing boronic acid **11** with boronic acid **14**, PS **33** was converted, *via* PS **41** and **42** into PS **43**: see Scheme 3. The bromination yield was 90%. Cleavage of PS **43** gave compound **32**[44] in 54% yield after column chromatography. It was characterized by melting point, ^{1}H NMR spectroscopy, mass spectroscopy and elemental analyses.

Conclusions

Thiophene-containing compounds **20–23** and **29–32** have been prepared successfully using PS reactions including a traceless linker based on Reaction 1. In each synthesis the key step is cleavage of an aryl 2-thienyl ketone, using the BWR, to give the thiophene-containing compound in solution. Previous work suggests that PS unsymmetrical diaryl ketones bearing, for example, *ortho*-methoxy,[35] *ortho*-chloro,[35,39] pyrrole,[45] and possibly furan or pyridine moieties could also function successfully as traceless linkers.

Experimental Section

All reagents, solvents and chromatographic materials were obtained from Sigma-Aldrich Co. The chemicals were of the highest purity available and were used as received. The

chloromethylated polystyrene beads were 1% crosslinked, of 200–400 mesh, with 4.11 mmol of chloromethyl groups per gram. Solids were generally dried overnight in a vacuum oven using a pressure of approximately 1 mm of Hg and a temperature of 60 °C except that in the case of low-melting solids drying was achieved at ambient temperature. Organic solutions were dried over magnesium sulfate. Column chromatography used silica gel as the stationary phase.

Melting points (Mps) were recorded using a Gallenkamp Hot Stage Melting Point Apparatus. Infrared (IR) absorption spectra were measured on an ATI Mattson Genesis series Fourier Transform Infrared (FTIR) spectrometer. UV-Vis measurements were obtained on a Varian Cary 5000 UV-vis-NIR spectrometer. ^{1}H NMR Spectra were recorded on either a Varian Inova 300 or a Bruker AMX 500 spectrometer. Chemical shifts (δ) are quoted in units of parts per million (ppm). Tetramethylsilane (TMS) was used as internal reference. The quoted splitting patterns are abbreviated to singlet (s), doublet (d), triplet (t), multiplet (m) and broad (b). Coupling constants (J) are reported in Hertz. Assignments, when they can be made with confidence, are identified using the numbers shown on the respective formulae. All mass spectra (MS) are EI/CI spectra and were obtained using a VG Trio-2000 instrument. For the CI spectra the reagent gas was ammonia. All elemental analyses were obtained in house. C and H analyses were made using a Carlo Erba Instruments EA1108 Elemental Analyser.

Demethylation of ketone 7. Sodium thiomethoxide (2.95 g, 42.1 mmol) was added to ketone **7** (3.00 g, 13.8 mmol) in DMF (40 mL). The mixture was stirred under nitrogen and heated

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under reflux for 10 h, then cooled to 20 °C. Aqueous phosphoric acid (70 mL of 10%) was added and the mixture extracted with ethyl acetate (4 × 25 mL). The combined extracts were washed with aqueous silver nitrate (0.5 N, 2 × 25 mL) and water (2 × 25 mL) then dried. The solvent was evaporated and the residue subjected to column chromatography. Elution with chloroform gave phenol **6** (2.64 g, 94%). It had Mp 116–117 °C (lit.,[46] 116 °C); IR (cast film, cm^{-1}) 1620; ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.83 (2H; m; H-2 and 4), 7.68 (1H; m; H-7), 7.64 (1H; m; H-5), 7.14 (1H; m; H-6), 6.93 (2H; m; H-1 and 3), 6.84 (1H; bs; OH).

