Nucleophilic attack of 2-sulfinyl acrylates: A mild and general approach to sulfenic acid anions†

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An increasing number of reactions of sulfenic acid anions are being demonstrated in the literature. As such, mild, general and reliable means for the generation of sulfenates are due. In the current paper, an addition/elimination of 2-sulfinyl acrylates using various nucleophiles is demonstrated and evaluated as a protocol for alkane- and arenesulfenate generation. Cyclohexanethiolate, methoxide and *n*-butyllithum each exhibit some merit for the reaction, and the thiolate is established as a mild, selective and effective reagent to release sulfenates from 2-sulfinyl acrylates. The stereospecificity of the addition/elimination of each nucleophile is recognized, and an explanation for the specificity is offered for thiolate and methoxide.

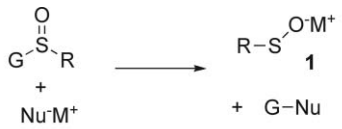
Introduction

Sulfenic acid anions (**1**)[1] represent important sulfur nucleophiles that have served as valuable precursors to a variety of sulfoxides. Although sulfenate anions may exhibit sulfur or oxygen reactivity, they can be selectively alkylated at sulfur to produce vinylic,[2–5] alkynyl,[6] aromatic[7–10] and alkyl sulfoxides,[7,8] in addition to specialty targets such as a paracyclophane,[11] cyclopropanes[12] and cysteine derivatives.[13] Though complementary to sulfide oxidation protocols,[14] sulfenate functionalization chemistry is expected to respond to an alternative set of experimental variables, and as such, represents a conceptually different approach to sulfoxides.

Sulfenates (**1**) are generally not isolable species and are created *in situ* for further functionalization. Notwithstanding this concern, increased exploration and recent advances with sulfenates have facilitated access to increasingly challenging targets.[11,13,15] Modern developments in the generation of sulfenates involve a sulfur oxidation protocol,[5,6,16] a retro-Michael reaction,[7] fluoride-induced desilylative fragmentation chemistry[10] and an addition elimination reaction of β-sulfinyl acrylates.[8] In that latter work, we introduced the first general protocol for the release of aryl- *and* alkyl-substituted sulfenates. In this paper, we outline our full study, offering additional examples, some mechanistic implications and the introduction of *n*-BuLi as a sulfenate-releasing reagent.

Results and discussion

As part of our studies regarding the sulfur substitution chemistry of α,β-unsaturated sulfenate esters, we encountered a situation where an alkoxide displaced a sulfenate anion under ostensibly an addition/elimination mechanism (Scheme 1).[17] The reaction resembles an intermolecular version of a Smiles rearrangement[18] on a sulfoxide, but also was similar to chemistry offered from the Furukawa group for the release of sulfenate anions from the 2-position of benzothiazoles, or from 2-sulfinyl substituted pyridine-*N*-oxides.[9] In keeping with our ongoing studies of unsaturated sulfinyl derivatives,[17,19] we decided to probe the general usefulness of the acrylate as a sulfenate-releasing group, believing that it may prove more reactive than the aromatic substrates of Furukawa, and may also permit access to a greater breadth of sulfenates. At the time this work was commenced, there were no general means to produce alkanesulfenates.



Smiles rearrangement: R and Nu tethered; G = Ar
Furukawa work: G = 2-benzothiazolyl or 2-pyridyl-N-oxide
Current work: G = 2-carbomethoxyethenyl

Scheme 1

A number of the requisite starting compounds (**2**) were obtained through simple conjugate additions of thiol to methyl propiolate, followed by MCPBA oxidation (yields over two steps: 21, 38, 45–87%).[20] There was no effort made to secure a preferred double bond isomer and both were obtained in many instances. During the course of these preparations, it was realized that a shorter exposure time between thiol and alkyne was preferred, and recent yields for the two step preparation are superior for that reason, with thiol conjugate addition reaction yields reaching 98%. *Z*,*E*- and *Z*,*Z*-bis[2-carbomethoxyethenyl] sulfoxides (**2j**) and homocysteine derivative **2l** were prepared using the newly introduced caesium 2-*Z*-carbomethoxyethenethiolate methodology.[21] Other methods may be suitable for the preparation of the requisite sulfoxides **2**, such as the sulfenic addition protocol of Aversa *et al.*,[22] which would yield selectively the *E*-isomer, but this was not exploited for the current work.

