A New Approach to the Synthesis of 4-Hydroxyethylsulfonylstyrene

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Abstract:

A new, more environmentally benign route to hydroxyethylsulfonylstyrene has been developed, starting from 4-bromobenzenethiol, involving a solventless thioether formation, water-based perborate oxidation, and Suzuki−Miyaura cross coupling with a vinylborate reagent.

Introduction

It is has long been recognised that volatile organics compounds (VOCs) are a huge environmental problem, with solvent-borne coatings (e.g., for paints, adhesives, etc.) providing their own substantial share of emissions.[1] In order to address this issue, we designed and developed a novel water-borne coating system based on novel bifunctional polymer monomers,[2] the first example of which is hydroxyethylsulfonylstyrene (HESS), **1**.[3] We showed that HESS, **1**, can be incorporated into water-borne latex particles where subsequent cross-linking upon coating involves *in situ* generation of a vinylsulfone function that then couples with other reactive functions (*e.g.*, hydroxyl) introduced into the polymer using existing commercial monomers (*e.g.*, hydroxypropyl methacrylate for OH groups).[3]

The success of the initial trials of HESS, **1**, as a latex monomer meant that scale up was required in order to provide increasingly larger quantities for evaluation purposes. However, examination of the initial synthesis route reported[3] and attempts to carry out >10 g scale reactions highlighted several major issues: (1) the starting material for the synthesis, sodium 4-styrenesulfonate, is relatively expensive; (2) a reduction of a sulfonyl chloride was required using zinc metal which raises major issues due to the costs of disposal of zinc waste and its associated environmental problems; (3) alternative reduction methods for the sulfonyl chloride were developed (based on either sodium sulfite or metabisulfite); however, the resulting HESS, **1**, was found to be extremely sensitive to polymerisation;

Scheme 1. Disconnection and proposed synthesis of HESS, 1
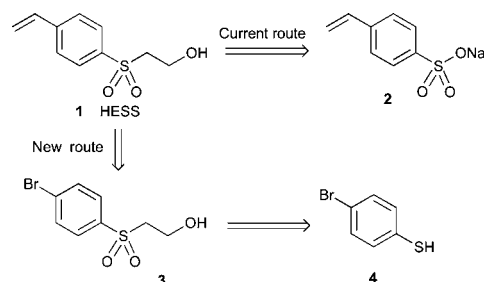
and (4) the last step in the original production of HESS, **1**, was not only found to be extremely capricious, but it also involved the use of toxic and volatile ethylene oxide. Therefore, an alternative route to HESS, **1**, had to be developed which would solve these problems and form the basis of a potentially commercially viable production process. In this paper, a new route to HESS, **1**, which is suitable for 100 g scale syntheses is reported.

Results and Discussion

HESS, **1**, can be disconnected to the commercial salt **2**, as shown in Scheme 1. Alternatively, one can consider attaching the sensitive styrene double bond as late as possible, for example, using a transition metal-catalysed coupling protocol and sulfone **3**, in which case, commercially available 4-bromothiophenol **4** should be a suitable starting material.

The new approach is outlined in Scheme 1 and involves commercially available starting materials and mild reaction conditions which are compatible with the sensitive functionality in **1**. Prior to scale up studies, the new route was tested on small (<1 g) scale, and after it was shown that the reaction sequence worked, each step was examined in detail. This involved obtaining all data required for the optimisation and scale up of the process to >100 g.

Step 1: Formation of Sulfide 5. Initial alkylation of 4-bromothiophenol, **4**, with chloroethanol in aqueous sodium hydroxide (eq 1) was adapted from a previously reported protocol[4] and proceeded in good yields (91%). However, a few problems needed to be addressed. It was noted that the reaction was very exothermic and it was necessary to separate the exotherm arising due to dissolution of NaOH pellets in water from the actual alkylation reaction; hence, 10% w/v NaOH

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(1) In 1991, the United Nations Economic Commission for Europe agreed on the Geneva Protocol concerning the Control of Emissions of Volatile Organic Compounds or their Transboundary Fluxes, which included substantial reductions in VOCs from member nations (http://www.unece.org/env/lrtap/vola_h1.htm).

(2) (a) Berrisford, D. J.; Lovell, P. A. L.; Whiting, A. Appl. No. 0227608.7, U.S. appl. no. 10/535333, PCT appl. no. PCT/GB2003/005240, 2003. (b) Whiting, A. P3322 GB PRO, 2006.

(3) Berrisford, D. J.; Lovell, P. A.; Suliman, N. R.; Whiting, A. *Chem. Commun.* **2005,** 5904–5906.

(4) Verhart, C. G. J.; Tesser, G. I. *Recl. Trav. Chim. Pays-Bas* **1988,** *107,* 621–626.

Table 1. Oxidation conditions for eq 5

entry	conditions	oxidant (equiv)[a]	solvent (mL)[b]	conversion %[c]	yield %[d]	purity %[e]
1	Mn(acac)$_2$ (1.1 mol %) NaHCO$_3$ (10.0 equiv) 0 °C	H$_2$O$_2$ (15)	MeCN/H$_2$O, 2/3 (214)	100	96	98
2	r.t.	Oxone (19)	MeOH/H$_2$O, 1/1 (86)	100	77	95
3	55 °C	NaBO$_3$.4H$_2$O (2.0)	MeCN/H$_2$O, 1/1 (18)	95	89	78[e]
4	NaBO$_3$·4H$_2$O (1.0 equiv) NaOH (0.01 equiv) 55 °C	H$_2$O$_2$ (2.0)	MeCN/H$_2$O, 1/1 (18)	100	89	95
5	NaBO$_3$·4H$_2$O (10 mol %) NaOH (0.2 mol %) 55 °C	H$_2$O$_2$ (2.2)	MeOH/H$_2$O, 1/1 (18)	95	70	<90[f]
6	NaBO$_3$·4H$_2$O (10 mol %) NaOH (0.2 mol %) 55 °C	H$_2$O$_2$ (2.2)[g]	MeCN/H$_2$O, 1/1 (18)	100	83	95
7	NaBO$_3$·4H$_2$O (5 mol %) NaOH (0.2 mol %) 55 °C	H$_2$O$_2$ (2.2)[g]	MeCN/H$_2$O, 1/1 (18)	100	87	98
8	B(OH)$_3$ (3.7 equiv) NaOH (3.8 equiv) 55 °C	H$_2$O$_2$ (5.5)	MeOH/MeCN, 8/1 (45)	100	97	95
9	B(OH)$_3$ (5 mol %) NaOH (6 mol %) 55 °C	H$_2$O$_2$ (2.02)[h]	MeCN/H$_2$O, 3/1 (15)	100	94	>99

