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Tetrabutylammonium Iodide Mediated Synthesis of β-Alkoxy Sulfides and Vinyl Sulfones by Using Benzenesulfonyl Chlorides as the Sulfur Sources under Acidic or Alkaline Conditions

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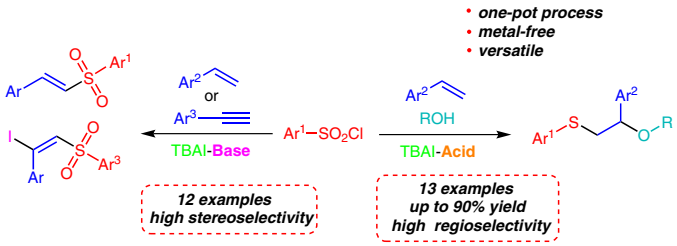

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Abstract The tetrabutylammonium iodide (TBAI)-promoted generation of sulfur-containing compounds from benzenesulfonyl chlorides and alkenes is described. Under acidic condition, a wide range of β-alkoxy sulfides were obtained in good to excellent yields, whereas under alkaline conditions, various vinyl sulfones were produced in moderate to good yields. A novel preparation of (*E*)-β-iodovinyl sulfones was achieved through direct difunctionalization of alkynes with benzenesulfonyl chlorides and TBAI.

Key words arenesulfonyl chlorides, oxysulfenylation, aralkenes, aralkynes, sulfides, sulfones

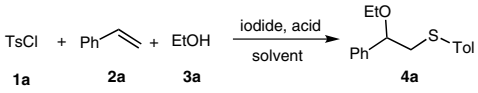
Because they exhibit good or excellent biological activities, sulfur-containing compounds play an integral role in industry and society.[1] They are also among the most significant chemicals in organic synthesis.[2] Over the years, many different ways have been developed to synthesize sulfur compounds, such as thiolation, sulfonylation, or thioetherification.[3] In all these synthetic methods, sulfur functionalization of unsaturated C–C bonds is regarded as a potential approach to the construction of C–S bonds, and it has found widespread use in synthetic transformations such as oxysulfenylation, disulfidation, iodosulfonylation, and oxysulfonylation.[4] In conventional synthesis and production, the sulfur functionalization of C–C unsaturated bonds catalyzed by transition metals (Fe, Ni, Cu, etc.) provides a highly efficient and convenient method for simultaneously producing two new vicinal carbon–heteroatom bonds.[5] Thiophenols and disulfides are often used as sulfur source of choice in organic syntheses. However, metallic catalysts and some sulfur sources are of great concern due to their widespread use and their adverse effects on the environment and human beings. From the ecological perspective, several problems associated with the above-mentioned synthetic methods need to be resolved: (1) the use of metallic catalysts is harmful to the environment; (2) the above-mentioned sulfur sources are frequently restricted by their high price, poor stability, and high toxicity; and (3) there are few reports on the generation of β-alkoxy sulfides or (*E*)-β-iodovinyl sulfones.

To address those issues, Tian and co-workers developed an I_2-catalyzed preparation of β-alkoxy sulfides by opening the C=C double bonds of styrenes with benzenesulfonylhydrazides as sulfur sources.[6] Other groups have reported novel approaches to β-alkoxy sulfides.[7] For vinyl sulfones, synthetic methods have been reported by Wang and co-workers,[8] Shi and co-workers,[9] and others.[10] The protocols proved to be convenient and flexible methods for synthesizing vinyl sulfones. Nevertheless, from the point of view of the raw materials, derivatives of the above-mentioned sulfur sources needed to be synthesized, because these derivatives are not readily available on the market. It is worth noting that the relevant substrates are prepared from benzenesulfonyl chlorides. Oddly, the synthesis of various thioethers by direct sulfur-functionalization of alkenes with benzenesulfonyl chlorides as sulfur sources has rarely been reported. In 2011, You and co-workers reported a PPh_3-mediated sulfenylation of indolizines and related hetarenes in which benzenesulfonyl chlorides were used as sulfur sources.[11] These facts suggest that a simple and efficient approach to β-alkoxy sulfides and vinyl sulfones from cheap and easily available sulfur compounds as sulfur sources under metal-free conditions is still required. We therefore developed a TBAI–acid/base-mediated protocol for the generation of β-alkoxy sulfides and vinyl sulfones by using benzenesulfonyl chlorides as the sulfur source.