Although a number of conditions and nucleophiles were evaluated for their sulfenate-releasing reactivity with sulfoxides **2**, the study herein focuses on *n*-butyllithium/hexane in THF, lithium cyclohexanethiolate in THF, and NaOMe/MeOH solution introduced into THF. The assessment of the chemistry occurred through quenching the mixtures with a reactive electrophile, so

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that the sulfenates could be efficiently captured through sulfoxide formation by way of S-alkylation. It is well established that the structure and intermediacy of the sulfenate can be inferred through characterization of the stable sulfoxide.[1] In this work, the electrophile, most commonly benzyl bromide or methyl iodide, was added as a THF solution 1–15 min after nucleophile addition. After warming and stirring for 12 h, the mixtures were concentrated and subjected to flash chromatography.

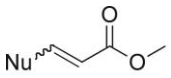
Table 1 shows the yields of isolated and purified sulfoxides. Overall, the chemistry is amenable to a wide variety of sulfenates, including both arene- and alkanesulfenates, making it only one of two methods possessing such general applicability.[7] There are nevertheless some important observations to glean from Table 1, which relate primarily to the selection of the nucleophile.

Sodium methoxide proved useful to release aromatic sulfenates, but yields were sometimes low and irreproducible for alkanesulfenates, most notably in the instances of methyl (**2b**) and benzyl (**2d**), where the carbon α to the sulfoxide may exhibit increased acidity toward the unhindered methoxide base. The effectiveness of *n*-BuLi was surprising in light of the electrophilic functional groups in each substrate. Nevertheless, *n*-BuLi is effective for aromatic substrates and some alkyl systems, such as benzyl.

Lithium cyclohexanethiolate appears to be the most mild, and presumably selective, reagent. In particular, it created sulfenate **1i** from sulfoxide **2i**. The latter would be expected to react differently under conditions of base treatment[7] and create sulfenate **1j**, assuming that conjugate addition did not occur. Clearly, the use of thiolate for the addition/elimination chemistry is preferred for base-sensitive substrates. This is underscored when viewing recently published chemistry, where a cysteinesulfenate (**1m**) can be prepared from a base-sensitive precursor.[13]

A direct comparison of electrophilicity is evident in the reaction of sulfoxide **2h** with thiolate: the acrylate was more receptive to nucleophilic addition than the benzothiazole. This provides a direct indication that the acrylate displacement chemistry presented herein is milder and more chemoselective than the benzothiazole-based method of Furukawa,[9] at least when thiolate is adopted as the nucleophilic reagent.

A final comment is due on the chemistry of sulfoxides ***E*,*Z*-2j** and ***Z*,*Z*-2j** and the sulfenate that results from them (**1j**). These compounds were prepared to explore the *E vs. Z* selectivity of the nucleophiles, and either of these compounds could represent commercial sources of a masked $[SO]^{-2}$ equivalent based on a double sulfenate release protocol. Using thiolate, the mildest reagent, neither sulfenate S-alkylation product (***E*/*Z*-2d**) nor double S-alkylation product (**3d**) could be detected. The presence of *Z*-methyl 3-cyclohexylthiopropenoate (*vide infra*) indicated sulfenate was being released, but alkylation was apparently too slow.[23] Similar results were obtained with *n*-BuLi where ***Z*-6**/***Z*-7** (Fig. 1) could be detected, but S-alkylation products (***E*/*Z*-2d**/**3d**) were not observed. Sodium methoxide proved superior for this substrate, but the reason may not have its origins in sulfenate generation, but more likely in sulfenate *reactivity*. It was previously established that potassium and sodium sulfenate exhibit greater reactivity than lithium sulfenates.[24] The isolation of sulfoxide ***E*-2d** in 42% yield (alongside the formation of ***Z*-5**), and the lack of alkylation product using lithium thiolate, suggests that Na-**1j** is more reactive than Li-**1j**. It should also be mentioned that the high yield of sulfenate capture product with a non-activated electrophilic iodide affording **3aa** may be brought about because sodium is the counterion.



