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Unexpected Steric Effects of "Remote" Alkyl Groups on the Rate of Conjugate Additions to Alkyl α,β-Ethylenic Sulfones, Sulfoxides, and Esters

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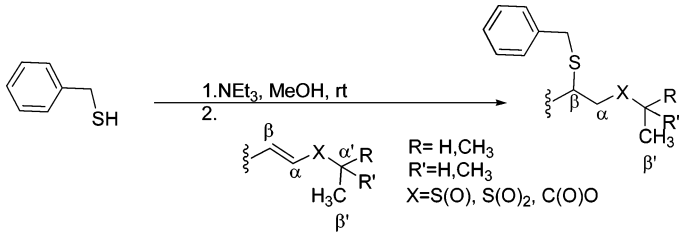

Examination of conjugated ethylenic sulfones, sulfoxides, and esters in Michael-type addition reactions reveals, for the first time, that the size of the heteroatom-attached alkyl group affects the rate of conjugate addition. Molecular modeling strongly suggests that what are generally considered to be "remote" alkyl groups in $-C^{\beta}H{=}C^{\alpha}HS(O)_n-$alkyl systems and $-CH_2C^{\beta}H{=}C^{\alpha}HCOO-$alkyl systems are actually not remote from the β-carbon atom of the Michael accepting unit. Molecular modeling clearly shows that the alkyl groups in these Michael acceptors shield the β-carbons in the following order: Et < *i*-Pr < *t*-Bu. Competition experiments establish the relative rates of Michael additions to be in the following order: Et > *i*-Pr > *t*-Bu.

Introduction

Conjugate (1,4) additions to α,β-ethylenic compounds are reliable and popular bond-forming reactions and are oftentimes essential to the assembly of complex organic molecules. There are, however, many factors that affect the nature of the reaction and the formation of product during this process. The structure of both the nucleophile and the electrophilic olefin, specifically bulky groups at the α, β, or β′ positions and the *E*/*Z* configuration of the double bond, can significantly affect the stereochemistry of the conjugate addition product (Figure 1).[1−3] The stereochemistry of the product can be affected by the size of the alkyl groups attached directly to X in ethylenic systems (Figure 1).[4−6]

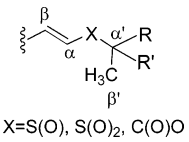

FIGURE 1.

Substituents on the olefin not only affect the stereochemistry of the reaction, but also influence the rate of reaction. Olefinic α- or β-substituents on a phenyl ethylenic sulfone are shown to greatly reduce the rate of addition.[7] In addition, the use of sterically hindered reactants requires increased reaction times and/or temperature compared to reactions with less bulky substrates.[8]

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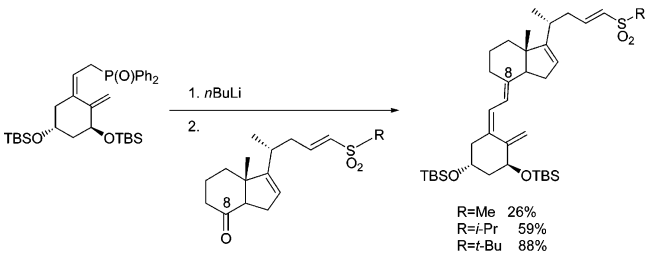
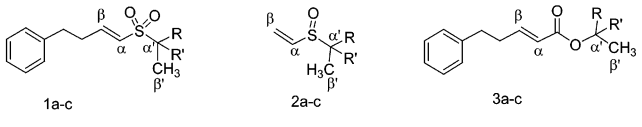


FIGURE 2.



a: R,R'=H
b: R=CH_3 R'=H
c: R,R'=CH_3

FIGURE 3.

Substituents at the α or β positions can also produce profound rate effects, accelerating or slowing the reaction process depending on electron-withdrawing or -donating ability.[1] Roush recently showed that phenyl vinyl sulfonate esters are 3000-fold more reactive than corresponding phenyl vinyl sulfonamides.[9]

Although there are many known factors contributing to the outcome of a conjugate addition reaction, there are only two relevant reports addressing the steric effects of the "remote" α′,β′-substituent on the rate of conjugate addition. Tanaka showed that the yields of products via intramolecular conjugate addition to alkyl crotonate esters decreased in the series Et > *i*-Pr > *t*-Bu.[10] In another study, the yield of products or success of a Pauson−Khand reaction with CH_2═CHS(O)R sulfoxides was lowest with bulky R groups.[11]

