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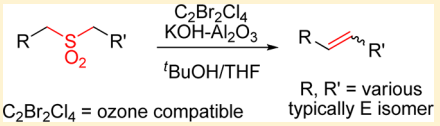
1,2-Dibromotetrachloroethane: An Ozone-Friendly Reagent for the in Situ Ramberg–Bäcklund Rearrangement and Its Use in the Formal Synthesis of *E*-Resveratrol

Stefan C. Söderman and Adrian L. Schwan*

Department of Chemistry, University of Guelph, Guelph, Ontario N1G 2W1, Canada

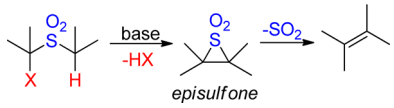
Supporting Information

ABSTRACT: Dibromotetrachloroethane ($C_2Br_2Cl_4$) is demonstrated as a halogenating reagent for the one-pot conversion of sulfones to alkenes by way of the Ramberg–Bäcklund rearrangement. Dibromotetrachloroethane successfully replaces known ozone depleting agents CCl_4, CBr_2F_2 and $C_2Br_2F_4$. A formal synthesis of *E*-resveratrol is demonstrated using $C_2Br_2Cl_4$.



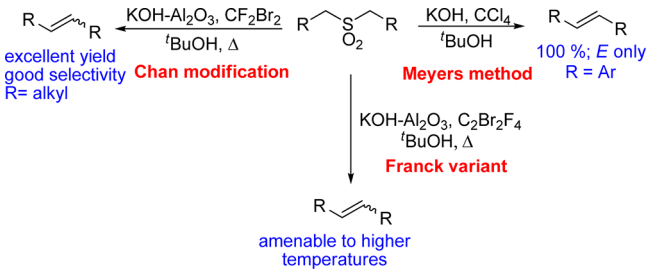
Since its inception by Swedish chemists in 1940, the Ramberg–Bäcklund rearrangement (RBR) has endured as a classic carbon–carbon bond forming reaction used time and time again through the modern history of organic synthesis.[1,2] The rearrangement has been applied in the synthesis of important organic building blocks,[3−5] natural products and several stilbenoid anticancer agents.[6−11] The RBR is the base promoted conversion of an α-halosulfone into an episulfone followed by the loss of SO_2 to give an alkene through connection of the sulfone's two α-carbons. (Scheme 1).[1] In the beginning the transformation was a two-pot process; the halogenation of the sulfone was followed by the base induced rearrangement.[2]

Scheme 1. General Ramberg–Bäcklund Rearrangement



An important breakthrough came when Meyers discovered a one-pot RBR with in situ halogenation of the sulfone followed by rearrangement and alkene formation.[12] This was achieved for benzyl sulfone using a carbon tetrachloride (CCl_4), potassium hydroxide (KOH) and *t*-butyl alcohol reaction system (Scheme 2).[12] For benzyl sulfone, the chemistry worked very well, giving quantitative yield of exclusively *E*-stilbene. However, Meyers' method is plagued by polyhalogenation and carbene-alkene insertion for dialkyl sulfone systems often giving complex mixtures of products.[12] Many of these problems were remedied by Chan's modification, which employed alumina-supported KOH (KOH-Al_2O_3), dibromodifluoromethane (CF_2Br_2), and *tert*-butanol.[13,14] Chan's protocol gave excellent yields and moderate selectivities for dialkyl systems without any significant carbene insertion or polyhalogenation. Although Chan's modification was a significant breakthrough for the in situ RBR reaction, there existed examples of sulfones that required higher temperatures to undergo the RBR and provided

Scheme 2. Key Improvements to the Ramberg–Bäcklund Rearrangement



poor yields using Chan's conditions.[15] Low yields were attributed to loss of the low boiling CF_2Br_2 when reactions required increased temperatures. Franck solved this problem by trading relatively low boiling CF_2Br_2 (23 °C) for its higher boiling homologue dibromotetrafluoroethane ($C_2Br_2F_4$, 47 °C).[15] Using Chan's system with $C_2Br_2F_4$, in place of CF_2Br_2, Franck was able to achieve the in situ RBR on some otherwise stubborn glycolipid precursors to give the corresponding alkenes in good yields.[15]

Although there is no disputing the efficacy of the halogenating agents in the aforementioned in situ RBR protocols, significant economic and environmental drawbacks do exist. One problem with using these reagents is that they are relatively expensive. The other major problem is that CCl_4, CF_2Br_2 and $C_2Br_2F_4$ are all listed as ozone depleting substances (ODS) in North America and are being actively phased out.[16] In fact, to our knowledge in the US, only one supplier provides CF_2Br_2 and $C_2Br_2F_4$. However, these materials could not be shipped to Canada because of federal regulations.[17] Hence, these practical limitations to the common in situ halogenating reagents for the RBR create a demand for a new halogenating agent devoid of such restrictions. After a literature search, it was discovered that the non-ODS, hexachloroethane (C_2Cl_6), had