First, we examined the reaction of 4-methylbenzenesulfonyl chloride (**1a**; tosyl chloride), styrene (**2a**), ethanol (**3a**), and NaI in the presence of HBr at 80 °C in toluene for 15 hours, and we obtained the desired production **4a** in 28%

yield (Table 1, entry 2). To make further improvement, we tested various iodides and we found that TBAI was the best choice, giving the corresponding compound **4a** in 55% yield (entries 1–5). We then tested several acids (such as HCl, HCO_2H, and TsOH) for this transformation, and we found that HBr gave the best results (entries 5–11). We also screened a number of solvents in an attempt to improve the reaction conditions, and we found that EtOAc was the optimal reaction medium for this transformation (entries 5 and 12–18). We also examined the effect of the molar ratio of TBAI and HBr, and we found that the best results were obtained with four equivalents each of TBAI and HBr (entries 19–21). Finally, when the reaction was performed at a lower temperature of 50 °C, a 62% yield of **4a** was obtained (entry 22).

Table 1 Optimization of the Reaction Conditions[a]

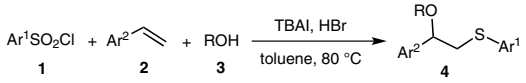


Entry	Iodide (equiv)	Acid (equiv)	Solvent	Yield[b,c] (%)
1	I_2 (4.0)	HBr (4.0)	toluene	trace
2	NaI (4.0)	HBr (4.0)	toluene	28
3	NH_4I (4.0)	HBr (4.0)	toluene	17
4	KI (4.0)	HBr (4.0)	toluene	32
5	TBAI (4.0)	HBr (4.0)	toluene	55
6	TBAI (4.0)	HCl (4.0)	toluene	11
7	TBAI (4.0)	HF (4.0)	toluene	16
8	TBAI (4.0)	HCOOH (4.0)	toluene	trace
9	TBAI (4.0)	AcOH (4.0)	toluene	21
10	TBAI (4.0)	TsOH (4.0)	toluene	35
11	TBAI (4.0)	PvOH (4.0)	toluene	trace
12	TBAI (4.0)	HBr (4.0)	DCE	75
13	TBAI (4.0)	HBr (4.0)	DME	47
14	TBAI (4.0)	HBr (4.0)	1,4-dioxane	15
15	TBAI (4.0)	HBr (4.0)	DMSO	trace
16	TBAI (4.0)	HBr (4.0)	DMF	trace
17	TBAI (4.0)	HBr (4.0)	EtOAc	85
18	TBAI (4.0)	HBr (4.0)	H_2O	27
19	TBAI (3.0)	HBr (4.0)	EtOAc	65
20	TBAI (5.0)	HBr (4.0)	EtOAc	84
21	TBAI (4.0)	HBr (3.0)	EtOAc	60
22[d]	TBAI (4.0)	HBr (4.0)	EtOAc	62

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), **3a** (0.8 mmol), acid (0.8 mmol), solvent (1.0 mL), 80 °C, 15 h.
[b] In all cases, compound **4a** was obtained as a single regioisomer.
[c] Yield of isolated product.
[d] Reaction performed at 50 °C.

The scope and limitations of the TBAI/HBr-promoted reactions of various alkenes with substituted benzenesulfonyl chlorides in the presence of various alcohols was tested under the optimized reaction conditions. Generally, the target compounds **4** were obtained in good to excellent yields (Table 2). Benzenesulfonyl chlorides **1** with electron-rich aromatic groups showed higher reactivities than did those bearing electron-accepting groups (entries 1–5). For various substituted alkenes, the difference between electron-donating groups and electron-withdrawing groups was not great (entries 6–8). Unfortunately, when the reaction was carried out with alcohols other than ethanol, we did not obtain the corresponding product. By analyzing ^{1}H NMR spectra, we deduced that in the presence of the acid, an ester-exchange reaction occurred between EtOAc and other alcohols to form ethanol. We therefore examined the reactions of several other alcohols in DCE, and we obtained the desired products **4i**–**k** in 62–71% yield (entries 9–11). We found that the steric hindrance of the alcohols had some effects on the yield of this reaction. In addition, other kinds of alkene were also subjected to the addition reaction under the standard reaction conditions. Note that 1,1′-ethene-1,1-diyldibenzene reacted with tosyl chloride (**1a**) in the presence of EtOH to give a different product **4l** (entry 12). Based on previously reported results[12] we reasoned that TsCl was reduced to TolSCl, which reacts with 1,1′-ethene-1,1-diyldibenzene to give an unstable three-membered cyclic sulfonium compound **B** (see Scheme S1 in the Supporting Information). This intermediate **B** can be easily transformed into carbocation **C**. Finally, deprotonation of intermediate **C** generates the corresponding product **4l**. To our delight, nonaromatic alkenes could also be used in this reaction system; for example, product **4m** was obtained by using cyclohexene as the substrate (entry 13).