Recently, during the synthesis of vitamin D_3 α,β-unsaturated sulfone analogues, we discovered that the success of the critical Horner−Wadsworth coupling is strongly affected by the size of the terminus (R) of the conjugated ethylenic sulfone C,D-ring side chain (Figure 2).[12] The anion of the A-ring phosphine oxide may be participating not only in the desired Horner−Wittig coupling with the C-8 ketone, but also may be adding in a Michael fashion to the conjugated sulfone system. The less sterically hindered methyl or isopropyl terminus may facilitate this competing conjugate addition and thereby lower the yield of the desired product. To investigate this hypothesis, conjugated sulfones, sulfoxides, and esters with various R,R′-alkyl substituents were studied (Figure 3).

Results and Discussion

During competition experiments, two unsaturated compounds (1 equiv each) with different remote substituents were treated with 1 equiv of benzyl mercaptan in the presence of triethylamine (1.1 equiv) (Figure 4). Due to the general reversibility of conjugate additions, methanol was used as a solvent to quench

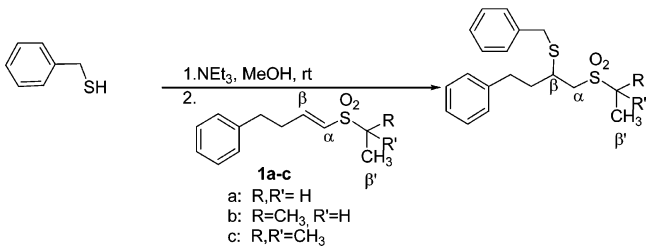


FIGURE 4.

the reaction upon addition of the nucleophile to the olefin. To confirm the irreversibility of the reaction under these conditions, an isolated conjugate addition product was stirred in methanol for 16 h, and no reversibility was observed. The ratios of reactants consumed or products formed were measured by GC, which indicated the rate difference of conjugate addition.

The molecular modeling program Spartan '02 calculated the lowest energy conformation from which we measured the β to β′ distance.[13] On the basis of Spartan '02 and literature,[14] the sulfones are held in a conformation such that the β-hydrogen atom of the olefin eclipses one of the sulfonyl oxygen atoms (Figure 5).[14] This desired conformation may create more steric hindrance around the olefin than initially expected. This same oxygen−hydrogen eclipsing interaction may also control the low-energy conformation of the sulfoxide and crotonate series, leading to a more hindered olefin than would be predicted. Since the molecular modeling distances were measured in vacuo, the calculations were also carried out with a molecule of methanol bound to an oxygen atom of the sulfone unit to investigate solvent effects. In comparing the β to β′ distance of the in vacuo model (3.573 Å) to that of the methanol-bound structure (3.591 Å), there is a difference of less than 0.02 Å, which demonstrates that the reaction solvent has little effect on the conformation of the reactant (Table 1).

In examining the ethylenic sulfones, the distance of β to β′ increases by approximately 0.5 Å as the size of the remote substituent decreases from *tert*-butyl (**1c**) to isopropyl (**1b**) and approximately 0.8 Å as the size decreases from isopropyl (**1b**) to ethyl (**1a**) (Table 1). As this distance increases between the β-carbon atom and the β′-carbon atom, the Michael addition rate also increases. When an isopropyl terminus (**1b**) at a β to β′ distance of 4.025 Å is compared to a *tert*-butyl terminus (**1c**) at a β to β′ distance of 3.573 Å, the rate of reaction increases by a factor of 3. As the terminus becomes even more remote at a β to β′ distance of 4.806 Å, the ethyl sulfone (**1a**) displays a significant rate increase by a factor of greater than 10 when compared to the *tert*-butyl sulfone (**1c**). In comparing ethyl (**1a**), isopropyl (**1b**), and *tert*-butyl (**1c**) remote substituents, it is obvious that the steric hindrance of the remote substituent inversely affects the rate of conjugate addition.