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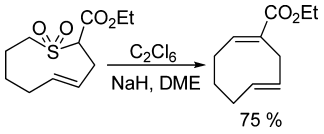
been attempted before for the in situ RBR.[18] However, the reaction proved to be highly substrate specific, working only on activated cyclic systems containing an ethyl ester α to the sulfonyl group as in the example of Scheme 3.[18]

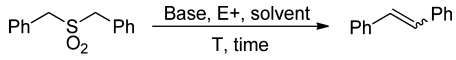
Scheme 3. RBR Using Hexachloroethane



1,2-Dibromotetrachloroethane ($C_2Br_2Cl_4$) is a common brominating reagent in organic synthesis and has been used numerous times to this end.[19−23] The compound has several attractive properties compared with the aforementioned RBR reagents. As a solid, it is practical to use quantitative molar equivalents that can be measured and introduced with ease. CBr_2F_2, on the other hand, has a boiling point of 23 °C, and challenges may arise for its quantitation. Indeed, some papers report the use of 75[5] and even >1000[24] molar equivalents of CBr_2F_2 under the Chan conditions. As noted, 1,2-dibromotetrachloroethane is relatively inexpensive, and it is not listed as an ODS. To our knowledge, $C_2Br_2Cl_4$ has never been used as a reagent for the α-bromination of sulfones or in an in situ RBR, although there is a literature report of the reagent being used to halogenate a cyclic sultone.[23] Given this lack of literature precedent and its superior price,[25] the plan was to evaluate $C_2Br_2Cl_4$ as a general reagent for the in situ RBR on unactivated substrates.

Benzyl sulfone was chosen as the substrate to begin initial investigations using $C_2Br_2Cl_4$ as the halogenating agent, because this substrate is known to undergo the in situ RBR with excellent yields and selectivity using Meyers' conditions.[2,12] In the first attempt, benzyl sulfone was dissolved in a mixture of ^{t}BuOH:H_2O (5:1) and stirred at room temperature (rt). Potassium hydroxide (KOH) was added followed by $C_2Br_2Cl_4$. The reaction was sluggish, and after 3 days of stirring at rt, NMR analysis revealed only 10% conversion of starting material to exclusively the *E*-stilbene product (entry 1, Table 1). In hopes of improving the reaction rate, the base component of Chan's reagent (KOH-Al_2O_3) was evaluated and gave an improved conversion of starting material/product ratio after 24 h of stirring at rt, and increasing the $C_2Br_2Cl_4$ to 1.5 equiv advanced the conversion further (entries 2 and 3, Table 1). In a parallel result, increasing the temperature to reflux for 12 h gave an improved conversion to 90% *E*-stilbene (entry 4, Table 1). Next, in entry 5, the amounts of both KOH-Al_2O_3 and $C_2Br_2Cl_4$ were increased and the mixture was refluxed for 12 h. Gratifyingly, increasing the amounts of both reagents brought about full substrate conversion to *E*-stilbene as analyzed by ^{1}H NMR and an eventual 95% isolated yield.

Table 1. Optimization of in Situ RBR with $C_2Br_2Cl_4$ as the Halogenating Agent



#	base (equiv)	equiv of $C_2Br_2Cl_4$	solvent[a]	temp	time	conv. (%)[b]	yield (%)[c]
1	KOH (1.0)	1.1	TBA/H_2O (5/1)	rt	3 d	10	nd
2	KOH-Al_2O_3 (15.1)	1.1	TBA	rt	24 h	72	nd
3	KOH-Al_2O_3 (15.1)	1.5	TBA	rt	24 h	77	nd
4	KOH-Al_2O_3 (15.1)	1.2	TBA	reflux	12 h	90	nd
5	KOH-Al_2O_3 (18.9)	1.8	TBA	reflux	12 h	100	95
6	KOH-Al_2O_3 (18.9)	1.8	TBA/THF (3/1)	rt	4 h	100	91

[a]TBA = ^{t}BuOH. [b]% Reaction conversion estimated by NMR. [c]The *E*/*Z* ratio was 100:0 in all cases (NMR).

To achieve the RBR on more sensitive substrates, it was felt that a lower reaction temperature should be sought. By visual inspection, the solubility of benzyl sulfone in ^{t}BuOH was rather low, which may have been a cause for the long reaction times at rt. To combat solubility issues, THF was added initially to a flask charged with benzyl sulfone to ensure full solubility. Upon complete dissolution of benzyl sulfone in THF at rt, ^{t}BuOH was added. Next, KOH-Al_2O_3 was added followed immediately by the dropwise addition of a solution of $C_2Br_2Cl_4$ in THF. Evaluation of a ^{1}H NMR spectrum of the crude reaction mixture showed complete conversion to *E*-stilbene after 4 h of stirring at rt without any detection of the Z isomer. Purification by filtration through a silica plug and subsequent flash chromatography gave exclusively *E*-stilbene in excellent yield (Table 1, entry 6).

Using the optimized reaction protocol, an exploration of the scope the reaction to other substrates was undertaken (Table 2). This was initially done by evaluating the chemistry of a series of stilbenoid derivatives (entries 2−9). Substituted 3-nitro and 3-bromo benzyl sulfones also gave excellent yields and complete stereoselectivities (entries 2 and 3). As expected, the 2-naphthyl substituted sulfone gave excellent yield and complete *E* stereoselectivity (entry 9).