General procedure for attaching phenols to chloromethylated polystyrene beads: attachment of phenol 6 to give PS 5. Chloromethylated 1% crosslinked polystyrene beads (3.650 g, 15.0 mmol of chloromethyl groups) were added to a mixture of phenol **6** (3.33 g, 16.3 mmol), anhydrous potassium carbonate (1.23 g, 9.0 mmol) and potassium iodide (0.99 g, 6.0 mmol) in NMP (30 mL) under nitrogen. The suspension was stirred and heated at 140 °C for 48 h. It was then cooled to 20 °C, the beads filtered off and washed successively with NMP (2 × 25 mL), water (3 × 25 mL) and acetone (2 × 25 mL) before being dried to give PS **5** (5.691 g). The weight gain (2.041 g) corresponds to 12.2 mmol of thiophene derivative **5** (81% yield), equal to 2.14 mmol of residues **5** per g. It had IR (KBr disc, cm^{-1}) 1629; microanalysis: found sulfur 7.21%: this corresponds to a loading of 2.25 mmol of thiophene derivative **5** per g.

Synthesis of bromo compound 10. *i*) *Direct bromination of compound 7*: Compound **7** (1.50 g, 6.88 mmol) was dissolved in DMF (20 mL) at 50 °C. NBS (1.23 g, 6.87 mmol) was added slowly to the stirred solution and the mixture was heated under reflux for 12 h. A solution of aqueous tartaric acid (10 g of acid in 25 mL of water) was then added and the mixture stirred at 60 °C for 4 h. The resulting hot solution was filtered and the filter cake washed with dichloromethane (50 mL). The combined filtrates were evaporated to dryness under reduced pressure. The residue was shown by thin layer chromatography to contain three major components. The ^{1}H NMR spectrum indicated that the sample contained several components.

ii) *Via cyclic ketal 9*: *a*) *Synthesis of ketal 9*: A mixture of ketone (**7**) (1.74 g, 8.00 mmol), 1,2-ethanediol (0.74 g, 12 mmol), PTSA (80 mg) and toluene (25 mL) was heated under reflux in a flask equipped with a Dean–Stark apparatus. After 12 h no more water was produced so the reaction mixture was cooled then evaporated to dryness under vacuum. The residue was purified by column chromatography. Elution with a mixture of hexane and ethyl acetate (4 vo 1 : 1 vol) gave the cyclic ketal **9** (1.94 g, 93% yield). It had Mp 65–67 °C; IR (film, cm^{-1}) 2958, 1603; ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.95 (2H; m), 7.82 (2H; m), 7.37 (1H; m; H-7), 6.96 (2H; m; H-1 and 3), 4.50 (2H; m; H-9 or 10), 4.38 (2H; m; H-9 or 10) and 3.85 (3H; s; H-8); MS (EI) *m/z* (%): 262 (82), [M$^+$]; microanalyses: calc: for C$_{14}$H$_{14}$O$_3$S C, 64.11%, H, 5.38%, S, 12.20%; found: C, 63.88%, H, 5.27%, S, 12.10%.

b) *Bromination of ketal 9 followed by cleavage of the acetal*: Following the procedure described above for compound **7**, ketal **9** (1.00 g, 3.81 mmol) in DMF (20 mL) was brominated using NBS (0.680 g, 3.83 mmol). The procedure also caused the ketal

moieties to hydrolyze. The crude product was purified by column chromatography. Elution with a mixture of hexane and ethyl acetate (4 vo 1 : 1 vol) gave bromo compound **10** (1.02 g, 90%). It had Mp 104–105 °C (lit.,[46] 103 °C); IR (film, cm^{-1}) 1616; ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.94 (2H; m; H-2 and 4), 7.61 (1H; m: H-5), 7.39 (1H; m; H-6), 7.03 (2H; m; H-1 and 3), 3.93 (3H; s; H-7); MS (EI) *m/z* (%): 296 (70) and 298 (74), [M$^+$].