Nu = $cC_6H_{11}S$, **4**
MeO, **5**
Bu, **6**
BuO, **7**

Fig. 1 By-products of the addition/elimination reactions.

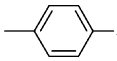
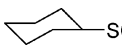
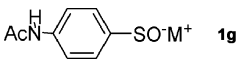
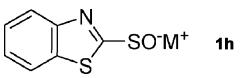
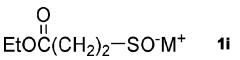
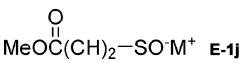
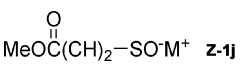
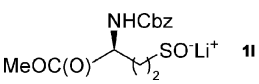
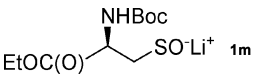
In order to better understand the mechanism of sulfenate release, additional experiments regarding stereochemistry and by-products were performed. In the case of methoxide and thiolate reagents, methyl 3-methoxypropenoate and methyl 3-cyclohexylsulfanylpropenoate were observed, respectively, pointing to an addition/elimination mechanism. In those instances (**2a**, **2h**) where a single double bond isomer was reacted, the by-product maintained the geometry of the starting material, indicating a stereospecific addition/elimination sequence. An elimination/addition pathway would be expected to afford a mixture of by-products, by way of non-selective conjugate addition to propiolate. In addition, many of the starting sulfoxides display ^{13}C NMR resonances for the electrophilic carbons of 147–150 ppm. De Lucchi and coworkers have suggested that electron-deficient compounds with alkene chemical shifts in the order of 138–140 ppm favour addition/elimination over elimination/addition.[25]

The mechanism for the reactions with *n*-BuLi is less certain. Unsaturated ester **6** and lesser amounts of **7** were consistently observed as part of the reaction profiles of the reaction with *n*-BuLi. Hexenoate **6** is consistent with an addition/elimination mechanism, but **7** is probably formed by a different mechanism, one that may begin with Bu^- attack at the sulfinyl sulfur or oxygen. However, no other products diagnostic of additional reaction mechanism steps were observed.

Also of interest is the rate at which *E- vs. Z*-sulfinyl acrylates react with nucleophiles. In separate experiments, a 50 : 50 mixture of methyl *E*- and *Z*-*p*-toluenesulfinylacrylates (***E*-2a**, ***Z*-2a**) were treated with 0.25 molar equivalents of nucleophile. As shown in Table 2, in each example, the *Z*-isomer reacted preferentially, releasing sulfenate and affording the *Z*-acrylate as a by-product. The sulfenate was then captured with benzyl bromide.

The data in Table 2 indicate that the *Z*-isomer reacts preferentially faster than the *E*-isomer, and the results underscore the stereospecificity of the reaction. Additional evidence was obtained from the reaction of the nucleophiles with ***E*-2a**, the *E*-isomer of byproducts **4**–**7** was observed in each case. The specificity has been observed previously in a number of related addition/elimination reactions, with substrates possessing comparable structural features.[26,27] That mechanism is most likely to occur when there is some, but not extensive, stabilization of the Michael adduct and when there is a good leaving group. The sulfenate, whose conjugate acid has a pK_a in the range 6–10,[28] would be considered a mid-strength to weak nucleofuge, and as such would permit bond rotation in the conjugate addition intermediately prior to leaving group release. However, the reaction that releases sulfenate is almost instantaneous in THF at –78 °C.[13] Given this,

Table 1 Sulfoxide formation through sulfenate intermediacy (Scheme 2)