[a] Oxidant added portionwise in order to maintain the temperature. [b] The volume of solvent is given based on 1.0 g of starting thioether **5**. [c] Conversion is defined as percentage of starting material **5** consumed, as estimated by ^{1}H NMR. [d] Total mass recovery. [e] Purity of the final material isolated after an aqueous work up and estimated by ^{1}H NMR. [f] Major impurity is sulfoxide **6**. [g] H$_2$O$_2$ added over period of 6 h using syringe pump. [h] H$_2$O$_2$ added over period of 7 h using syringe pump.

solution was used instead of direct addition of pellets to the reaction mixture.

(1)

4   **5** 98%
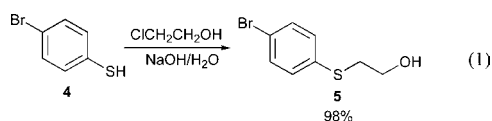
The deprotonation of thiophenol **4** with NaOH is an exothermic process in its own right; however, the heat evolved is not enough to initiate the alkylation reaction. Through calorimetry experiments it was established that after the initial addition of NaOH to thiophenol **4** the reaction must be warmed up to 40 °C, and only then can a steady addition of chloroethanol be carried out as a safe process and the exotherm be controlled. The calorimetry data has also allowed estimating the total heat of the reaction ($\Delta H = -96.9$ kJ mol^{-1} wrt thiophenol **4**) and obtaining a preliminary kinetic model. The overall process can be postulated to consist of two steps represented in eqs 2 and 3.

(2)

(3)
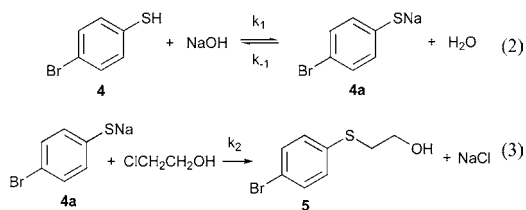
Under the reaction conditions the equilibrium in eq 2 lies significantly to the right (thiol/thiolate pK_a = 5.8)[5] which means that the reaction can be adequately represented by the sole addition of **4a** to chloroethanol (eq 3). If this is the case, the rate of the reaction is given by:

$$\text{Rate} = k_2[\mathbf{4a}][\text{ClCH}_2\text{CH}_2\text{OH}] \qquad (4)$$

where [**4a**]$_0$ = [**4**]$_0$.

The rate constant was regressed against the reaction exotherm data using the BatchCAD software,[6] and a value for k_2 (1.87 × 10^{-3} dm^3 mol^{-1} s^{-1}) was estimated. These data were then used to model effects of material accumulation and, therefore, led to the development of a safer operating procedure.

Importantly, while establishing a safe protocol for the alkylation, the yield was increased (>99%), and purity of the final product was improved. The product obtained was sufficiently pure for use in the next stage of the synthesis. Recrystallisation of **4** prior to its use did improve the purity of final product; however, up to 25% of **4** can be lost during the recrystallisation, and therefore, it is uneconomical for an industrial process.

Step 2: Formation of Sulfone 3. The cheapest oxidizing agents are chlorine, nitric acid, hydrogen peroxide, and air (oxygen).[7] For the oxidation of sulfide air requires a heterogeneous catalysis or biocatalysis and involves high capital plant costs. Both chlorine and nitric acid procedures are unsuitable for this transformation, first because of the potential chlorination side reactions, and second due to the instability of the hydroxyethyl group towards elimination. On the other hand, hydrogen peroxide is cheap, easy to handle, and environmentally friendly. However, since it is a relatively weak oxidant, it requires activation. In an initial attempt to oxidize sulfide **5** to sulfone **3** *via* sulfoxide **6** (eq 5), a previously reported procedure was

(5)
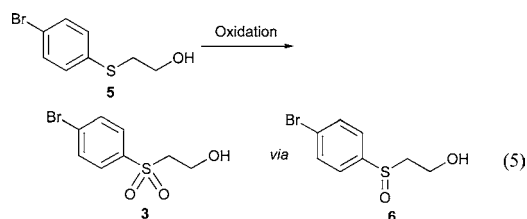
adopted which uses Mn(acac)$_2$ as a homogeneous catalyst (Table 1, entry 1).[8] The reaction proceeded in high yield and gave products of excellent purity. However, due to a substantial

(5) Dalby, K. N.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1555–1563.
(6) *Aspen BatchCAD*, v 8; Aspen Technology: Burlington, MA, U.S.A.; http://www.aspentech.com.
(7) For a recent survey of methods used in the pharmaceutical industry, see: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347, and references therein. .
(8) Alonso, D. A.; Najera, C.; Varea, M. *Tetrahedron Lett.* **2002**, *43*, 3459–3461.

level of catalase-like activity of Mn(acac)$_2$ large amounts of hydrogen peroxide (up to 15 equiv) and NaHCO$_3$ (10 equiv) were required. Despite relatively environmentally benign conditions, rapid evolution of oxygen and excessive use of oxidant (cost implications) would forbid any industrial use, and an alternative route was required. It was decided to look at two other industrially acceptable options, i.e. Oxone- and sodium perborate-based oxidations.[9]

The reaction with Oxone (Table 1, entry 2) proceeded in good yield, and the final product was obtained in acceptable purity. However, a large amount of Oxone (19 equiv) was required to drive the reaction to completion.

On the other hand, sodium perborate in stoichiometric amounts produced the product in better yields, albeit at a loss of purity, entry 3. Since the use of perborates in oxidation chemistry is well documented[9] and would provide a cost efficient and industrially viable option, it was decided to concentrate on the optimisation of the oxidation using perborate.