Bromination of PS-thiophene 5. (*i*) *Ketal formation*: A mixture of PS-thiophene **5** (7.500 g, 16.1 mmol of thiophene residues), ethylene glycol (50 mL), PTSA (0.10 g) and toluene (30 mL), in a flask equipped with a Dean–Stark apparatus, was heated and stirred under gentle reflux. After 12 h no more water was produced, so the resin beads were filtered off, washed copiously with dry THF, then dried. This gave the PS-ketal (8.150 g). The IR (KBr disc) showed only a small band at 1625 cm^{-1} in the carbonyl region. The weight gain (0.650 g) corresponds to a yield of 92%, and 1.81 mmol of the ketal per g.

(*ii*) *Bromination followed by deketalization*: NBS (2.30 g, 12.8 mmol) was added to a stirred mixture of the PS-acetal (8.000 g) in dry DMF (60 mL) at 20 °C under nitrogen and then the suspension was heated at 90 °C for 72 h. Aqueous tartaric acid (20 g in 30 mL) was added *via* a dropping funnel, and the reaction was continued under the same conditions for another 10 h. Finally the solids were collected by filtration and washed successively with DMF (3 × 25 mL), water (3 × 25 mL) and acetone (3 × 25 mL) before being dried. This gave PS **8** (8.460 g). The weight gain (460 mg) corresponds to 12.77 mmol of bromothiophene derivative, equal to 1.56 mmol of bromothiophene residues per g. It had IR (KBr disc, cm^{-1}) 1632; elemental analyses gave bromine 12.72% and sulfur 6.34%. The bromine content corresponds to a loading of 1.59 mmol of PS **8** per g: the sulfur to a loading of 1.98 mmol of thiophene residues per g. This corresponds to a bromination yield of 80%. The product is labeled PS **8a** to distinguish it from PS **8** prepared by another route (see PS **8b** below).

General Suzuki coupling procedure: coupling of boronic acid 11 to the PS 8a. The results of this experiment are summarized in Table 1, entry 1. PS **8a** (1.500 g, 2.39 mmol) and 4-biphenyl-boronic acid (**11**) (0.590 g, 3.00 mmol) were charged into a round-bottomed flask and flushed with nitrogen for 1 h prior to successive additions, *via* a syringe, of degassed THF (20.0 mL), tetrakis(triphenylphosphine)palladium(0) (0.209 g, 0.180 mmol) in degassed THF (4.0 mL) and aqueous potassium carbonate (2.0 M, 8.48 mL, 17 mmol). The reaction mixture was stirred at 60 °C for 72 h, then it was cooled and the beads collected by filtration. They were washed successively with THF (3 × 25 mL), water (3 × 25 mL) and acetone (3 × 25 mL), then dried. This gave PS **15a** (1.640 g). It is labeled PS **15a** to distinguish it from a sample of PS **15** prepared by another route (see PS **15b** below). The weight gain (140 mg) corresponds to 1.91 mmol (80% yield) of residues **15**, equal to 1.17 mmol per gram. It had IR (KBr disc, cm^{-1}) 1627. Elemental analysis for bromine gave 0.18% (2.1% recovered).

Suzuki couplings of boronic acids 12–14 to PS 8a. These were carried out on the same scale (1.500 g, 2.39 mmol, of PS **8a**) and using the same procedure given above. This gave PS **16a**,

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17 and 18 respectively. The results are summarized in Table 1, entries 2–4 respectively.

Entry 2: PS **8a** gave PS **16a** (2.160 g). The weight gain (660 mg), corresponds to 2.13 mmol of thiophene-containing residues (89% yield), equal to 0.99 mmol per g. It had IR (KBr disc, cm^{-1}) 1630. Elemental analysis gave bromine 0.14% (1.6% recovered).

Entry 3: PS **8a** gave PS **17** (1.596 g). The weight gain (96 mg) corresponds to 2.04 mmol of naphthalene-containing residues (86% yield), equal to 1.28 mmol of derivative per g. It had IR (KBr disc, cm^{-1}) 1633. Elemental analysis gave bromine 0.22% (2.5% recovered).