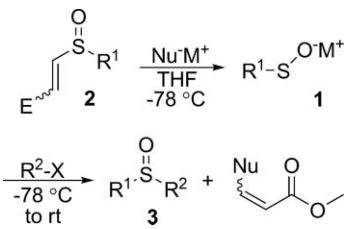
Starting material	Sulfenate	Reagent (eq.)[a]	R^2X (eq.)[b]	Sulfoxide/%
***E*/*Z*-2a**	 **1a**	MeO^-Na^+ MeO^-Na^+ *n*-BuLi CyS^-Li^+	BnBr $C_{16}H_{33}I$ BnBr BnBr	**3a**/84 **3aa**/87 **3a**/78 **3a**/84
***Z*-2a**		*n*-BuLi MeO^-Na^+	BnBr BnBr	**3a**/88 **3a**/81
***E*-2a**		*n*-BuLi *n*-BuLi	BnBr MeI	**3a**/81 **3ab**/85
***E*/*Z*-2b**	$CH_3-SO^-M^+$ **1b**	MeO^-Na^+ CyS^-Li^+	BnBr BnBr	**3b**/0–27 **3b**/62
***E*-2c**	 **1c**	MeO^-Na^+ *n*-BuLi CyS^-Li^+	BnBr BnBr BnBr	**3c**/65 **3c**/53 **3c**/55
***E*/*Z*-2d**	$PhCH_2-SO^-M^+$ **1d**	MeO^-Na^+ MeO^-Na^+ *n*-BuLi CyS^-Li^+	BnBr MeI BnBr BnBr	**3d**/13-84 **3b**/12-48 **3d**/74 **3d**/75
***E*-2e**	$nC_6H_{13}-SO^-M^+$ **1e**	MeO^-Na^+	MeI	**3e**/63
***E*-2f**	$nC_{16}H_{33}-SO^-M^+$ **1f**	MeO^-Na^+ *n*-BuLi	BnBr BnBr	**3f**/77 **3f**/29
***Z*-2g**	 **1g**	MeO^-Na^+ *n*-BuLi	BnBr BnBr	**3g**/50 **3g**/54
***E*/*Z*-2h**	 **1h**	CyS^-Li^+	BnBr[c]	**3h**/70
***Z*-2h**		MeO^-Na^+ *n*-BuLi CyS^-Li^+	BnBr[c] BnBr[c] BnBr[c]	**3h**/33 **3h**/49 **3h**/66
***E*-2h**		CyS^-Li^+	BnBr[c]	**3h**/78
***E*/*Z*-2i**	 **1i**	CyS^-Li^+	2-$BrC_6H_4CH_2Br$[c]	**3i**/57
***E*,*Z*-2j**	 **E-1j**	CyS^-Li^+ MeO^-Na^+ *n*-BuLi	BnBr[c] BnBr[c] BnBr[c]	*E*/*Z*-**2d**/0 *E*-**2d**/42% *E*/*Z*-**2d**/0
***Z*,*Z*-2j**	 **Z-1j**	CyS^-Li^+ *n*-BuLi	BnBr[c] BnBr[c]	*E*/*Z*-**2d** /0 *E*/*Z*-**2d**/0
***E*,*E*-/*E*,*Z*-2k**	$M^+O^-S-(CH_2)_3-SO^-M^+$ **1k**	CyS^-Li^+ [c]	BnBr[d]	**3k**/74 (1.25)[e]
***Z*-2l**	 **1l**	CyS^-Li^+	BnBr	**3l**/45 (1.5)[e]
***E*-2m**	 **1m**	CyS^-Li^+[f]	Various $ArCH_2Br$[g]	**3m**/51–76[g]

[a] 1.0 molar equivalents of nucleophile were employed, unless otherwise noted. [b] 1.2 molar equivalents of electrophile were employed, unless otherwise noted. [c] 2.0 molar equivalents were employed. [d] 2.4 molar equivalents were employed. [e] Ratio of diastereomers. [f] 0.95 molar equivalents were employed. [g] See ref. 13.

Table 2 Outcome of reactions of methyl *E*- and *Z*- *p*-toluenesulfinylacrylates (**2**) with reduced nucleophile equivalents

	Isolated compounds' yields (%)			
Nucleophile	***E*-2a**[a]	***Z*-2a**[a]	**3a**[a]	Nu O
$cC_6H_{11}S^-Li^+$	50	27	23	***Z*-4, 95%**[b]
MeO^-Na^+	50	25	18	***Z*-5**[c]
Bu^-Li^+	50	25	20	***Z*-6**, **7**[c]

[a] Isolated yields are based on starting materials (50 : 50 = *E*/*Z*-*p*-tolylsulfinylacrylate). [b] Yield based on thiolate. [c] Yield not obtained.