Table 2 Scope of the Reaction with Alkenes[a]



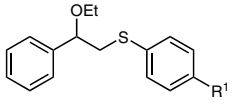
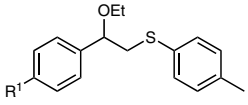
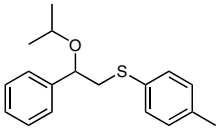
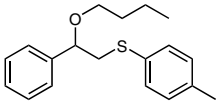
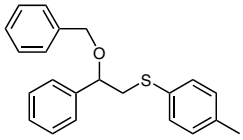
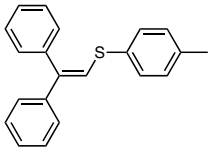
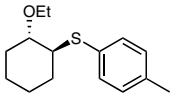
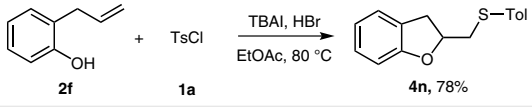
Entry	Product[b]			Yield[c] (%)
1		R^1 = 4-Me	**4a**	85
2		R^1 = H	**4b**	76
3		R^1 = 4-MeO	**4c**	90
4		R^1 = 4-F	**4d**	80
5		R^1 = 4-Br	**4e**	81
6		R^1 = 4-Me	**4f**	78
7		R^1 = 4-Cl	**4g**	80
8		R^1 = 4-O_2N	**4h**	72

Table 2 (continued)

Entry	Product[b]		Yield[c] (%)
9[d]		**4i**	69
10[d]		**4j**	71
11[d]		**4k**	62
12		**4l**	89
13		**4m**	65

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), **3** (0.80 mmol), TBAI (0.80 mmol), HBr (0.80 mmol), EtOAc (1.0 mL), 80 °C, 15 h.
[b] No regioisomer was detected by ^{1}H NMR spectroscopic analysis of the crude product.
[c] Yield of isolated product.
[d] The reaction was carried out in DCE.

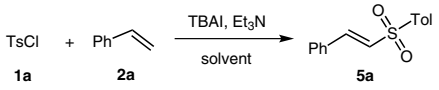
On the basis of the above satisfactory results, we wished to apply this reaction system in organic synthesis. We selected 2-allylphenol (**2f**) as substrate to synthesize the 2-substituted 2,3-dihydrobenzofuran **4n** in a preliminary experiment (Scheme 1). As expected, **4n** was successfully prepared in good yield. We believe that this method provides an alternative way to prepare 2-substituted 2,3-dihydrobenzofurans.



Scheme 1 Reaction of 2-allylphenol (**2f**) with tosyl chloride (**1a**)

To go a step further and to confirm that different products can be obtained under different conditions, we carried out the reaction in the presence of Et_3N instead of HBr. We were pleased to see that (*E*)-2-phenylvinyl 4-tolyl sulfone (**5a**) was obtained in 42% yield (Table 3, entry 1). We therefore reexamined the optimal conditions for the formation of vinyl sulfones by screening various iodides, bases, and solvents (entries 2–16). When the amount of TBAI or Et_3N was reduced to 1.5 equivalents, the yield fell to 55% and 63% yield, respectively (Table 3, entries 14 and 16). When we tried to increase the amount of TBAI to 2.5 equivalents, the yield of **5a** showed no improvement (entry 15).