Entry 4: PS **8a** gave PS **18** (1.670 g). The weight gain (174 mg) corresponds to 2.05 mmol of the dithienyl-containing derivative (86% yield), equal to 1.23 mmol per gram of resin. It had IR (KBr disc, cm^{-1}) 1632. Elemental analysis gave bromine 0.13% (2.5% recovered).

General cleavage procedure:.[40] Cleavage of the PS 5 to give PS 19. PS **5** (1.000 g, 2.14 mmol) was added to a stirred solution of potassium *t*-butoxide (2.01 g, 17.9 mmol) in THF (10 mL) at 20 °C under nitrogen. Stirring was continued for 1 h to allow the alkoxide to diffuse into the beads, then water (0.09 mL, 5.0 mmol) was added. The resulting heterogeneous mixture was stirred and heated under reflux. After 72 h the mixture was cooled, the beads filtered off and washed successively with dichloromethane (2 × 100 mL), hydrochloric acid (10 mL of 2 N) in THF (25 mL), water (2 × 100 mL) and acetone (2 × 50 mL) then dried. This gave PS **19** (0.903 g): a weight loss of 97 mg. It had IR (KBr disc, cm^{-1}) 1730, 1683. Elemental analysis indicated 0.15% of sulfur (2.3% recovered).

Cleavages of the PS 15a, 16a, 17 and 18. These were carried out on the same scale and using the same procedure as given above. This gave **20**, **21**, **22** and **23** respectively. The results are summarized in Table 1, entries 1–4 respectively.

Entry 1, *cleavage of PS 15a*. PS **15a** (1.000 g, 1.17 mmol) gave polymer beads (0.781 g), a weight loss of 219 mg. The organic washings were combined, dried and the solvent evaporated off. The residue in dichloromethane (2.0 mL) was chromatographed over a short column of silica gel. Elution with dichloromethane gave a fraction (215 mg, crude yield 78%) that from the ^{1}H NMR spectrum was mainly (>95%) compound **20**. Recrystallization from hexane gave a sample of compound **20** (180 mg, 0.762 mmol, 65% yield) with Mp 171–173 °C (lit.,[47] 172 °C); ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.63 (m, 2 H), 7.54 (2H; m), 7.39–7.36 (5H; m), 7.29 (1H; m), 7.28 (1H; m), 7.03 (1H; m); MS (CI): *m/z*: 237 (100), [MH$^+$].

Entry 2, *cleavage of PS 16a*. The cleavage gave beads (0.640 g), a weight loss of 0.360 g. Chromatography of the organic extracts gave compound **21** as a colourless oil[48] (274 mg, 0.581 mmol, 59%). It had ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.69 (2H; m), 7.56 (2H; m), 7.30–7.46 (4H; m), 7.25–7.10 (2H; m), 1.88 (4H; m; CH$_2$), 1.25–0.89 (20H; m; CH$_2$), 0.76 (6H; t, *J* = 7.5; CH$_3$), 0.60 (4H; q; CH$_2$). This spectrum is in good agreement with that reported by Belletête *et al.*[48] MS (CI) *m/z* (%): 473 (100), [MH$^+$]. Elemental analysis calculated (%) for C$_{33}$H$_{44}$S: C 83.84%, H 9.39%, S 6.77%; found: C 83.68%, H 9.30%, S 6.69%.

Entry 3, cleavage of PS 17. The cleavage gave resin beads (0.760 g), a weight loss of 0.240 g. Chromatography of the soluble products gave a fraction (211 mg, crude yield 79%) that from the ^{1}H NMR spectrum was mainly (>95%) compound **22**. Recrystallization from methanol gave compound **22** (0.179 g, 0.852 mmol, 67%) with Mp 105–106 °C (lit.,[49] 104–105 °C); ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 8.05 (1H; m), 7.90–7.65 (4H; m), 7.45–7.30 (3H; m), 7.22 (1H; m), 7.05 (1H; m); MS (CI: *m/z* (%): 211 (90), [MH$^+$].