Similar to the sulfones, the alkyl vinyl sulfoxides **2a**−**c** show an inverse correlation between the distance between the β-carbon atom and the β′-carbon atom and the rate of conjugate addition (Table 2). The sulfoxide Michael addition products coeluted using gas chromatography, and for this reason, the rate of reaction was measured by disappearance of reactant. The rates of reaction were too difficult to detect using ^{1}H NMR

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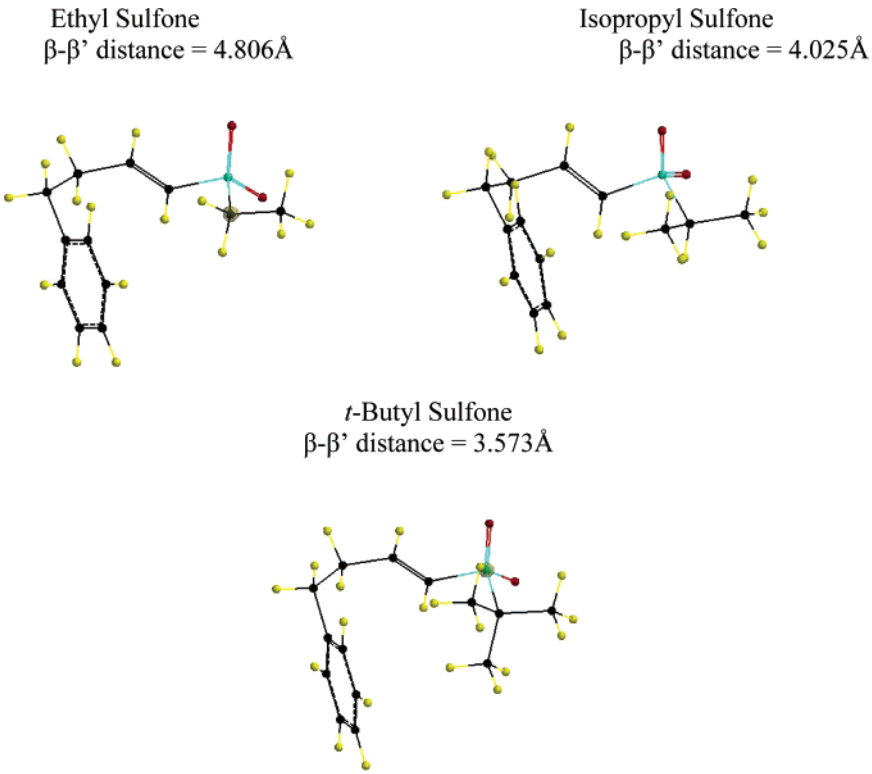

FIGURE 5. $Ph(CH_2)_2CH{=}CHS(O)_2CH_nCH_3RR'$ (n = 0−2; R = H, CH_3; R′ = H, CH_3).

TABLE 1

sulfone	rel rate of formation of product	distance from β to β' (Å)
1a	10.3	4.806
1b	3	4.025
1c	1	3.573

TABLE 2

sulfoxide	rel rate of consumption of starting material	distance from β to β' (Å)
2a	15	5.244
2b	3	4.654
2c	1	4.094

spectroscopy. The distance of β to β' increases by approximately 0.6 Å as the size of the remote substituent decreases from *tert*-butyl (**2c**) to isopropyl (**2b**) and from isopropyl (**2b**) to ethyl (**2a**). This increased remoteness of the β'-carbon atom to the β-carbon atom directly correlates with an increase in the rate of consumption of starting material. When the isopropyl sulfoxide (**2b**) with the β'-carbon 4.654 Å away from the β-carbon is compared to the *tert*-butyl (**2c**) β'-carbon, only 4.094 Å away from the β-carbon, the rate increases by a factor of 3. The significantly smaller ethyl terminus of sulfoxide **2a** exhibits even less shielding of the olefin with a β to β' distance of 5.244 Å. This increased remoteness results in a significant increase in reaction rate of 15 times that of the *tert*-butyl sulfoxide (**2c**).

Both the sulfones **1a**−**c** and the sulfoxides **2a**−**c** exhibit a clear inverse correlation between steric hindrance and rate of conjugate addition. However, would a conjugated ester system that has a more remote β'-substituent exhibit the same trend in steric effects on the rate of conjugate addition?

The difference in $\beta-\beta'$ distance among the alkyl crotonates **3a**−**c** follows the same trend of increasing distance as the size of the alkyl group becomes smaller (Table 3). The distance of β to β' increases by approximately 0.05 Å as the alkyl group decreases in size from *tert*-butyl (**3c**) to isopropyl (**3b**). This small difference still creates a 2.2-fold increase in the rate of conjugate addition to the isopropyl (**3b**) compared to the *tert*-butyl (**3c**) crotonate. As the size of the remote substituent decreases from isopropyl (**3b**) to ethyl (**3a**), a β to β' distance increase of approximately 0.55 Å and a rate increase of approximately 2 are observed. The crotonate systems **3a**−**c** are compared by disappearance of starting materials due to coelution of products. Although the crotonates exhibit increased remoteness and less pronounced rate differences, in comparing ethyl (**3a**), isopropyl (**3b**), and *tert*-butyl (**3c**) crotonates, it is clear that steric hindrance of the alkyl substituent still inversely affects the rate of conjugate addition.