The major impurity obtained in entry 3 (Table 1) was the corresponding sulfoxide **6**, indicating that the reaction required more oxidant. Therefore, hydrogen peroxide was used in conjunction with sodium perborate to see if it was possible to drive the reaction to completion (Table 1, entry 4). The results were encouraging, and the product was obtained in high yield and acceptable purity, and the procedure could be carried out on 100 g scale without compromising either the yield or purity of the product. However, since the reaction was exothermic, its thermochemistry needed to be studied if it were to be carried out on large scale. Preliminary adiabatic calorimetry was performed in a Dewar vacuum flask using a digital thermometer. Initial experiments showed that the mixture of NaBO$_3$ and sulfide **5** required heating in order to initiate the reaction. Once the reaction initiated, it became exothermic and under adiabatic conditions; the heat output was sufficient to boil the solvent (Figure 1).
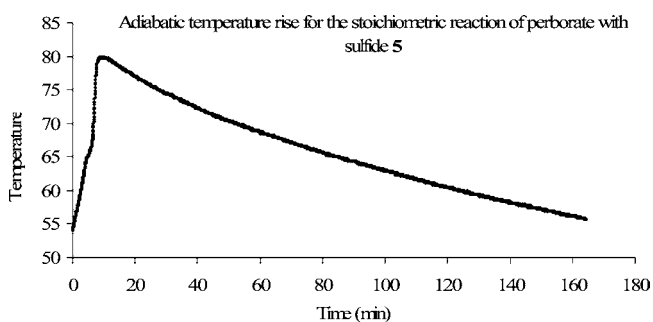

Figure 1. Adiabatic temperature rise for the reaction between sodium perborate and sulfide 5 in MeCN/H$_2$O.

The reaction was very rapid (~15 min), and once complete, the temperature dropped back to the starting levels through heat loss by the flask. Such a temperature rise could be dangerous in an industrial process, and thus, an alternative catalytic approach was investigated. After several attempts, it was established that NaBO$_3$ could be used in catalytic amounts (5 mol %) without losing any activity and still produce the final

product with high purity (98%) (Table 1, entries 5−7). Under these conditions, the heat produced by the reaction was completely controlled by the rate of the addition of hydrogen peroxide. Although the results were promising, the high reactivity and flammability of NaBO$_3$ was still a concern. Thus, an attempt was made to use boric acid and generate perborate *in situ*, first stoichiometrically, and then catalytically (Table 1, entries 8 and 9). On both occasions, the reactions proceeded with excellent purity and high yields. Once the reaction conditions were established, concentration profiles and thermal data for the process were obtained (Figure 2).

Addition of a portion of oxidant (0.2 equiv) to the reaction mixture resulted in a sharp temperature increase. The temperature then dropped due to heat loss from the flask, and a further portion of oxidant could be added to give the same result. This could be repeated until all of the material was converted to sulfone **3**. This type of sharp temperature rise means that the exothermic process can be controlled by the feeding rate of peroxide into the reaction mixture. Also, since the overall reaction was fast, it prevented any buildup of hydrogen peroxide, making it a safer process. Furthermore, the reaction proceeds in a reasonably stepwise manner, initially to give sulfoxide **6** which is then oxidized further to give sulfone **3** (Figure 2b). Finally, before moving on to nonadiabatic full-scale calorimetry and reaction modelling, a final adiabatic run was attempted wherein H$_2$O$_2$ was fed *via* syringe pump over a period of 5 h with both the temperature and concentration profiles of the reaction being monitored simultaneously (Figure 2c). As expected, the steady addition of hydrogen peroxide resulted in an increasing temperature. A reduction in the peroxide feeding time resulted in a slightly different reaction composition wherein all three species (sulfide **5**, sulfoxide **6**, and sulfone **3**) were present simultaneously. However, the end result was the same: high yield and high purity of the final product. Also, it is worth noting that, once all the product was formed, there was no further increase in temperature, even though the peroxide was still being introduced into the reaction. From these preliminary results using standard laboratory equipment, it was possible to design the calorimetry experiments required for a more detailed analysis of the reaction.

A calorimetry run was carried out to provide an estimate for the overall enthalpy of the reaction ($\Delta H = -858$ kJ mol^{-1} wrt sulfide **5**) and from which, a reaction model could be proposed, based upon the following observations: (1) At high peroxide concentrations, the oxidation of sulfides is known to show a second-order dependence on both peroxide and boric acid (characteristic of diperborate).[10] However, in this case, where peroxide was dosed into the system, the concentration of H$_2$O$_2$ at any particular time t was relatively low, and the contribution from diperborate could be discarded; (2) the reaction was carried out under basic conditions ([NaOH] = 2.8 × 10^{-2} M); therefore, the borate is the major species present in solution (pK_a of boric acid = 8.98),[9] and hence, eq 6 alone represents the equilibrium with perborate; (3) it was shown that no reaction took place in the absence of borate; therefore, sulfide **5** was not oxidized by hydrogen peroxide alone. It can be assumed that the less reactive sulfoxide **6** behaved similarly;