Entry 4, cleavage of PS 18: The cleavage gave resin beads (0.730 g), a weight loss of 270 mg. Chromatography gave a fraction (247 mg, crude yield 81%) that from the ^{1}H NMR spectrum was mainly (>95%) compound **23**. Recrystallization from hexane gave compound **23** (219 mg, 0.883 mmol, 72%) with Mp 95–96 °C (lit.,[50] 94–95.5 °C); ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.19 (2H; m), 7.15 (2H; m), 7.10 (2H; m), 6.95 (2H; m); MS (CI): *m/z* (%): 249 (80), [MH$^+$].

Demethylation of ether 10. Using the procedure described above for the demethylation of ether **7**, ether **10** was converted into phenol **24**. It was obtained as a white solid (88% yield) with Mp 134 °C (lit.,[46] 133 °C); IR (KBr disc, cm^{-1}) 1633; ^{1}H NMR (300 MHz, CDCl$_3$, ppm) δ 7.85 (2H; m; 2H; H-2 and 4), 7.62 (1H; m; H-5), 7.41 (1H; m; H-6), 6.95 (2H; m; H-1 and 3), 6.80 (1H; br s; OH).

Attachment of phenol 23 to chloromethylated beads to give PS 8b. Using the general procedure given above, phenol **24** was attached to the chloromethylated beads (5.000 g, 20.55 mmol). This gave PS **8b** (9.372 g), a weight gain of 4.372 g. This corresponds to 17.7 mmol (86% yield) of residues **8**, equal to 1.89 mmol per g. It had IR (KBr disc, cm^{-1}) 1629. Elemental analysis gave 5.90% sulfur and 14.81% bromine. Based on the sulfur content this corresponds to a loading of 1.84 mmol of thiophene residues **8** per gram of beads; based on the bromine analysis 1.85 mmol per g.

Suzuki couplings of boronic acids 11, 12 and 25 and boronate 26 to PS 8b. These were carried out using the general procedure and on the same scale (1.500 g, 2.84 mmol of PS **8b**) as above. This gave PS **15b**, **16b**, **27** and **28** respectively. The results are summarized in Table 1, entries 5–8 respectively.

Entry 5: Reaction with boronic acid **11** gave PS **15b** (1.668 g), a weight gain of 168 mg, corresponding to 2.30 mmol of residues **15** (81% yield), equal to 1.38 mmol per gram. It had IR (KBr disc, cm^{-1}) 1631. Elemental analysis gave bromine 0.10%.

Entry 6: Reaction with boronic acid **12** gave PS **16b** (2.196 g), a weight gain of 696 mg, corresponding to 2.45 mmol of residues **16** (79% yield), equal to 1.12 mmol of derivative per gram of resin. It had IR (KBr disc, cm^{-1}) 1630. Elemental analysis gave bromine 0.27%.

Entry 7: Reaction with boronic acid **25** gave PS **27** (1.677 g), a weight gain of 177 mg, corresponding to 2.01 mmol (71% yield) of residues **27**, equal to 1.20 mmol per gram of resin. It had IR (KBr disc, cm^{-1}) 1633. Elemental analysis gave bromine 0.14%.

Entry 8: Reaction with boronate **26** gave PS **28** (1.495 g), a weight loss of 5 mg. Elemental analysis gave bromine 0.19%, suggesting that >99% of the bromo groups had reacted. If they had been replaced by hydrogen the expected weight of the

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recovered beads would be 1.299 g. On the basis that the gain in weight (196 mg) is due to the Suzuki coupling, this corresponds to 2.36 mmol of residues **27** (83% yield), equal to 1.58 mmol per g. It had IR (KBr disc, cm^{-1}) 1631.