Table 3 Optimization of Reaction Conditions[a]

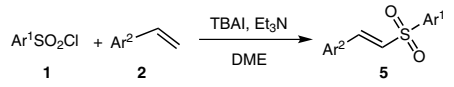


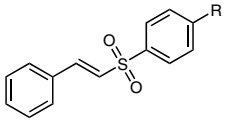
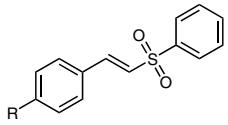
Entry	Iodide (equiv)	Base (equiv)	Solvent	Yield[b] (%)
1	TBAI (2.0)	Et_3N (2.0)	EtOAc	42
2	NaI (2.0)	Et_3N (2.0)	EtOAc	25
3	KI (2.0)	Et_3N (2.0)	EtOAc	27
4	NH_4I (2.0)	Et_3N (2.0)	EtOAc	18
5	I_2 (2.0)	Et_3N (2.0)	EtOAc	11
6	TBAI (2.0)	py (2.0)	EtOAc	39
7	TBAI (2.0)	K_2CO_3 (2.0)	EtOAc	23
8	TBAI (2.0)	Na_2CO_3 (2.0)	DCE	25
9	TBAI (2.0)	Et_3N (2.0)	MeCN	43
10	TBAI (2.0)	Et_3N (2.0)	toluene	57
11	TBAI (2.0)	Et_3N (2.0)	1,4-dioxane	67
12	TBAI (2.0)	Et_3N (2.0)	DMSO	trace
13	TBAI (2.0)	Et_3N (2.0)	DME	75
14	TBAI (1.5)	Et_3N (2.0)	DME	55
15	TBAI (2.5)	Et_3N (2.0)	DME	72
16	TBAI (2.0)	Et_3N (1.5)	DME	63

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), solvent (1.0 mL), 100 °C, 12 h, sealed Schlenk tube.
[b] Yield of isolated product.

By using the standard conditions, a range of benzenesulfonyl chlorides and terminal alkenes were employed in the procedure to test the scope and universality of this method (Table 4). A variety of substituents on the aromatic ring of the benzenesulfonyl chloride were well tolerated, including electron-accepting groups (chloro or bromo; entries 6 and 8) and electron-donating groups (methyl or methoxy; entries 1 and 3). It must be pointed out that sensitive functional groups (F, Cl, and Br) on the phenyl group of benzenesulfonyl chlorides did not affect the reaction, and the corresponding products were obtained in moderate yields (entries 4–6). Furthermore, a series of styrenes were subjected to the reaction, and some gave the corresponding products in moderate to good yields (entries 7 and 8). However, with a styrene bearing a strongly electron-attracting group (4-O_2N), the yield of the target product was low (entry 9).

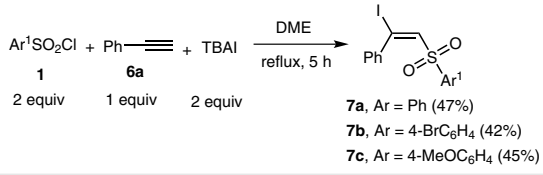
Table 4 Scope of the Reaction with Alkynes[a]



Entry	Product			Yield[b] (%)
1		R = 4-Me	**5a**	75
2		R = H	**5b**	69
3		R = 4-MeO	**5c**	72
4		R = 4-F	**5d**	55
5		R = 4-Cl	**5e**	64
6		R = 4-Br	**5f**	67
7		R = 4-Me	**5g**	76
8		R = 4-Cl	**5h**	61
9		R = 4-O_2N	**5i**	52

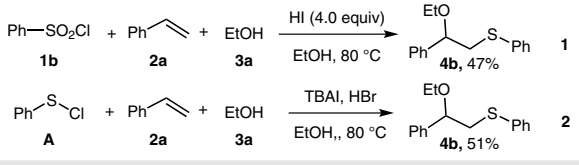
[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), Et_3N (0.4 mmol), TBAI (0.4 mmol), DME (1.0 mL), 100 °C, 12 h, sealed Schlenk tube.
[b] Yield of isolated product.

In addition, when the reaction was carried out in absence of Et_3N by using ethynylbenzene (**6a**) as substrate in DME, the corresponding (*E*)-β-iodovinyl sulfones were obtained in moderate yields (Scheme 2).