Indeed all the stilbenoid substrates gave yields of ≥82% with complete *E* selectivity, including a 2-pyridyl based system, which was generated from the corresponding sulfone in 92% yield (entry 5). A 2,6-disubstituted pyridine disulfone substrate was also attempted and yielded the corresponding *E*,*E*-bis(2-styryl)pyridine with complete selectivity in moderate yield (entry 10).

These RBR conditions also worked reasonably well for a primary dialkyl system (Table 2, entry 11), which can be plagued with polyhalogenation and carbene insertion byproducts (for CCl_4).[2] The dioctyl sulfone gave the corresponding alkene in moderate yield and a selectivity comparable to that garnered by Chan's protocol without any detection of polyhalogenated byproducts.[13] Unfortunately, dicyclopentyl sulfone did not undergo the in situ RBR with the $C_2Br_2Cl_4$ system. Even with prolonged heating, increased equivalents or microwave irradiation, starting material remained without any observed evidence of alkene formation (Table 2, entries 14 and 15). This result contrasts Chan's conditions, which can bring about the conversion of dicyclopentyl sulfone to the corresponding alkene. The difference in reactivity could be attributed to steric factors of the brominating agent; $C_2Br_2Cl_4$ is a bulkier reagent than Chan's CBr_2F_2 and may be unable to brominate an already sterically hindered sulfonyl α-anion of dicyclopentyl sulfone. It is anticipated that CBr_2F_2 also has reduced entropic requirements in the transition state for the release of a Br to a nucleophile.

Cyclic sulfones have proved to be quite acquiescent to in situ RBR. As such *N*-Boc protected 1,4-thiazine *S*,*S*-dioxide was exposed to the RBR conditions, which delivered the

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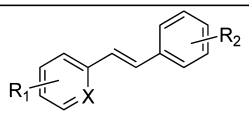
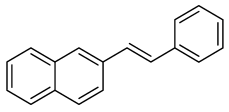
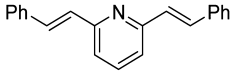
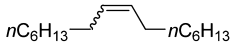
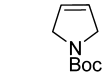
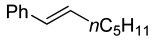
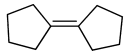
Table 2. Scope of the $C_2Br_2Cl_4$ Mediated Ramberg–Bäcklund Rearrangement

#	product	equiv. of $C_2Br_2Cl_4$	time (h)	yield (%)[a]
	 R1, R2, X			
1	H, H, CH	1.8	8	91
2	3-Br, H, CH	1.8	8	90
3	3-NO_2, H, CH	1.8	8	88
4	4-CF_3, H, CH	1.8	8	82
5	H, H, N	1.8	2	92
6	4-MeO, 3,5-bis(MeO), CH	1.8	8	81
7	4-MeO, H, CH	1.8	8	95
8	3,5-bis(MeO), H, CH	1.8	8	87
9		1.8	8	87
10		2.8	8	49
11		3.6	39	51[b]
12		1.8	4	52
13		1.2	8	64[c]
14		7.0	48[d]	0
15		3.6	4.5[e]	0

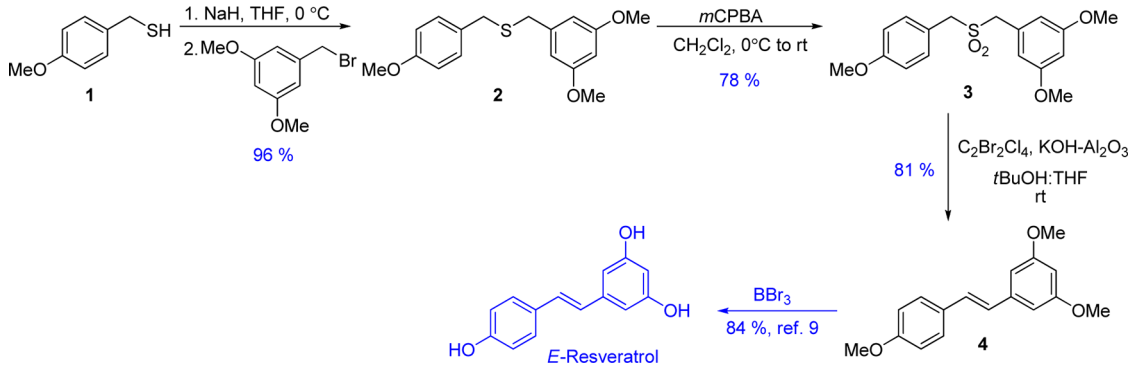
[a]Isolated yield of pure material unless otherwise indicated. [b]Obtained as an *E*:*Z* isomeric ratio of 72:28. [c]Products were obtained 91% pure. Contaminants were monobrominated congeners. [d]Mixture was heated at 79 °C. [e]Reaction performed under microwave conditions (300 W instrument) at 78 °C.