Cleavages PS 15b, 16b, 27 and 28. These were carried out using the general procedure and on the same scale (1.000 g of starting material) as above. This gave **20**, **21**, **29** and **30** respectively. The results are summarized in Table 1, entries 5–8 respectively.

*Entry 5, cleavage of PS **15b***: The cleavage gave recovered beads (0.695 g), a weight loss of 0.305 g. Chromatography of the soluble products gave compound **20** as a gum (300 mg, crude yield 92%). Crystallisation from hexane gave compound **20** (241 mg, 1.02 mmol, 74% yield) with Mp 170–172 °C. It had an ^{1}H NMR spectrum identical to that described above.

*Entry 6, cleavage of PS **16b***: The cleavage gave recovered beads (0.501 g), a weight loss of 499 mg. Chromatography of the soluble products gave compound **21** as an oil (418 mg, 79% yield). The ^{1}H NMR spectrum was identical to that described above for compound **21**.

*Entry 7, cleavage of PS **27***: The cleavage gave recovered beads (0.750 g), a weight loss of 250 mg. Chromatography of the soluble products gave an oil (250 mg, crude yield 96%) that, by ^{1}H NMR spectroscopy, was >95% compound **29**. Crystallization from hexane gave plates (0.229 g, 88% yield), Mp 67–68 °C (lit.[51] 68.0–68.4 °C); ^{1}H NMR (300 MHz, CDCl$_3$, ppm) δ 7.04–7.70 (6H; m); MS (CI): m/z (%): 167 (100), [MH$^+$].

*Entry 8, cleavage of PS **28***: The cleavage gave recovered beads (0.720 g), a weight loss of 0.280 g. Chromatography of the soluble products gave compound **30** as an oil[52] (252 mg, 84% yield). ^{1}H NMR (300 MHz, CDCl$_3$, ppm) δ 7.32 (1H; m), 7.17 (1H; m), 7.10 (1H; m), 7.08 (1H; m), 6.91 (1H; m), 2.73 (2H; m), 1.65 (2H; m), 1.32 (2H; m), 1.28 (4H; m), 0.91 (3H; m); MS (CI): m/z (%): 251(100), [MH$^+$]. Elemental analysis calculated for C$_{14}$H$_{18}$S$_2$: C, 64.18%, H, 7.26%, S, 25.58%; found: C, 63.88%, H, 7.27%, S, 25.30%.

Synthesis of PS 33. The reaction scheme is shown in Scheme 1.

*(i) Synthesis of 2-bromo-3-n-hexylthien-5-yl 4-methoxyphenyl ketone (**35**)*: To a solution of 4-methoxybenzoyl chloride (5.12 g, 30.00 mmol) and 2-bromo-3-n-hexyl-thiophene (**34**)[41] (7.41 g, 30.00 mmol) in dichloromethane (60 mL) tin tetrachloride (2.49 g, 36 mmol) was added and the mixture stirred at 60 °C for 10 h. It was then cooled and added to a mixture of water (150 mL) and hydrochloric acid (20 mL of 5 M). The acidity was neutralised (to litmus) by treatment with saturated aqueous sodium bicarbonate. The aqueous layer was then extracted with dichloromethane (3 × 30 mL). The combined extracts were dried, evaporated to dryness, and the residue subjected to column chromatography. Elution with hexane/dichloromethane (1 vo 1 : 4 vols) gave compound **35** (6.74 g, 59% yield) as a gum. It had IR (film, cm^{-1}) 1631; ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.61 (2H; m; H-2 and 4), 7.50 (1H; s; H-5), 6.90 (2H; m; H-1 and 3), 3.84 (3H; s; H-6), 2.70 (2H; m; H-7), 1.62 (2H; m; CH$_2$), 1.41-1.22 (6H; m; CH$_2$), 0.89 (3H; m; H-8); MS (EI) m/z = 382 (M$^+$). Elemental analysis calculated for C$_{18}$H$_{21}$BrO$_2$S:

C, 56.69%, H, 5.56%, S, 8.36%, found C, 56.88%, H, 5.35%, S, 8.50%.