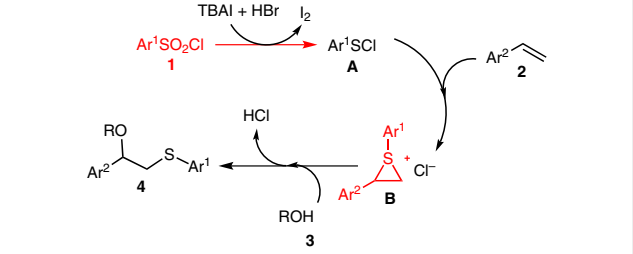
Scheme 2 Scope of the reaction with ethynylbenzene

We also performed a preliminary study to gain further insight into the reaction mechanism for the generation of β-alkoxy sulfides (Scheme 3). When the reaction was completed by using 4.0 equivalents of HI as a reducing agent in a closed tube, the target product was obtained in 47% yield. When the reaction was carried out with benzenesulfenyl chloride (**A**) instead of benzenesulfonyl chloride as a substrate, the corresponding product **4b** was obtained in 51% yield.



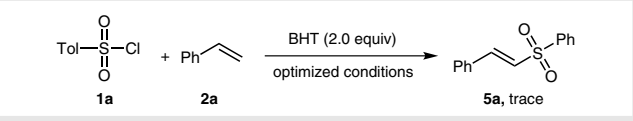
Scheme 3 Control experiments for the generation of β-alkoxy sulfides

On the basis of these observations and previous reports,[7,11,13,14] a plausible reaction pathway is proposed (Scheme 4). First, the benzenesulfonyl chloride is reduced to the corresponding sulfenyl chloride **A** by HI formed by the reaction of TBAI with HBr. Sulfenyl chloride **A** then reacts with styrene **2** to form thiiranium ion **B**. Finally, ring opening of intermediate **B** with alcohol **3** generates the corresponding thio ether **4** and acid (HCl).



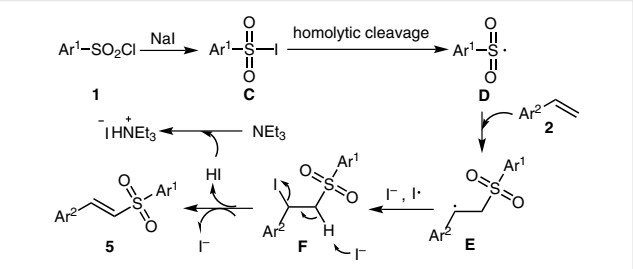
Scheme 4 A plausible mechanism for oxysulfenylation of alkenes

We also performed relevant control experiment for vinyl sulfones (Scheme 5). When the reaction was carried out in the presence of butylated hydroxytoluene (BHT) under the standard conditions, the progress of the reaction was severely suppressed and only a trace amount of target product **5a** was obtained.



Scheme 5 Control experiments for the generation of vinyl sulfones

We therefore reason that a radical process is involved in this reaction. We propose a plausible mechanism for the formation of vinyl sulfones (Scheme 6), based on previous reports.[8–10] First, the arenesulfonyl chloride **1** reacts with TBAI to generate the sulfonyl iodide **C**. This undergoes homolytic cleavage to produce a sulfonyl radical **D**, which reacts with styrene **2** to form intermediate **E**. Intermediate **E** reacts with an iodine radical to form iodo compound **F**. Elimination of HI from F finally gives the product **5** together with HI, which reacts with Et_3N to form the amine salt.



Scheme 6 Plausible mechanism for the formation of vinyl sulfones

In summary, two simple and efficient approaches have been developed for the synthesis of β-alkoxy sulfides and vinyl sulfones.[15–17] Easily available and cheap benzenesulfo-

nyl chlorides are used as sulfur sources to generate the corresponding sulfides. These two synthetic methods might be useful for the functionalization of aromatic alkenes or alkynes, and they are complementary to previous strategies.