corresponding Boc protected 3-pyrroline in 52% isolated yield (Table 2, entry 12), a value similar to other 5-membered cyclic alkenes prepared under RBR conditions.[2,5,26] Finally, the RBR protocol was evaluated for the olefination of benzyl hexyl sulfone, a reaction which gave the corresponding alkene with complete *E*-stereoselectivity and 64% yield by NMR analysis. However, there was significant formation of brominated alkene byproducts, assigned to be *E*- and *Z*-PhBrC=CHC_5H_{11} (ca. 10%, inseparable by flash chromatography, detectable by GC–MS), as a consequence of dihalogenation of the sulfone substrate. This result can be explained by differences in the relative basicities of the α-protons on the benzylic and hexyl sides of the sulfone. The benzylic protons are more acidic (lower $pK_a \sim 23.4$)[27] than the alkyl α-protons ($pK_a \sim 31.0$).[27] Therefore, assuming kinetic deprotonation mirrors thermodynamic pK_a values, the benzylic carbon is more readily deprotonated and subsequently brominated than the hexyl α-carbon. Consequently, dibromination could occur at the benzylic site in competition with anion formation at the α-carbon on the hexyl side of the molecule. If two bromines are incorporated at the benzyl site, eventual formation of the α-sulfonyl anion on the hexyl side of the molecule leads to the formation of a brominated episulfone. Fast extrusion of SO_2 would yield a brominated alkene byproduct. Indeed, an analysis of the ^{1}H NMR spectrum of the reaction mixture indicated that the minor products of this 2-pentylstyrene-forming mixture possessed triplets for their lone vinylic resonance, fully consistent with bromine incorporation at the benzylic site and not the 2 position of the 2-pentylstyrene byproducts (vide supra). Substantial effort was expended to adapt the reaction conditions to reduce the amount of monobromoalkene, but improvements were minimal.

The RBR chemistry of benzyl hexyl sulfone and particularly the presence of a monobrominated alkene allow some conclusions about the reaction chemistry of the electrophile with α-sulfonyl anions. Although there is an instance of $C_2Br_2Cl_4$ acting as a source of electrophilic chlorine in the literature,[23] GC–MS analysis of the benzyl hexyl sulfone RBR mixture did not reveal any evidence in support of chlorine incorporation. On the basis of this example, $C_2Br_2Cl_4$ delivers only bromine atoms to the sulfones.

In addition to the preference for bromination and the steric arguments noted above, the observed chemistry permits additional comments about the bromination chemistry of $C_2Br_2Cl_4$, particularly in relation to that of CF_2Br_2. Since the RBR with both reagent systems occurs with the same solid phase base, the dehydrohalogenation step of the RBR under each set of conditions might be expected to be comparable, particularly since the two conditions share related solvent systems. If this is true, then differences in observed chemistry should be based on bromine incorporation. One difference has already been noted for steric effects. The chemistry of benzyl hexyl sulfone suggests that the bromination chemistry using $C_2Br_2Cl_4$ may be faster than with CF_2Br_2, presumably since the reagent at hand brominates with concurrent E2 chemistry as

Scheme 4. Formal Synthesis of Resveratrol



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opposed to carbanion or carbene formation. Chan evaluated CF_2Br_2 with benzyl hexyl sulfone in the original paper, and there is no mention of additional bromination,[13] whereas the $C_2Br_2Cl_4$ system delivered some minor brominated impurities as outlined above. For comparison, there are several examples of CCl_4 delivering unwanted chlorines.[2] It would appear that the balance between bromination and dehydrobromination is ideal for the Chan reagent, and minor problems arise in the current work with benzyl alkyl sulfones.

Given the success of this RBR method for the synthesis of stilbenoids, the total synthesis of *E*-resveratrol, a naturally occurring phenolic stilbenoid found in the skins of red grapes, was attempted. Currently *E*-resveratrol is the subject of numerous biological studies for several properties including antioxidant, cardiovascular, anti-inflammatory and antiaging properties.[28] The synthesis of *E*-resveratrol has been achieved before using an in situ RBR protocol employing the ODS, CCl_4, as the halogenating reagent.[9] The synthesis began with a thioetherification reaction between thiol **1** and 3,5-dimethoxybenzyl bromide, which gave the resulting crude sulfide (**2**) in 96% yield (Scheme 4). Next, crude sulfide **2** was oxidized to sulfone **3** with *m*CPBA in good yield. The sulfone (**3**) was then exposed to the in situ RBR protocol to give *O*-permethylated *E*-resveratrol **4** with complete stereoselectivity and excellent yield, concluding the formal synthesis of *E*-resveratrol. Subsequent demethylation with boron tribromide to give the phenolic *E*-resveratrol is well established chemistry, and in one example has been reported in 84% yield.[9]