*(ii) Synthesis of 2-bromo-3-n-hexylthien-5-yl 4-hydroxyphenyl ketone (**36**)*: 2-Bromo-3-n-hexyl-5-thienyl 4-methoxyphenyl ketone (**35**) (6.00 g, 15.7 mmol) in dichloromethane (60 mL) under nitrogen was cooled in an acetone-dry ice bath. A solution of boron tribromide (15.9 g, 3.0 mL, 32 mmol) in dichloromethane (40 mL) was added dropwise with stirring. When the addition was complete, the reaction mixture was allowed to attain 20 °C and stirred overnight. It was then poured over a mixture of ice and water (100 mL) and after 30 min extracted with dichloromethane (3 × 50 mL). The extracts were dried and the solvent evaporated off. The residue was purified by column chromatography over silica gel. Elution with chloroform to give phenol **36** (5.37 g, 93% yield) as a gum. It had IR (film, cm^{-1}) 1631; ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.60 (2H; m; H-2 and 4), 7.51 (1H; s; H-5), 6.84 (2H; m; H-1 and 3), 2.70 (2H; m; H-7), 1.62 (2H; m), 1.42–1.22 (6H; m), 0.90 (3H; m; H-8); MS (CI): m/z (%): 368 (100), [MH$^+$]. Elemental analysis calculated for C$_{17}$H$_{19}$BrO$_2$S: C, 55.59%, H, 5.22%, S, 8.71%, Br, 21.77%, found: C, 55.68%, H, 5.32%, S, 8.70%, Br, 22.00%.

*(iii) Attachment of phenol **36** to chloromethylated beads to give PS **33***: Using the general procedure given above, phenol **36** (5.700 g) was attached to the chloromethylated polystyrene beads (3.700 g). This gave PS **33** (6.970 g). The weight gain (3.270 g) corresponds to 13.00 mmol of thiophene-containing residues, equal to 1.86 mmol per g. PS **33** had IR (KBr disc, cm^{-1}) 1633. Elemental analysis for sulfur gave 5.80% and for bromine 14.56%. These correspond respectively to loadings of 1.81 and 1.82 mmol per g of thiophene-containing residues **33**.

Synthesis of compound 31. The reactions involved are summarized in Scheme 2.

*(i) Suzuki coupling of boronic acid **11** to PS **33***: Following the general procedure a Suzuki reaction was carried out between PS **33** (2.000 g, 3.64 mmol) and boronic acid (**11**) (0.79 g, 4.00 mmol). This gave PS **37** (2.220 g). The weight gain (0.220 g), corresponds to 3.02 mmol of the Suzuki product (83% yield), equal to 1.36 mmol per gram of resin. It had IR (KBr disc, cm^{-1}) 1630. Elemental analysis for bromine gave 0.38%.

*(ii) Bromination of the PS **37***: PS **37** (2.000 g, 2.72 mmol) was suspended in DMF (65 mL) and NBS (0.490 g, 2.76 mmol) was added. The mixture was stirred at 90 °C for 72 h. It was then cooled. The beads were collected and washed successively with DMF (2 × 25 mL), water (2 × 25 mL), and acetone (2 × 25 mL) before being dried. This gave PS **38** (2.180 g). The weight gain (0.180 g) corresponds to 2.31 mmol of bromo residues (85% yield), equal to 1.05 mmol per gram. It had IR (KBr disc, cm^{-1}) 1631. Elemental analysis for bromine gave 8.72% this corresponds to a loading of 1.09 mmol of residues **38** per g.

*(iii) Suzuki coupling of boronate **26** to PS **38***: Following the usual Suzuki reaction procedure boronate **26** (0.880 g, 3.00 mmol) was reacted with PS **38** (2.000 g, 2.10 mmol). This gave PS **39** (2.170 g). The weight gain (0.170 g) corresponds to 1.98 mmol of residues **39** (94% yield), equal to 0.91 mmol per g. It had IR (KBr disc, cm^{-1}) 1632. Elemental analysis for bromine gave 0.27%.