References and Notes

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(15) **β-Alkoxy Sulfides 4; General Procedure**

40% aq HBr (117 μL, 0.8 mmol) was added to a solution of the appropriate benzenesulfonyl chloride 1 (0.20 mmol), styrene 2 (0.24 mmol), alcohol **3** (0.8 mmol), and TBAI (295.5 mg, 0.8 mmol) in EtOAc or DCE (2 mL), and the mixture was stirred at 80 °C for 15 h in a sealed Schlenk tube. When the reaction was complete, the mixture was diluted with EtOAc, the reaction was quenched with sat. aq $Na_2S_2O_3$ (10 mL), and the mixture was extracted with EtOAc (2 × 15 mL). The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–PE).

1-[(2-Ethoxy-2-phenylethyl)sulfanyl]-4-methylbenzene (4a)

Colorless oil; yield: 46.3 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 7 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 4.39–4.35 (m, 1 H), 3.42–3.26 (m, 3 H), 3.09–3.05 (m, 1 H), 2.31 (m, 3 H), 1.17 (t, *J* = 8.0 Hz, 3 H).

1-{1-Ethoxy-2-[(4-tolyl)sulfanyl]ethyl}-4-nitrobenzene (4h)

Colorless oil; yield: 45.6 mg (72%). 1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 4.47–4.44 (m, 1 H), 3.41–3.31 (m, 3 H), 3.27–3.03 (m, 1 H), 2.32 (s, 3 H), 1.19 (t, *J* = 8.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 147.6, 136.7, 131.9, 130.5, 129.8, 127.6, 123.7, 80.0, 65.3, 41.9, 21.0, 15.2. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NNaO_3S$: 340.0978; found: 340.0972.

1-{[2-(Benzyloxy)-2-phenylethyl]sulfanyl}-4-methylbenzene (4k)

Colorless oil; yield: 41.4 mg (62%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 12 H), 7.05 (d, *J* = 4.0 Hz, 2 H), 4.49–4.47 (m, 2 H), 4.29 (d, *J* = 4.0 Hz, 1 H), 3.37–3.34 (m, 1 H), 3.12–3.09 (m, 1 H), 2.30 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 138.0, 136.1, 132.8, 130.1, 129.7, 128.6, 128.3, 128.2, 127.8, 127.7, 127.6, 80.1, 70.8, 42.4, 21.0. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}NaOS$: 357.1284; found: 357.1280.

(16) **Vinyl Sulfones 5; General Procedure**

Et_3N (56 μL, 0.4 mmol) was added to a solution of the appropriate benzenesulfonyl chloride **1** (0.40 mmol), styrene **2** (0.20 mmol), and TBAI (147.8 mg, 0.4 mmol) in DME (1 mL), and the mixture was stirred at 100 °C for 15 h in a sealed Schlenk tube. When the reaction was complete, the mixture was diluted with EtOAc, the reaction was quenched with sat. aq $Na_2S_2O_3$ (10 mL), and the mixture was extracted with EtOAc (2 × 15 mL). The

organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–PE).

1-Methyl-4-{[(*E*)-2-phenylvinyl]sulfonyl}benzene (5a)

White solid; yield: 38.7 mg (75%); mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 4.0 Hz, 2 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.46 (s, 2 H), 7.35 (t, *J* = 8.0 Hz, 5 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 2.42 (s, 3 H).

(17) **(*E*)-β-Iodovinyl Sulfones 7; General Procedure**

TBAI (147.8 mg, 0.4 mmol) was added to a solution of the appropriate benzenesulfonyl chloride **1** (0.40 mmol) and aralkyne **2** (0.20 mmol) in DME (1 mL), and the mixture was stirred in a sealed tube at reflux for 5 h. When the reaction was complete, the mixture was diluted with EtOAc, the reaction was quenched with sat. aq $Na_2S_2O_3$ (10 mL), and the mixture was extracted with EtOAc (2 × 15 mL). The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–PE).

(*E*)-2-Iodo-2-phenylvinyl 4-Methoxyphenyl Sulfone (7c)

Yellow oil; yield: 35.9 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 4.0 Hz, 2 H), 7.37 (s, 1 H), 7.30–7.22 (m, 5 H), 6.84 (d, *J* = 4.0 Hz, 2 H), 3.85 (s, 3 H). 13C NMR (100 MHz, $CDCl_3$): δ = 163.55, 141.4, 132.5, 132.1, 131.0, 129.9, 129.0, 128.5, 127.9, 114.6, 55.7. HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{17}INO_3S$: 417.9968; found: 417.9963.