Scheme 2

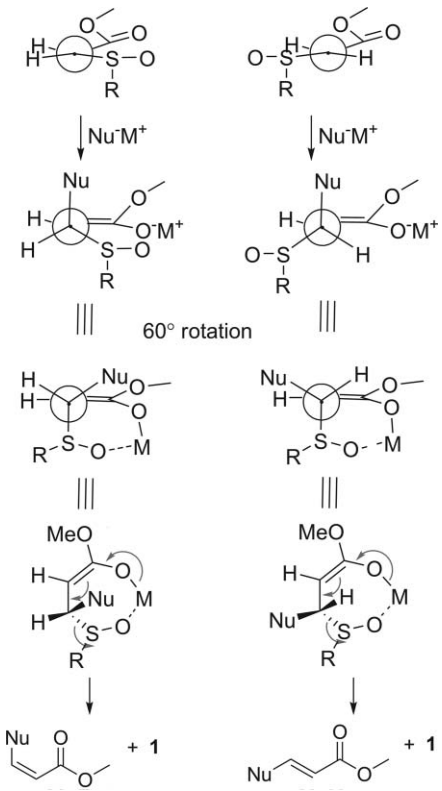
we suggest a mechanism as shown in Scheme 3, which can account for the chemistry involving methoxide and thiolate nucleophiles.

In the scheme, the nucleophile could add from either face and presumably has a preference based on the configuration of the sulfinyl group.[29] Since the substrates are racemic, the face selectivity was not brought into consideration. For both *E* and *Z*-substrates, Michael addition would deliver the Nu α to the sulfinyl group and the counterion (M^+) to the carbonyl oxygen. From that point, a 60° rotation is required to align the S–C bond with the p-orbitals of the enolate π systems, a configuration optimum for elimination. Many substrates have exhibited a preference for the small 60° rotation *vs.* a less desirable 120° option.[26] Elimination of the sulfenate follows.

An additional benefit of the 60° rotation is the creation of a stabilizing interaction between the ester enolate counterion and the Lewis acidic sulfinyl oxygen which, in turn, accelerates sulfenate loss, as shown by the mechanism arrows in Scheme 3. This interaction is readily available in the *Z*-isomer prior to the 60° rotation and, indeed, a preliminary interaction between the metal ion and the sulfinyl oxygen may assist in the conjugate addition, which could be the reason for the observed higher reactivity of the *Z*-isomer.

Conclusions

It is increasingly apparent that creating an (conjugated) anion β to a sulfinyl group is a preferred method for the generation of a sulfenate anion.[2,7,9,10,30,31] Those protocols that can achieve this under mild and selective conditions should be useful for preparing sulfenates. The current work outlines details of an inviting approach which can be performed with various common nucleophilic agents. Sulfinyl acrylates are readily available and the double bond configuration does not affect the chemical yield of eventual sulfoxide generation, but does exert an influence on the rate of the reaction. Lithium cyclohexanethiolate is the preferred mild choice, and should be utilized for base-sensitive substrates.[13] The chemistry presented herein is suitable for a wide variety of sulfenates and can be achieved at low temperature with some functional group selectivity.



Scheme 3

Experimental

General experimental aspects are summarized in the ESI†. Procedures for, and characterization of, the starting 2-carbomethoxyethenyl sulfoxides (**2**), data for known sulfoxides **3**, and by-products **4–7** are found in the ESI†. Data for new sulfoxides **3** are shown below.

General procedure for the liberation of sulfenates and synthesis of Ar(alk)yl sulfoxides 3

Method A. A solution of cyclohexyl thiol (1 eq.) was prepared in dry THF and cooled to −78 °C under N_2. While stirring, *n*-BuLi (1.0 eq. as a 2.5 M or 1.6 M solution in hexanes) was added *via* syringe. The mixture was stirred for 30 min at −78 °C, taken up into a syringe, and transferred to a solution of α,β-unsaturated sulfoxide (**2**) (1 eq.) in dry THF (1 mL/10 mg; 1–2 mL for thiolate and 8–9 mL for sulfoxide flasks) at −78 °C. The reaction was stirred for 1–15 min, and a −78 °C solution of RX (1.2 eq.) in THF (1-2 mL) was then added. The reaction mixture was stirred overnight while slowly warming to RT, concentrated under reduced pressure, and purified by flash chromatography using EtOAc–hexanes as the eluent. Sulfoxide yields are obtained from the starting α,β-unsaturated sulfoxide.