In conclusion, $C_2Br_2Cl_4$ has proven to be an effective reagent for the in situ RBR of dibenzylic, primary dialkyl and cyclic alkyl sulfones. The principal drawbacks occur for highly hindered alkyl sulfones and when pK_a differences of the groups on the sulfones are the largest. The reagent system is clearly a greener, more pactical and more economical alternative to the ozone-depleting reagents that have been successfully used in the recent past for in situ RBRs. As such, the $C_2Br_2Cl_4$ reagent system is recommended for future syntheses requiring a Ramberg–Bäcklund protocol.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. Infrared (IR) spectra were obtained on a FT-IR spectrometer as a neat film. NMR spectra for ^{1}H NMR and ^{13}C NMR were recorded at 600 and 150.9 MHz or 400 and 100.6 MHz, respectively, in $CDCl_3$ unless otherwise noted. ^{1}H NMR and ^{13}C NMR chemical shifts are referenced to $CHCl_3$ or tetramethylsilane and are recorded in parts per million (ppm). Tetrahydrofuran (THF) was freshly distilled from benzophenone and sodium. All chemicals including benzyl bromides, benzyl thiols and benzyl sulfane were obtained from commercial sources unless otherwise noted. *m*-CPBA was obtained commercially and was dried and calibrated with benzyl sulfide before use. All air and water sensitive reagents were transferred via oven-dried nitrogen-purged syringes into flame-dried flasks under an inert nitrogen atmosphere. Flash chromatography was performed on 200–450 mesh Type 60 Å silica gel. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm, extra hard layer, 60 Å F_{254} glass-backed silica gel plates. Microwave reactions were carried out in a CEM Discover S-class reactor. Microwave reactions were carried out in vessels equipped with a Teflon cap. The temperature of the reaction mixture was monitored using a surface sensor. The dynamic method with maximum power 300W, 250 psi setting for maximum pressure and without powermax option was used. (***Caution!*** *Cardiac pacemakers require magnets to control their operation during checkout. Some danger exists if a pacemaker is positioned in close proximity to the instrument cavity.*) GC–MS experiments were performed using a Factor Four column (30 m length × 0.25 mm × 0.25 μm thickness). Spectra of ^{1}H NMR and ^{13}C NMR are presented for all purified novel compounds and for alkene products (Supporting Information).

General Procedure for Preparation of Benzyl Sulfanes. Starting thiol (3.2–12.9 mmol) was placed under a N_2 atmosphere and dissolved in dry THF (5–10 mL [25 mL for hexanethiol]). The solution was chilled to 0 °C, solid 95% NaH (1.0–1.3 equiv) was added, and the mixture was stirred for 10 min. The coreacting bromide (1.05–1.2 equiv [0.5 equiv for {bromomethyl}benzotrifluoride and bis{bromomethyl}pyridine]) in THF (2–4 mL) was added dropwise, and the mixture was stirred overnight. The reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed successively with a 10% NaOH (aq.) solution (2 × 15 mL), H_2O (15 mL), and then brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude sulfide of sufficient purity for the next step. 2.1 equiv of NaH was employed when 2-(bromomethyl)pyridine hydrobromide was the electrophile. Crude yields: 77, 88–99%. Except for the three noted below, all benzyl sulfanes have been previously reported, and characterization data (NMR and/or MP) matched that of the literature.[9,29−34] Dicyclopentyl sulfane,[35] di(*n*-octyl) sulfane[36] and *N*-Boc thiomorpholine[37] were prepared according to literature procedures.

General Procedure for MCPBA Oxidation of Sulfanes. The crude sulfane (2.8–14 mmol) was dissolved in DCM (60–75 mL) and stirred at 0 °C. MCPBA (calibrated to 77 or 83%, 2.5–3.5 equiv; 4 equiv for 2,6-bis[benzylsulfanylmethyl]pyridine) was added, and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with saturated $Na_2S_2O_3$ (aq.), $NaHCO_3$ (aq.), H_2O and brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent. Yields were 37, 53–89%. The characterization data (NMR and/or MP) for known sulfones matched literature data.[9,29,31,37−41]

Data for New Sulfones. *3-Bromobenzyl benzyl sulfone.* Crude 3-bromobenzyl benzyl sulfane (98% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (s, 1H), 7.41–7.30 (m, 6H), 7.27–7.13 (m, 2H), 3.59 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.6, 137.8, 132.0, 130.1, 130.0, 129.0, 128.6, 127.7, 127.2, 122.5, 35.7, 35.0) was subjected to oxidation as above to provide 3-bromobenzyl benzyl sulfone as a white solid (63%): mp 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (td, *J* = 1.6, 7.8 Hz, 1H), 7.48 (t, *J* = 1.6 Hz, 1H), 7.45–7.35 (m, 5H), 7.35–7.31 (m, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 4.17 (s, 2H), 4.06 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 133.8, 132.2, 130.8, 130.5, 129.5, 129.5, 129.2, 129.1, 127.3, 122.8, 58.6, 57.1; IR (neat) cm^{-1} 3064, 3033, 2987, 2941, 1643, 1633, 1412, 1302, 1277, 1116, 1072, 793. Analysis calc'd for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.79; H, 4.19.