(9) (a) Webb, K. S. *Tetrahedron Lett.* **1994**, *35*, 3457–3460. (b) McKillop, A.; Tarbin, J. A. *Tetrahedron Lett.* **1983**, *24*, 1505–1508. (c) McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145–6166.
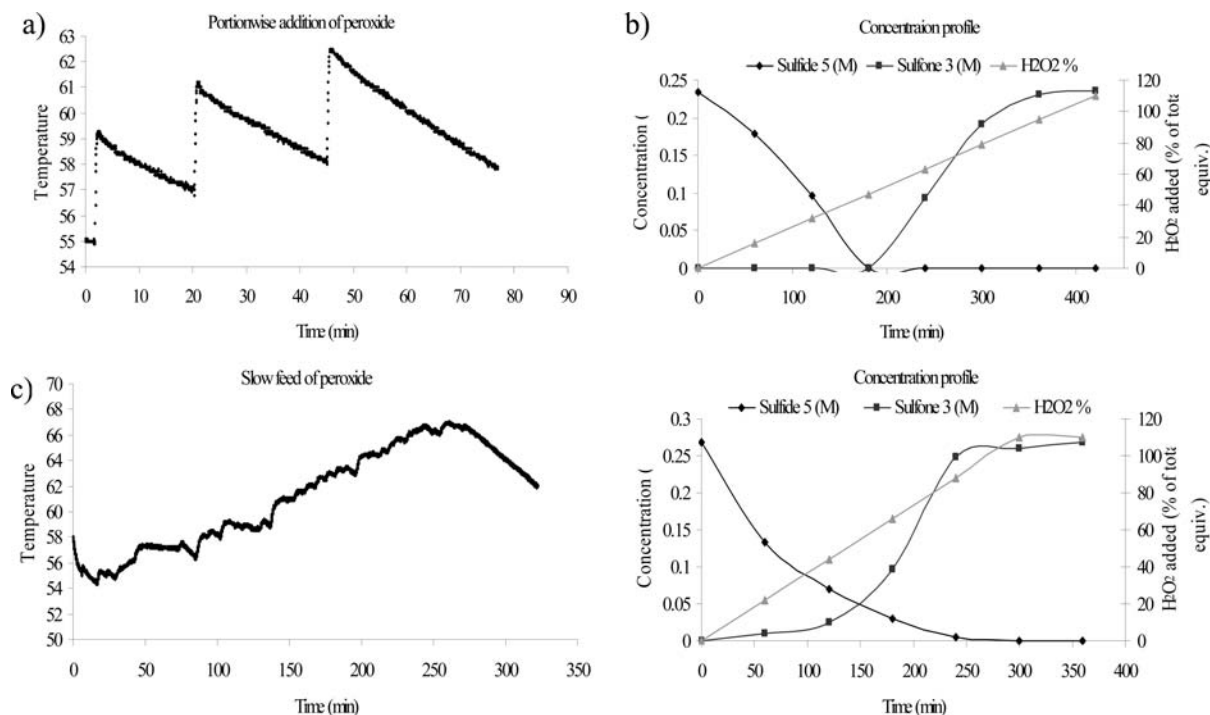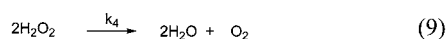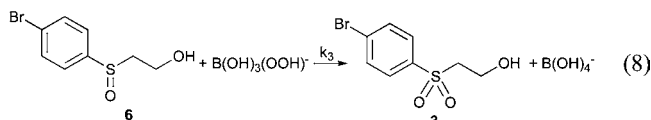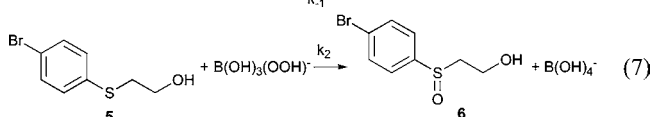
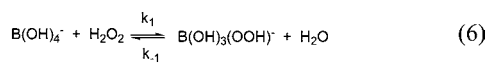(10) Pizer, R.; Tihal, C. *Inorg. Chem.* **1987**, *26*, 3639–3642.

Figure 2. Thermal chemistry and concentration profiles (obtained by GC using 1,2-dichlorobenzene (DCB) as internal standard; sulfoxide 6 could not be calibrated accurately with respect to DCB, and thus, its concentration is not given) for the oxidation of sulfide 5 with H_2O_2 in the presence of catalytic amount of $B(OH)_3$. (a) Adiabatic temperature rise during portionwise (0.2 equiv at a time) addition of H_2O_2 (showing first 3 steps only); (b) concentration profile of the reaction wherein H_2O_2 is added over 7 h; (c) adiabatic temperature rise during a 5 h long addition of H_2O_2 and corresponding concentration profile.

(4) it is believed that at high pH, the decomposition of peroxide is second order with respect to peroxide.[11] Consequently, the reaction network proposed for the modeling purposes is as described by eqs 6−9.

$$B(OH)_4^- + H_2O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B(OH)_3(OOH)^- + H_2O \quad (6)$$

(7)

(8)

$$2H_2O_2 \xrightarrow{k_4} 2H_2O + O_2 \quad (9)$$

The rate constants were regressed against the reaction exotherm data using BatchCAD,[6] and the results are presented in Table 2.

These data were used to estimate the peroxide accumulation, its potential effects on temperature, and the conditions under which a possible thermal runaway could occur. The modelling showed that, under the dilution conditions used, thermal runaway would be unlikely. However, at the concentrations used on plant, the increase in temperature could become significant, and the flow rates of peroxide addition would need to be adjusted. A greater hazard would be if the oxidation reaction
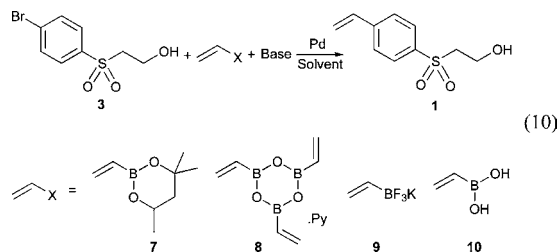
(11) (a) Špalek, O.; Balej, J.; Paseka, I. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 2349–2359, and references therein. (b) Erdey, L.; Inczedy, I. *Acta Chim. Acad. Sci. Hung.* **1958**, *17*, 93–111.

Table 2. Heats of the reaction and estimated rate constants for the oxidation of sulfide 5[a]

rate expression	ΔH_r (kJ mol^{-1})	rate constants
$k_1[B(OH)_4^-][H_2O_2]$	−15	0.18 dm^3 mol^{-1} s^{-1}
$k_{-1}[B(OH)_3(OOH)^-]$	15	5.21×10^{-8} s^{-1}
$k_2[5][B(OH)_3(OOH)^-]$	−350	6.85×10^{-2} dm^3 mol^{-1} s^{-1}
$k_3[6][B(OH)_3(OOH)^-]$	−410	0.24 dm^3 mol^{-1} s^{-1}
$k_4[H_2O_2]^2$	−98	1.21×10^{-2} dm^3 mol^{-1} s^{-1}

[a] Note: data derived from a single experiment. Fitting was performed by integrating simultaneously the five differential equations using BatchCAD. The accuracy of the fit (indicated by percentage variation in each individual observed variable in the model) was 98.39%.

stalled or was operated at a reduced rate due, for instance, to insufficient charge of catalyst. The exceptionally high heat of reaction of the oxidation process ($\Delta H_r = -858$ kJ mol^{-1} of sulfide) would have the potential to produce a major exotherm, and thus, appropriate cooling systems would be required.

Step 3: Formation of 1. Having accessed sulfone **3** in good yields, high purity, and under environmentally benign conditions, the conversion of the bromide **3** using Suzuki−Miyaura (SM) coupling conditions into **1** (eq 10, Table 3) was examined.