Method B. To a solution of **2** (1 eq.) in dry THF (1 mL/10 mg) at −78 °C was added MeO^-Na^+ or *n*-BuLi (1.0 eq., 25% sodium methoxide solution in MeOH; 1.6 M or 2.5 M *n*-BuLi in hexanes) and the solution was stirred for 1–15 min. A −78 °C solution of RX (1.2 eq.) in THF (1–2 mL) was then added. Procedure followed as per Method A.

Synthesis of 2-carboethoxyethyl *o*-bromobenzyl sulfoxide (3i) (Method A)

Sulfoxide (***E*/*Z*-2i**) (500 mg, 2.13 mmol) in anhydrous THF (20 mL) was treated with a CySH (0.26 mL, 2.13 mmol)/*n*-BuLi (1.33 mL, 1.6 M in hexane, 2.13 mmol) solution in anhydrous THF (5 mL), followed by the addition of 2-bromo benzyl bromide (1.07 g, 4.27 mmol). Sulfoxide **3i** (395 mg, 57%) was recovered as a liquid after flash chromatography (EtOAc–hexanes 30 : 70) which solidifies as yellowish solid on prolonged standing under vacuum. Recrystallization with ethyl acetate–hexane gave a white solid. Mp: 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.59 (m, 1H), 7.37 (m, 1H), 7.30 (m, 1H), 7.18 (m, 1H), 4.24-4.10 (m, 4H), 3.08-3.01 (m, 1H), 2.90-2.78 (m, 3H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ: 170.9, 132.9, 132.2, 129.8, 127.7, 124.8, 60.9, 58.4, 45.7, 26.7, 13.9; IR ($CDCl_3$), cm^{-1}: 2980, 2929, 1732, 1237, 1182, 1043. Analysis calc'd for $C_{12}H_{15}O_3SBr$: C, 45.15; H, 4.74; found: C, 44.13; H, 4.61.

Synthesis of Cbz-homoCys((O)-Bn)-OMe (3l) (Method A)

Z-Cbz-homoCys((O)-2-carbomethoxyethenyl)-OEt (**2l**) (120 mg, 0.313 mmol) in THF (10 mL) was treated with a solution of CySH/*n*-BuLi (38.3 µL, 0.313 mmol; 1.6 M, 199 µL, 0.319 mmol) followed by the addition of benzyl bromide (44.7 µL, 0.376 mmol). Sulfoxide **3l** (54.5 mg, 45%) was isolated as an oil after flash chromatography (eluted with 50% EtOAc–hexanes, then 3% MeOH–EtOAc) as a mixture of diastereomers (*dr* 1.5 : 1). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35 (m, 8H), 7.26 (m, 2H), 5.81 (two d, $J = 7.7$ Hz, $J = 7.7$ Hz, 1H), 5.10 (s, 2H), 4.43 (m, 1H), 3.96 (AB_q, $J = 12.9$ Hz, 2H), 3.72 (s, 3H), 2.67 (m, 2H), 2.33 (m, 1H), 2.12 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.7, 155.9, 136.1, 129.9, 129.5, 129.0, 128.9, 128.5, 128.4, 128.1, 67.1, 58.1, 53.0, 52.6, 46.3, 25.6; IR ($CHCl_3$), cm^{-1}: 3424, 2996, 1740, 1721, 1346, 1017; MS (EI), *m*/*z* (%): 389 (M^+, 2), 345 (4), 238 (3), 182 (2), 181 (12), 140 (3), 108 (2), 107 (3), 92 (8), 91 (100), 83 (2), 79 (2), 65 (4), 55 (3); Calc'd for $C_{20}H_{23}NO_5S$: 389.1298; found: 389.1296.

Reactions of bis(carbomethoxyethenyl) sulfoxides *E*,*Z*/*Z*,*Z*-2j

Method A (with CySLi). ***E*,*Z*** or ***Z*,*Z*-2j** (200 mg, 0.917 mmol) in THF (15 mL) was treated with CySH/*n*-BuLi (101 µL, 0.825 mmol; 1.6 M, 510 µL, 0.825 mmol) at −78 °C. After 1–2 min, a solution of benzyl bromide (217 µL, 1.83 mmol) in THF (1 mL) was added. The reaction mixture was stirred overnight while slowly warming to RT and then concentrated under reduced pressure. Formation of ***E*/*Z*-2d** or **3d** was not observed, while ***Z*-4** (165 mg, 95%) was isolated as a major product after flash chromatography.