4-Trifluoromethylbenzyl benzyl sulfone. Crude 4-trifluoromethylbenzyl benzyl sulfane (89% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.33–7.29 (m, 5H), 3.61 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.4, 137.7, 129.3 (q, *J* = 32.3 Hz), 129.3, 129.0, 128.6, 127.2, 125.4 (q, *J* = 3.7 Hz), 122.2 (q, 272.3 Hz), 35.7, 35.1) was subjected to oxidation as above to provide 4-trifluoromethylbenzyl benzyl sulfone as a white solid (82%): mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.45–7.36 (m, 5H), 4.20 (s, 2H), 4.15 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 131.6, 131.3, 131.2 (q, *J* = 31.4 Hz), 130.8, 129.3, 129.2, 127.4, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 271.6 Hz), 58.9, 57.2; IR (neat) cm^{-1} 3048, 2982, 2938, 1636, 1417, 1332, 1298, 1155, 1120, 858. Analysis calc'd for $C_{15}H_{13}F_3O_2S$: C, 57.32; H, 4.17. Found: C, 57.31; H, 4.30.

2,6-Bis[benzylsulfonylmethyl]pyridine. Obtained as a white solid (82%): mp 228–229 °C; ^{1}H NMR (400 MHz,DMSO-d_6) δ = 7.93 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.46–7.42 (m, 4H), 7.40–7.36 (m, 6H), 4.66 (s, 4H), 4.63 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.6, 138.1, 131.3, 128.4, 128.4, 128.3, 125.7, 58.9, 57.8; IR (nujol mull) cm^{-1} 3084, 3063, 3004, 2853, 1589, 1299, 1284, 1126, 774, 694. Analysis calc'd for $C_{21}H_{21}NO_4S_2$: C, 60.70; H, 5.09. Found: C, 60.59; H, 5.16.

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Benzyl 3,5-dimethoxybenzyl sulfone. Crude benzyl 3,5-dimethoxybenzyl sulfane (96% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34−7.23 (m, 5H), 6.46−6.44 (m, 2H), 6.35−6.34 (m, 1H), 3.78 (s, 6H), 3.62 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.8, 140.5, 138.1, 129.1, 128.5, 127.0, 106.9, 99.2, 55.3, 35.8, 35.7) was subjected to oxidation as above to provide benzyl 3,5-dimethoxybenzyl sulfone as a white solid (71%): mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (m, 5H), 6.56−6.52 (m, 2H), 6.47 (m, 1H), 4.14 (s, 2H), 4.06 (s, 2H), 3.79 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0, 130.9, 129.6, 129.0, 129.0, 127.5, 108.8, 101.0, 58.3, 57.9, 55.5; IR (neat) cm^{-1} 3063, 3004, 2967, 2937, 2839, 1597, 1457, 1431, 1312, 1206, 1154, 1116, 1064, 932. Analysis calc'd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92. Found: C, 62.72; H, 5.81.

Benzyl 4-methoxybenzyl sulfone. Obtained as a white solid (75%): mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41−7.37 (m, 5H), 7.29 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.11 (s, 2H), 4.07 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.2, 132.1, 130.9, 129.0, 127.7, 119.3, 114.5, 57.8, 57.4, 55.4; IR (neat) cm^{-1} 3003, 2979, 2961, 2935, 2837, 1638, 1611, 1586, 1306, 1285, 1249, 1142, 1127, 1033, 832. Analysis calc'd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.40; H, 5.81.

General One-Pot RBR Procedure for Preparation of Alkenes. The sulfone (100−120 mg, 0.307−0.510 mmol) was dissolved in THF/^{t}BuOH (2.5 mL/7.5 mL) and stirred at rt. Next, KOH-Al_2O_3 (19 equiv) was added to the reaction mixture. Immediately following base addition, a solution of 1,2-dibromotetrachloroethane (equivalents indicated in Table 2) in THF (2 mL) was added slowly dropwise via a syringe. The reaction mixture was stirred for 2−48 h (see Table 2 for precise times) at rt. Upon sulfone consumption (TLC monitoring), the reaction mixture was flushed through a silica plug with EtOAc to remove inorganic components. Fractions were combined and concentrated. Purification by flash chromatography gave pure material. See Table 2 for yields.

E-Stilbene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. Purification by flash chromatography eluting with hexanes gave *E*-stilbene as a white solid (66 mg, 91%): mp 122−123 °C [lit.[42] 123.9−124.6 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52−7.49 (m, 4H), 7.51−7.33 (m, 4H), 7.28−7.24 (m, 2H), 7.11 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.4, 128.7, 127.7, 126.6.

E-2-(3-Bromophenyl) styrene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes to give exclusively the *E*-isomer as a white solid (72 mg, 90%): mp 88−89 °C [lit.[43] 89−90 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (t, J = 1.8 Hz, 1H), 7.53−7.47 (m, 1H), 7.44−7.32 (m, 4H), 7.28 (tt, J = 1.0, 7.3 Hz, 1H), 7.25−7.18 (m, 1H), 7.10 (d, J = 16.4 Hz, 1H), 7.01 (d, J = 16.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.5, 136.8, 130.4, 130.2, 129.3, 128.8, 128.1, 127.1, 126.7, 125.2, 122.9.

E-2-(3-Nitrophenyl) styrene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes to give exclusively the *E*-isomer as a white solid (68 mg, 88%): mp 96−97 °C [lit.[44] 92−95 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 8.07 (dd, J = 8.0, 1.2 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.54−7.48 (m, 3H), 7.39 (t, J = 7.2 Hz, 2H), 7.33−7.29 (m, 1H), 7.21 (d, J = 16.4 Hz, 1H), 7.11 (d, J = 16.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.7, 139.2, 136.3, 132.3, 131.8, 129.6, 128.9, 128.6, 126.9, 126.1, 122.0, 120.9.