(10)

Initial screening for the reaction described by eq 10 showed that neither **7**[12] nor **8**[13] was a good vinyl donor for this coupling

Table 3. Initial screening of four vinylboronates 7−10 for the SM coupling to give 1

entry	boronate	solvent (ratio)	base (equiv)	Pd source (loading %)	ligand (loading %)	temp °C	conversion[a]/ yield[b]	byproduct 11[c]
1	**7**	MeCN:H_2O (1:1)	NaOH (1.8)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	50/−	−
2	**8**	THF:H_2O (2.6:1)	Na$_2$CO$_3$ (8)	Pd(OAc)$_2$ (1)	PPh$_3$ (3)	70	0	−
3	**8**	MeCN:H_2O (1:1)	NaOH (15)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	50/−	−
4	**8**	THF:H_2O (8.5:1)	NaOH (8)	Pd(OAc)$_2$ (4)	PPh$_3$ (8)	70	100/−	−
5	**8**	THF:H_2O (10:1)	NaOH (8)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	100/91	4:1
6	**9**	THF:H_2O (10:1)	NaOH (4)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	100/95	6:1
7	**9**[d]	THF:H_2O (7.5:1)	NaOH (2) KF (1)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	100/95	10:1
8	**10**	THF:H_2O (7.5:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (2)	−	70	10/−	−

[a] Conversion is defined as percentage of starting material **3** consumed, as estimated by ^{1}H NMR. [b] Isolated yield of product including byproduct **11**. [c] The byproduct has not been isolated, but is proposed to be **11** (see text). [d] In situ generated.

Table 4. Screening of vinylboronic acid 10 in the SM coupling (using 10 g of sulfone 3 per reaction) to give 1
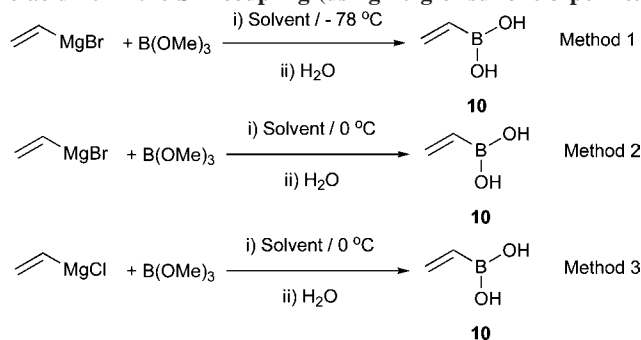
entry	source of 10	solvent (ratio)[a]	base (equiv)	Pd source and ligand (loading %)	temp °C	conversion[b]/ yield[c]	byproduct 11[d]
1	method 1	THF:H_2O (7.5:1)	NaOH (2) KF (1)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	70	100/95	10:1
2	method 1	THF:H_2O (7.5:1)	NaOH (2.2)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	65	90/80	10:1
3	method 1	toluene:H_2O (3:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (2) PPh$_3$ (5)	reflux	100/50	15:1
4	method 1	toluene:H_2O (4:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (2) PPh$_3$ (5)	reflux	100/85	20:1
5	method 2	toluene:H_2O (4:1)	NaOAc (2)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	reflux[e]	70/68	16:1
6	method 2	toluene:H_2O (4:1)	NaOAc (1)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	reflux	100/70	12:1
7	method 3	toluene:H_2O (4:1)	NaOAc (1)	Pd(OAc)$_2$ (1) PPh$_3$ (4)	reflux	50/40	2.8:1
8	method 3	toluene:H_2O (4:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	reflux	70/50	12:1
9	method 3	toluene:H_2O (4:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (2) PPh$_3$ (4)	50	20/10	−
10	method 3	toluene:H_2O (4:1)	buffer (pH = 7)[f]	Pd(OAc)$_2$ (2) PPh$_3$ (4)	reflux	10/10	−

[a] Dry organic solvent was used in generation of boronic acid, and then water was added prior to Pd coupling. [b] Conversion is defined as percentage of starting material **3** consumed, as estimated by ^{1}H NMR. [c] The yield was estimated by ^{1}H NMR spectroscopy. [d] The byproduct has not been isolated, but is proposed to be **11**. [e] Heating time was halved. [f] pH 7 phosphate buffer was used.

reaction (entries 1−5, Table 3). The reaction proceeded capriciously, giving complex mixtures of products whilst requiring high loadings of catalyst and bases. The next strategy was to employ a vinylfluoroborate system for the SM coupling,[14] either directly, using commercially available potassium vinyltrifluoroborate, **9**, or generated in situ following a previously reported protocol[14] (entries 6 and 7, respectively, Table 3). Entries 6 and 7 show that there was little difference in reaction efficiency between the in situ generated vinylboronate and the commercially sourced material; both resulted in efficient SM coupling of bromide **5** to give **1** in high yield, albeit contaminated with a byproduct. This byproduct has not been readily separated by standard methods, however, based mainly upon GC−MS analysis of the same sample and the ^{1}H NMR spectrum of **1** contaminated with the byproduct (see ESI), it is proposed to be the corresponding vinylsulfone **11** which is formed in the reaction mixture (samples of **1** with this byproduct present do show a number of other products appearing upon storage which appear to derive from reaction of the byproduct with **1** but have not been isolated). Evidence that the initial byproduct formed in

11
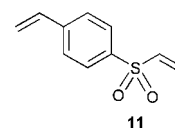
the SM reaction is **11** is as follows: (1) there are additional vinyl-type resonances around δ 7.6 in the ^{1}H NMR spectrum; (2) GC−MS reveals four compounds in the