Method B (with MeONa). ***E*,*Z*** or ***Z*,*Z*-2j** (200 mg, 0.917 mmol) in THF (15 mL) was treated with MeONa (25% in MeOH, 157 µL, 0.917 mmol) at −78 °C. After 1–2 min, a solution of benzyl bromide (217 µL, 1.83 mmol) in THF (1 mL) was added. The reaction mixture was stirred overnight while slowly warming to RT and then concentrated under reduced pressure. When ***E*,*Z*-2j** was used as the starting material, ***E*-2d** (65 mg, 42%) was isolated after flash chromatography (30% EtOAc–hexanes to 40% EtOAc–hexanes). ***Z*-5** was observed in the reaction mixture as a major product. The reaction of ***Z*,*Z*-2j** resulted in a complicated mixture.

Method B (with *n*-BuLi). ***E*,*Z*** or ***Z*,*Z*-2j** (200 mg, 0.917 mmol) in THF (15 mL) was treated with *n*-BuLi (1.6 M, 510 µL, 0.825 mmol) at −78 °C. After 1–2 min, a solution of benzyl bromide (217 µL, 1.83 mmol) in THF (1 mL) was added. The reaction mixture was stirred overnight while slowly warming to RT, and then concentrated under reduced pressure. ***E*/*Z*-2d** or **3d** was not observed, while ***Z*-6**/***Z*-7** were detected in the reaction mixture as major products.

Competitive reactions of 2-carbomethoxyethenyl *p*-tolyl sulfoxides *E*/*Z*-2a

Method A (with CySLi). 2-Carbomethoxyethenyl *p*-tolyl sulfoxide (1 : 1 mixture of ***E*/*Z*-2a**) (200 mg, 0.892 mmol) in THF (15 mL) was treated with CySH/*n*-BuLi (27.0 µL, 0.223 mmol; 1.6 M, 139 µL, 0.223 mmol) at −78 °C. After 1–2 min, a solution of benzyl bromide (212 µL, 1.78 mmol) in THF (1 mL) was added. The reaction mixture was stirred overnight while slowly warming to RT, and then concentrated under reduced pressure. ***E*-2a** (100 mg, 50%), ***Z*-2a** (54 mg, 27%), **3a** (47 mg, 23%) and ***Z*-4** (42 mg, 95%) were isolated after flash chromatography (2% EtOAc–hexanes to 40% EtOAc–hexanes).

Method B (with MeONa). 2-Carbomethoxyethenyl *p*-tolyl sulfoxide (1 : 1 mixture of *E*/*Z*-**2a**) (200 mg, 0.892 mmol) in THF (15 mL) was treated with MeONa (25% wt in methanol, 50.8 µL, 0.223 mmol) at −78 °C, followed by the immediate addition of a solution of benzyl bromide (212 µL, 1.78 mmol) in THF (1 mL). The reaction mixture was stirred overnight while slowly warming to RT, and then concentrated under reduced pressure. ***E*-2a** (100 mg, 50%), ***Z*-2a** (54 mg, 27%), **3a** (37 mg, 18%) and *Z*-**5** were isolated after flash chromatography (2% EtOAc–hexanes to 40% EtOAc–hexanes).

Method B (with *n*-BuLi). 2-Carbomethoxyethenyl *p*-tolyl sulfoxide (1 : 1 mixture of ***E*/*Z*-2a**) (200 mg, 0.892 mmol) in THF (15 mL) was treated with *n*-BuLi (139 µL, 0.223 mmol) at −78 °C, followed by the immediate addition of a solution of benzyl bromide (212 µL, 1.78 mmol) in THF (1 mL). The reaction mixture was stirred overnight slowly warming to RT, and then concentrated under reduced pressure. ***E*-2a** (100 mg, 50%), *Z*-**2a** (50 mg, 25%), **3a** (41 mg, 20%), ***Z*-6** and ***Z*-7** were isolated after flash chromatography (2% EtOAc–hexanes to 40% EtOAc–hexanes).

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