E-2-(4-Trifluoromethylphenyl) styrene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes to give exclusively the *E*-isomer as a clear colorless needles (64 mg, 82%): mp 131−132 °C [lit.[42] 132.1−133.4 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61−7.56 (m, 4H), 7.53 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 5.5 Hz, 2H), 7.32−7.28 (m, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.11 (d, J = 16.4 Hz, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ = 140.8, 136.7, 132.2, 129.3 (q, J = 32.4 Hz), 128.8, 128.3, 127.1, 126.8, 126.6, 125.7 (q, J = 3.7 Hz), 124.3 (q, J = 272.6 Hz).

E-2-Pyridyl styrene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was purified by flash chromatography using EtOAc/hexanes (2:98) as the eluent to give exclusively the *E*-isomer as a white solid (66 mg, 92%): mp 61−62 °C [lit.[45] 63−64 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (dd, J = 0.9, 4.8 Hz, 1H), 7.67−7.60 (m, 2H), 7.60−7.55 (m, 2H), 7.42−7.33 (m, 3H), 7.32−7.23 (m, 1H), 7.17 (d, J = 16.1 Hz, 1H), 7.12 (ddd, J = 1.0, 4.8, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 149.7, 136.7, 136.6, 132.7, 128.8, 128.4, 128.0, 127.1, 122.1, 122.1.

E-4-Methoxyphenyl-3′,5′-dimethoxyphenylethene. See details for compound **4** below.

4-Methoxystilbene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was purified by flash chromatography using EtOAc/hexanes (2:98) as the eluent to give exclusively the *E*-isomer as a white solid (86 mg, 95%): mp = 134−137 °C [lit.[46] 130−133 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50−7.44 (m, 4H), 7.34 (t, J = 7.6 Hz, 2H), 7.25−7.21 (m, 1H), 7.07 (d, J = 16.4 Hz, 1H), 6.97 (d, J = 16.4 Hz, 1H), 6.90 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.3, 137.7, 130.2, 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.1, 55.3.

3,5-Dimethoxystilbene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. Recrystallization of the residue from hexanes gave the pure *E*-alkene as a white solid (86 mg, 87%): mp = 53−54 °C [lit.[47] 53−55 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52−7.49 (m, 2H), 7.37−7.33 (m, 2H), 7.28−7.24 (m, 1H), 7.09 (d, J = 16.4 Hz, 1H), 7.03 (d, J = 16.4 Hz, 1H), 6.67 (m, 2H), 6.40 (t, J = 2 Hz, 1H), 3.83 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0, 139.4, 137.2, 129.2, 128.7, 128.7, 127.8, 126.6, 104.6, 100.0, 55.4.

E-2-Naphthyl styrene. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes to give exclusively the *E*-isomer as clear colorless crystals (67 mg, 87%): mp 145−147 °C [lit.[47] 144−146 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88−7.76 (m, 4H), 7.73 (dd, J = 1.7, 8.5 Hz, 1H), 7.59−7.52 (m, 2H), 7.49−7.40 (m, 2H), 7.40−7.33 (m, 1H), 7.31−7.18 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.4, 134.9, 133.7, 133.1, 129.1, 128.8, 128.8, 128.4, 128.0, 127.8, 126.7, 126.6, 126.4, 126.0, 123.5.

2,6-Bis(E-2-styryl) pyridine. No *Z*-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes/EtOAc to give exclusively the *E*-isomer as a white solid (33 mg, 49%): mp 164−165 °C [lit.[46] 165−166 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 16.0 Hz, 2H), 7.66−7.61 (m, 5H), 7.41−7.37 (m, 4H), 7.32−7.25 (m, 4H), 7.21 (d, J = 16.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4, 137.0, 136.8, 132.9, 128.7, 128.3, 127.2, 120.5.

E,Z-Diheptylethene. The crude product was purified by flash chromatography (100% hexanes). Fractions were combined and concentrated to give product as a clear colorless oil[13] (39 mg, 51%, *E*:*Z* = 72:28 by NMR integration). *E*-alkene: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.38 (m, 2H), 1.96 (m, 4H), 1.35−1.23 (m, 20H), 0.88 (t, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 130.5, 31.9, 29.7, 29.2, 29.1, 27.2, 22.7, 14.1; GC−MS m/z 224 [M$^+$] (1), 221 (6), 139 (17), 125 (53), 111 (100), 109 (18). *Z*-alkene: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.35 (m, 2H), 2.01 (m, 4H), 1.35−1.23 (m, 20H), 0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 129.9, 32.6, 29.8, 29.3, 29.2, 27.2, 22.7, 14.1; GC−MS m/z 224 [M$^+$] (2), 221 (3), 153 (9), 139 (17), 125 (56), 111 (100), 109 (14).