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Table 5. Screening of potassium trifluorovinylborate 9 in the SM coupling (using 10 g of sulfone 3 per reaction) to give 1

entry	solvent (ratio)	base (equiv)	Pd source (loading %)	ligand (loading %)	temp °C	conversion[a]/yield[b]	byproduct 11[c]
1	MeCN:H_2O (2:1)	NaOH (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	80	67/50	3:1
2	MeCN:H_2O (2:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	80	99/97	>20:1
3	THF:H_2O (10:1)	NaOH (4)	Pd(OAc)$_2$ (2)	PPh$_3$ (4)	70	100/95	6:1
4	THF:H_2O (2:1)	NaOH (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	80	93/87	13:1
5[d]	THF:H_2O (25:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	70	95/95	1:0
6	THF:H_2O (25:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	70	15/15	1:0
7	THF:H_2O (25:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (1)	Dppf (1.2)	70	10/10	1:0
8	IPA:H_2O (2:1)	NaOH (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	70	50/45	1:0
9	IPA:H_2O (2:1)	^{t}BuNH$_2$ (2.5)	Pd(OAc)$_2$ (1)	PPh$_3$ (2)	80	100/84	1:0
10	IPA:H_2O (2:1)	^{t}BuNH$_2$ (2.5)	Pd(OAc)$_2$ (1.2)	Dppf (1.2)	70	100/81	1:0
11	MeOH	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (1)	—	80	10/10	1:0
12	toluene:H_2O (6:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (2)	PPh3 (5)	80	100/97	22:1
13	toluene:H_2O (6:1)	^{t}BuNH$_2$ (3)	Pd(OAc)$_2$ (2)	PPh$_3$ (5)	80	100/97	>30:1
14	toluene:H_2O (4:1)	Et$_3$N (3)	Pd(OAc)$_2$ (2)	PPh$_3$ (5)	80	100/50	22:1
15	toluene:H_2O (4:1)	NaOAc (3)	Pd(OAc)$_2$ (2)	PPh$_3$ (5)	80	90/85	1:0
16	toluene:H_2O (6:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (0.2)	PPh$_3$ (0.5)	80	50/47	6:1
17	toluene:H_2O (6:1)[e]	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (0.5)	PPh$_3$ (2.5)	80	100/50	6:1
18[f]	toluene:H_2O (6:1)	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (0.5)	PPh$_3$ (2.5)	80	80/79	—
19[g]	toluene:H_2O (4:1)[e]	K$_2$CO$_3$ (3)	Pd(OAc)$_2$ (1)	PPh$_3$ (2.5)	80	100/88	10:1
20[h]	toluene:H_2O (4:1)	K$_2$CO$_3$ (1) NaOAc (2)	Pd(OAc)$_2$ (2)	PPh$_3$ (5)	80	100/90	1:0

[a] Conversion is defined as percentage of starting material 3 consumed, as estimated by ^{1}H NMR. [b] Isolated yield of product. [c] The precise nature of byproduct was not established. [d] 1 g of sulfone 3 was used. [e] Total amount of solvent was halved compared to other entries. [f] Vinyltrifluoroborate was prepared *in situ*, and the reaction was monitored by GC. [g] 50 g of sulfone 3 was used. [h] 100 g of sulfone 3 was used.

crude reaction mixture, three of which are clearly 1, PPh$_3$, and OPPh$_3$. The fourth component appears to have a molecular ion at m/z 193.9, corresponding to 1 minus water. It is unlikely that the loss of water occurs in the GC−MS instrument also, since TGA measurements on 1 (see ESI) show that loss of water does not occur until 170 °C. It is also noteworthy, that samples of 1 contaminated with this byproduct 11 tended to be less stable upon storage and under polymerisation. Hence, avoiding the formation of this byproduct was deemed essential.

The conclusions from these preliminary experiments were that the preparation of 1 using potassium vinyltrifluoroborate 9 was easier in terms of handling than the other vinylboron systems and that the isolated end product was stable if not contaminated with the byproduct 11. However, the high cost of 9 made it unattractive as a basis for a potentially commercial process. On the other hand, vinylboronic acid 10 can be generated *in situ* relatively cheaply using commercial materials, despite being a more complex process overall. Since different vinylboron reagents have their own advantages/disadvantages, it was decided to investigate coupling conditions with two different, readily available vinyl donors and see which would provide the more potentially commercially viable synthesis.

The initial target was to develop a route for the synthesis of 1 using vinylboronic acid 10 prepared *in situ*. Generation of 10 was achieved by addition of a vinylmagnesium bromide solution in THF to a solution of B(OMe)$_3$ in dry toluene at −78 °C (Method 1, Table 4). Although this is a standard laboratory method for generation of boronic acids, the cryogenic temperatures generally are not accessible on industrial scale. Hence, the reaction temperatures were raised to 0 °C (Method 2, Table 4). Vinylmagnesium bromide was also compared to vinylmagnesium chloride (Method 3). All three methods were tested in SM coupling in order to assess their applicability in the reaction (Table 4).

After several screening reactions on small scale, using different solvents, bases, and additives, and generating vinylboronic acid at different temperatures (entries 1−6, Table 4) it was concluded that the use of K$_2$CO$_3$ as the base gave the best results (entry 4, Table 4), although the byproduct 11 was still present. Vinylmagnesium chloride (entries 7 and 8, Table 4) showed the best conditions developed at that point in the study (entry 8, Table 4); however, the reaction did not proceed to 100% conversion, and the byproduct 11 was still present. Initially, the deactivation of the palladium catalyst was proposed as the problem for the lack of complete conversion, however, after careful analysis it was realised that the catalyst was still active and in solution. The problem was in fact due to competitive polymerisation of the vinylboronic acid;[14] polymerisation occurs rapidly at pH = 8 and temperatures above 50 °C in the presence of 2 mol % of a radical initiator. It was possible to prevent the polymerisation of vinylboronic acid using a lower reaction temperature or a phosphate buffer (see entries 9 and 10, Table 4); however, this was only achieved at the expense of the overall conversion. Hence, it was concluded that the use of *in situ* generated vinylboronic acid was inferior overall, compared to using vinyltrifluoroborate 9. Therefore, a full optimisation programme was carried out for the SM coupling using commercially available potassium vinyltrifluoroborate 9, and the results are recorded in Table 5.