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(*iv*) *Cleavage of PS 39*: The cleavage reaction was carried out on PS **39** (1.000 g, 0.91 mmol) using the procedure described above. This gave recovered beads (0.550 g), a weight loss of 0.450 g. The purified cleaved product was identified as **31** (0.340 g, 68%). It had Mp 35–37 °C; λ_{max} (ethanol) 309 nm (ε 40,100); ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.71 (4H; m; H-3 or 4), 7.55 (4H; m; H-3 or 4), 7.29 (2H; d, J = 4.5; H-1), 7.03 (2H; d, J = 4.5; H-2), 2.75 (4H; t, J = 7.7; α-CH$_2$), 1.65 (4H; m; β-CH$_2$), 1.30 (12H; m; CH$_2$), 0.91 (6H; t, J = 7.7; CH$_3$); MS (CI): m/z (%): 487 (100), [MH$^+$]. Elemental analysis calculated for C$_{32}$H$_{38}$S$_2$: C, 78.97%, H, 7.88%, S, 13.15%, found: C, 78.80%, H, 7.55%, S, 13.45%.

Synthesis of compound 32. The reactions involved are summarized in Scheme 3.

(*i*) *Suzuki coupling of boronic acid 14 to PS 33*: Following the usual procedure boronic acid **14** (0.86 g, 4.1 mmol) was reacted with PS **33** (3.000 g, 5.46 mmol). This gave PS **40** (2.280 g) a weight gain of 0.280 g, corresponding to 3.34 mmol of Suzuki product (61% yield), equal to 1.46 mmol per g. It had IR (KBr disc, cm^{-1}) 1632. Elemental analysis for bromine gave 0.20%.

(*ii*) *Bromination of the PS 40*: PS **40** (2.000 g, 2.84 mmol) was brominated using the procedure described for the preparation of PS **38**. This gave PS **41** (2.205 g) a weight gain of 0.205 g, corresponding to 2.56 mmol of residues **41** (90% yield), equal to 1.17 mmol per g. It had IR (KBr disc, cm^{-1}) 1629. Elemental analysis for bromine gave 9.75%. This corresponds to a loading of 1.22 mmol of residues **41** per g.

(*iii*) *Suzuki coupling of boronate 26 with PS 41*: PS **41** (2.000 g, 2.42 mmol) was reacted with boronate **26** (0.884 g, 3.00 mmol) using the usual procedure. This gave PS **42** (2.183 g). The weight (0.183 g) corresponds to 2.10 mmol of residues **42** (87% yield), equal to 0.96 mmol of per g. It had IR (KBr disc, cm^{-1}) 1632. Elemental analysis for bromine gave 0.19%.

(*iv*) *Cleavage of PS 42*: Following the usual procedure PS **42** (1.000 g, 0.98 mmol), gave recovered beads (0.624 g), a weight loss of 0.384 g. The soluble product was purified by chromatography. This gave compound (265 mg, 54%). It had Mp 30–32 °C (lit.,^{44} 28–30 °C); ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 7.09 (2H; d, J = 5.2; H-1), 7.04 (2H; m; H-3 or 4), 6.94 (2H; m; H-3 or 4), 6.82 (2H; d, J = 5.2; H-2), 2.73 (4H; m; α-CH$_2$), 1.60 (4H; m; β-CH$_2$), 1.25 (12H; m; CH$_2$), 0.81 (6H; m; CH$_3$); MS (EI): m/z (%): 498 (100), [M$^+$]. Elemental analysis calculated for C$_{28}$H$_{34}$S$_4$: C, 67.45%, H, 6.88%, S, 25.67%, found: C, 67.23%, H, 6.68%, S, 25.65%.

Acknowledgements

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