N-Boc-3-pyrroline. The crude product, as a clear, colorless oil was pure by ^{1}H NMR. (45 mg, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.77 (m, 2H), 4.11 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.3, 125.9, 125.8, 79.3, 53.1, 52.8, 28.5 (rotamers).[48]

E-1-Phenyl-1-heptene.[49] An inseparable mixture of *E*-1-phenyl-1-heptene and two isomeric 1-bromo-1-phenyl-1-heptenes were obtained, and the desired product as a clear liquid (53 mg; brominated:desired (91:9) by ^{1}H NMR; ca. 64% of desired alkene). No *Z*-isomer of *E*-1-phenyl-1-heptene was detected in the ^{1}H NMR or GC−MS of the reaction mixture. *E*-1-Phenyl-1-heptene: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34−7.25 (m, 4H), 7.21−7.15 (m, 1H), 6.37 (d, J = 15.6 Hz, 1H), 6.22 (dt, J = 15.6, 6.8 Hz, 1H), 2.19 (q, J = 6.9 Hz, 2H), 1.50−1.43 (m, 2H), 1.38−1.29 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.00, 131.3, 129.7, 128.5, 126.9, 125.9, 32.6, 31.6, 29.1, 22.6, 14.1; GC−MS m/z 174 [M$^+$] (100), 175 (63), 173 (43), 161 (10), 143 (9), 117 (21), 105 (14).

Minor, inseparable components. 1-Bromo-1-phenyl-1-heptene **1**: GC−MS m/z 252 [M^+] (63), 254 (62), 197 (14), 195 (15), 171 (18), 143 (9), 131 (10), 117 (36), 105 (100). 1-Bromo-1-phenyl-1-heptene **2**: GC−MS m/z 252 [M^+] (100), 254 (98), 197 (14), 195 (15), 173 (78), 171 (33), 157 (11), 143 (17), 129 (10), 117 (42), 105 (89).

Specific Protocols for Preparation of Trimethyl Resveratrol (4). *4-Methoxyphenyl-3′,5′-dimethoxyphenyl sulfone (**3**).* 4-Methoxyphenylmethanethiol (**1**, 1.87 mL, 12.9 mmol) was dissolved in dry THF (5 mL) under a nitrogen atmosphere. The solution was chilled to 0 °C, solid 95% NaH (0.326 g, 13.6 mmol) was added, and the mixture was stirred for ∼10 min. A solution of 1-(bromomethyl)-3,5-dimethoxybenzene (3.15 g, 13.6 mmol) in THF (2 mL) was added dropwise, and the mixture was stirred overnight. The reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed successively with a 10% NaOH (aq.) solution (2 × 15 mL), H_2O (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude sulfide **2** as a clear yellow oil (3.42 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.45−6.44 (m, 2H), 6.35−6.34 (m, 1H), 3.80 (s, 3H), 3.78 (s, 6H), 3.58 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.8, 158.6, 140.6, 130.1, 130.1, 113.9, 106.9, 99.1, 55.3, 55.3, 35.8, 35.1. Crude sulfide **2** (3.30 g, 10.8 mmol) was dissolved in DCM (70 mL) and stirred at 0 °C. To this solution was added MCPBA (ca. ∼77%, 5.61 g, 25.0 mmol), and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with saturated $Na_2S_2O_3$ (aq.), $NaHCO_3$ (aq.), H_2O and brine. After these successive washes the organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield sulfone **3** as a white solid (2.85 g, 78%): mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 2.2 Hz, 2H), 6.47 (t, J = 2.2 Hz, 1H), 4.11−4.07 (m, 2H), 4.06−4.01 (m, 2H), 3.80 (s, 3H), 3.78 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0, 160.2, 132.2, 129.7, 119.2, 114.4, 108.8, 100.9, 58.1, 57.3, 55.4, 55.3. The ^{1}H NMR and ^{13}C NMR were in good agreement with literature data.[9]

*E-4-Methoxyphenyl-3′,5′-dimethoxyphenylethene (**4**).* The sulfone (0.100 g, 0.297 mmol) was dissolved in THF/^{t}BuOH (2.5 mL/7.5 mL) and stirred at rt. Next, KOH-Al_2O_3 (0.713 g, 5.61 mmol) was added to the reaction mixture. Immediately following base addition, a solution (THF, 2 mL) of 1,2-dibromotetrachloroethane (0.174 g, 0.535 mmol) was added slowly dropwise via syringe. The reaction mixture was stirred overnight (8 h) at rt. Following reaction completion (by TLC monitoring) the reaction mixture was flushed through a silica plug with EtOAc to remove inorganic components. Fractions were combined and concentrated to give a white solid. No Z-isomer was detected in the ^{1}H NMR of the crude reaction mixture. The crude product was recrystallized from hexanes to give exclusively the E-isomer of **4** as a white solid (65 mg, 81%): mp 52−54 °C [lit.[47] 52−54 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 16.4 Hz, 1H), 6.92−6.89 (m, 3H), 6.65 (d, J = 2.4 Hz, 2H), 6.38 (t, J = 2 Hz, 1H), 3.83 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0, 159.4, 139.7, 129.9, 128.8, 127.8, 126.6, 114.2, 104.3, 99.6, 55.4.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of alkenes and of new sulfones. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: schwan@uoguelph.ca.

Notes

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