The use of organotrifluoroborates in SM coupling is well recorded;[16] however, the choices of solvents and bases that can be employed for a potentially industrially acceptable processes is a consideration. Hence, different solvents and bases (both organic and inorganic) were examined. From an examination of the results outlined in Table 5, it was found that the reaction

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proceeded in all of the solvents examined (MeCN, THF, IPA, MeOH, and toluene−water mixtures); however, the higher-boiling conditions involving toluene−water were consistently the best performing (entries 12−20, Table 5). In addition, the use of organic bases (^{t}BuNH$_2$ or Et$_3$N) produced **1** in high yields, but most importantly with little or none of the undesired byproduct **11** being produced (entries 2, 5, 9, 10, 13, 14). Unfortunately, the resulting **1** was coloured (orange-yellow) and was susceptible to rapid polymerisation upon standing. The colouration and polymerisation were attributed to traces of residual Pd, and the instability seemed to be correlated to the presence of the byproduct **11**. In contrast, when inorganic bases were used, the final product was almost always contaminated with the undesired byproduct **11**. An important finding was that the impurity **11** could be eliminated completely by dropping the pH of the reaction with the use of NaOAc as the base (entry 15, Table 5); however, the reaction stalled prematurely, and despite extensive efforts, it was not possible to improve the conversion. Considering the mode of action of **1** as a cross-linking agent[3] which can generate the vinylsulfone, it not surprising that this can occur under the reaction conditions and that simple pH control could avoid the problem. However, reaction conditions needed to be found which both avoided the formation of the byproduct **11** (lower pH) and allowed the reaction to proceed to completion. Further conditions examined, therefore, included preparation of the vinyltrifluoroborate **9** *in situ* using an adaptation of the literature protocol[14] (entry 18). Despite extensive efforts, this reaction also stalled prematurely, giving a maximum of conversion of 80%. The best results were obtained when using toluene−water and K$_2$CO$_3$, which on a 10 g scale proceeded to 97% conversion with only a small amount of byproduct **11** present (entry 12, Table 5). However, this reaction could not be scaled up to 50 g without a drop in yield and an increase in byproduct formation. The solution to both prevention of the formation of the byproduct **11** and high conversion was a combination of K$_2$CO$_3$ and NaOAc; when tested on large scale (100 g), it was pleasing to find that this reaction proceeded in high yields (90%), and more importantly, the isolated **1** was pure and stable (entry 20, Table 5). The advantage of this procedure is that the pure **1** obtained by this method has a longer shelf life; it can be stored in a freezer (∼−30 °C) for at least 6 months, or for up to 3 weeks at room temperature without polymerisation. The stability of **1** can be improved further by washing it with an aqueous solution of sodium ascorbate during the workup. It is likely that this washing process removes any free radicals from the organic phase and, hence, stabilises **1** when all of the solvent is removed *in vacuo*. **1** obtained from this protocol was tested in emulsion polymerisation and gave positive, reproducible results when subjected to emulsion polymerisation reactions, as reported.[3]

Conclusions

Using the best processes discussed herein, it is possible to produce reproducible batches of 70 g quantities of **1** from 100 g quantities of sulfone **3** in a clean and efficient manner, with minimal waste. Most importantly, the HESS obtained by this process is pure and stable for reasonable periods, even at ambient temperature, and is therefore ideal for safe pilot-plant-

based production of quantities which are suitable in emulsion polymerisation. However, for larger-scale, longer-term production, a cheaper process is likely to be required. This new route to HESS avoids all of the handling, environmental, and waste issues associated with the stryenesulfonate route which uses ethylene oxide, thionyl chloride, and zinc.[3] The effective mass yield (EMY)[17] is calculated to be 8.8% (assuming solvents are recycled) for this route versus 4.4% (also assuming solvents are recycled) for the original styrenesulfonate-based process. However, there are further major advantages to this new HESS synthesis which is not summarised by the EMY, i.e. that there is one reaction stage carried out without reaction solvent, one carried out in water−acetonitrile, one in toluene−water, and no problematic waste disposal issues. This compares with the previous route which used an excess of phosphorous oxychloride (removed by distillation), a reduction reaction which produces two equivalents of zinc-based waste, and a reaction which involved use of ethylene oxide and a diethyl ether extraction. Hence, this represents a substantial improvement in the overall process in terms of yield, reproducibility, and environmental impact, and it is suitable for the development of a potentially commercial viable process route to HESS.

Experimental Section

General Experimental. All ^{1}H NMR spectra were recorded on either a Varian Mercury-400 or Bruker Avance-400 spectrometers. ^{13}C NMR spectra were recorded on the Varian Mercury-400 and Bruker Avance-400 instruments at frequencies of 100 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS. GC−MS analysis was carried out on an Agilent 6890N GC equipped with a 5973N MSD Performance Turbo CI running in EI mode, and an Anatune Focus Autosampler/liquid handler. GC analysis was carried out on HP 5890 series II using Varian Factor Four column at 200 °C using 1,2-dichlorobenzene (DCB) as internal standard (calibration plots were obtained with $R^2 = 0.995$). EI mass spectrometry was performed on a 973N MSD Performance Turbo ci. ES was performed on either Waters ZQ 400 or Micromass Quattro II (EPSRC facilities, Swansea). All IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. UV−vis spectra were recorded on a Unicam UV2 spectrometer. All adiabatic reactions were carried out using a Thermos model 32-34-50 flask, Filler 32-50F with a 0.5 L capacity and equipped with magnetic stirring. All temperature readings were made using a Testo 946 digital thermometer with a Testo type T temperature probe linked to a PC via an RS232/USB connector. Data was stored directly on the PC using the Testo Comfort software and exported to MS Excel for data processing. The calorimetry was carried out using a E459 Simular HEL Reaction Calorimeter equipped with a 1 L double-jacketed glass vessel, a PT100 temperature probe, a 150 W internal heater, and a Julabo FP50HD refrigerating and heating circulator to control oil temperature. Dosing was ensured by either a Prominent Gala 1601 pump (dosing by mass) or a Harvard 11 syringe pump fitted with a 50 mL syringe (dosing by volume). Melting points were obtained using Gallenkamp

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SG95/05/244 apparatus. When required glassware was oven-dried (130 °C) before use and cooled under a positive pressure of argon. Dry solvents were obtained from commercial drying system. Chemical reagents and materials were purchased directly from Aldrich and used without further purification, unless stated otherwise. Potassium vinyltrifluoroborate was purchased from Frontier Scientifc Ltd. Pd-scavengers, 3-mercaptopropyl ethyl sulfide silica, SPM3, and SPM36, were purchased from PhosphonicS Ltd., ethylenediaminotriacetic acid acetamide polymer bound was purchased from Sigma-Aldrich.

Synthesis of 4-Hydroxyethylthiobromobenzene 5. 2-Chloroethanol (142 mL, 2.2 mol) was added at steady stream over a 1 h period to a stirred suspension of 4-bromothiophenol (400 g, 2.12 mol) in an aqueous solution of NaOH (85 g, 2.12 mol, 1.00 equiv in 500 mL) at 40 °C. Upon addition, the exotherm was detected. The mixture was then allowed to cool to room temperature and stirred for a period of 4 h. After completion of the reaction was confirmed (GC analysis), the mixture was diluted with brine (200 mL) and ethyl acetate (500 mL), and the two layers were separated. The organic phase was dried (MgSO$_4$) and solvent removed to give the sulfide (490 g, >99%) as a yellow oil; δ_H (CDCl$_3$) 2.02 (1H, br s, OH), 3.10 (2H, t, J 5.6, CH_2), 3.75 (2H, t, J 5.6, CH_2), 7.25 (2H, dt, J 8.8 and 2.8, ArH), and 7.42 (2H, dt, J 8.8 and 2.8); δ_C (CDCl$_3$) 37.5 (CH_2), 60.5 (CH_2), 120.7 (ipso ArC), 131.8 (ortho ArC), 132.3 (ortho ArC), and 134.4 (ipso ArC); ν_{max}/cm^{-1} (film) 3480 (broad, OH), 2920 (C—H), 1570 (C=C), 1470 (s), 1290 (s), 1170, 1090 (s), 1060 (s, two bands), 1000 (s), and 804 (arom. C—H bend, 1,4-di subs.); m/z (ES$^+$) 232.9631 (MH$^+$, C$_8$H$_{10}$SOBr$^+$ requires 232.9630); m/z (EI) 234, 232, 203, 201, 190, 188, 122 (100%), and 108.

Synthesis of 4-Hydroxyethylsulfonylbromobenzene 3. A solution of 4-hydroxyethylthiobromobenzene, **5** (200 g, 0.86 mol), in MeCN (1 L) was added to a solution of NaOH (2.07 g, 0.052 mol) and B(OH)$_3$ (2.67 g, 0.043 mol) in water (0.8 L). The mixture was then heated until the internal temperature of the reaction was 55 °C. At this point the heating was removed, and aqueous H$_2$O$_2$ (35% w/v, 158 mL, 1.81 mol) was added at such a rate that the internal temperature of the reaction remained between 55−60 °C. Once the addition of hydrogen peroxide was complete, the reaction mixture was allowed to cool to room temperature. Ethyl acetate (500 mL) was added to the reaction mixture, and the phases were separated. The organic phase was washed with aqueous sodium thiosulfate (10% w/v) until the test for peroxide became negative. The organic phase was then washed with brine (500 mL) and solvent removed *in vacuo* to give the sulfone (210 g, 92%) as a white solid; δ_H (CDCl$_3$) 2.62 (1H, t, J 5.5, OH), 3.33−3.37 (2H, m, CH_2OH), 3.99−4.04 (2H, m, CH_2−SO$_2$), 7.74 (2H, dt, J 8.5, 4.5, ArH) and 7.80 (2H, dt, J 8.5, 4.5, ArH) Addition of D$_2$O lead to the disappearance of the peak at 2.62; δ_C (CDCl$_3$) 56.4

(CH_2OH), 58.5 (CH_2SO$_2$), 129.6 (Br−C), 129.7 (ortho ArC), 132.9 (ortho ArC) and 138.3 (C−SO$_2$); Mp 61.9−63.4 °C; ν_{max}/cm^{-1} (neat) 3480 (O−H), 3090 (C−H), 1640 (C=C), 1570 (C=C), 1470, 1390, 1310 (S=O), 1270 (s, C−O), 1140 (s, S=O), and 840 (arom. C−H bend, 1,4-di subs.); m/z (ES$^+$) 281.9794 (M + NH$_4$$^+$, C$_8H_{13}NO_3SBr^+$ requires 281.9798); m/z (CI$^+$) 284 (100%), 282, and 204.

Synthesis of 4-Hydroxyethylsulfonylstyrene 1. A suspension of K$_2$CO$_3$ (50 g, 0.38 mol), NaOAc (60 g, 0.76 mol), 4-hydroxyethylsulfonylbromobenzene, **3** (100 g, 0.38 mol), potassium vinyltrifluoroborate (66 g, 0.50 mol), and PPh$_3$ (5 g, 0.19 mmol) in toluene (4 L) and water (0.5 L) was thoroughly degassed for a period of 30 min by sparging with argon. Palladium(II) acetate (1.7 g, 7.6 mmol, 2 mol %) was added and the stirred mixture heated to 80 °C under argon. The mixture was then refluxed for 12 h and cooled to room temperature, and since HESS is susceptible to radical-catalysed polymerization, a radical trap di-*tert*-butylphenol (0.5 mg) was added. The aqueous phase was then separated. The organic phase was washed with a 10% w/v aqueous solution of sodium ascorbate (0.5 L) and brine (0.5 L) and dried (MgSO$_4$). The solution was then stirred for 15 h with Pd scavengers (SPM3) which were then removed by filtration. The solvent was evaporated to give yellow oil out of which PPh$_3$O precipitated and was removed by filtration to give HESS (72 g, 90%). δ_H (CDCl$_3$) 3.00 (1H, br s, OH), 3.34 (2H, t, J 5.5, CH_2OH), 3.97 (2H, t, J 5.5, CH_2SO$_2$), 5.46 (1H, d, J 11.0, CH=CHH), 5.90 (1H, d, J 17.5, CH=CHH), 6.75 (1H, dd, J 17.5, 10.5, CH=CH$_2$), 7.56 (2H, d, J 8.5, ArH), and 7.86 (2H, d, J 8.0, ArH); δ_C (CDCl$_3$) 56.4 (CH$_2$OH), 58.3 (CH$_2$SO$_2$), 118.4 (ArCHCH$_2$), 127.1 (ArCH), 128.4 (ArCH), 135.2 (ArCHCH$_2$), 137.7 (CCHCH$_2$), and 143.3 (C-SO$_2$); all other spectroscopic and analytical data were identical to those reported in the literature.[2,3]

Supporting Information Available

General experimental methods, ^{1}H and ^{13}C spectra for compounds **5**,**3**,**1**, and GC, MS, and TGA data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.