TABLE 3

ester	rel rate of consumption of starting material	distance from β to β' (Å)
3a	4.3	5.944
3b	2.2	5.395
3c	1	5.338

In attempts to enhance the difference in rates, the competition experiments were performed at both 0 and −78 °C, but no difference in rate ratio was observed compared to reactions carried out at room temperature. Temperature has no effect on the rate ratio of conjugate addition. The differences in rates of conjugate addition were also measured at 2% and 20% completion of the reaction to ensure that the rate difference was not changing as the more reactive unsaturated system was being consumed. The competition of benzyl mercaptan conjugate addition to isopropyl and *tert*-butyl unsaturated sulfones gave a 3:1 ratio of products at 2%, 20%, and 100% reaction completion.

Conclusion

In conclusion, we show here that what are widely considered to be remote alkyl groups in −CH═CHS(O)$_n$−alkyl systems and in −CH$_2$CH═CHCOO−alkyl systems are actually not remote from the β-carbon of these Michael acceptors. Molecular modeling shows clearly that the alkyl groups in these conjugated systems shield the β-carbons in the following order: *t*-Bu > *i*-Pr > Et. Although the termini differ by only one carbon, using competition experiments, we show for the first time that a compound with a bulkier *tert*-butyl terminus has a slower conjugate addition reaction rate than the corresponding compound having an isopropyl terminus. This isopropyl compound, in turn, has a slower rate than the corresponding molecule with a less sterically hindering ethyl terminus.

Experimental Section

All air- and moisture-sensitive reactions were carried out in flame-dried or oven dried (at 120 °C) glassware under an inert atmosphere of argon. All reactive liquids were transferred by syringe or cannula and were added to the flask through a rubber septum. All other solvents and reagents were used as received unless otherwise stated. Melting points were obtained on a metal block apparatus and are not corrected. ^{1}H and ^{13}C spectra were obtained on a 300 or 400 MHz spectrometer. All NMR spectra were obtained in a solution in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm). Multiplicities of signals in the ^{1}H spectra are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), etc. Infrared spectra were obtained on an FR-IR spectrometer as liquid films or as a thin layer with NaCl cells. Intensities were reported as s (strong, 67−100%), m (medium, 34−66%), and w (weak, 0−33%) with the following notations: br (broadened), sh (shoulder), etc. Analytical thin layer chromatography (TLC) was performed on silica gel plates (0.25 mm thickness) with F_{254} indicator. Compounds were visualized under a UV lamp and/or by developing with iodine, vanillin, *p*-anisaldehyde, $KMnO_4$, or phosphomolybdic acid followed by heating on a hot plate. FAB mass spectra were obtained using a double focusing magnetic sector mass spectrometer equipped with a Xe gas FAB gun (8 kV at 1.2 mA), an off-axis electron multiplier, and a data system at Johns Hopkins University. The resolution of the instrument was set at 10000 (100 ppm peak width). Samples were mixed with *m*-nitrobenzyl alcohol matrix deposited on the target of a direct insertion probe for introduction into the source. Nominal mass scan spectra were acquired with a mass scan range of 10−950 amu using a magnet scan rate of 25 s/decade. For accurate mass measurements, a narrower mass scan range was employed, with the matrix containing 10% PEG mass calibrant.

The isopropyl and *tert*-butyl β-hydroxy sulfides were prepared according to the experiment of Clive.[15] The ethyl vinyl sulfoxide (**2a**) and *tert*-butyl vinyl sulfoxide (**2b**) were prepared according to Jenks.[16] Ethyl 4-phenyl-2(*E*)-pentenoate (**3a**) and *tert*-butyl 4-phenyl-2(*E*)-pentenoate (**3c**) were synthesized according to a procedure by Pandolfi.[17] The compounds **2a**,[18] **2c**,[19] **3a**,[20] and **3c**[21] are all known, and their structures are consistent with their published data.

Sulfones. (i) Ethyl 4-Phenyl-1(*E*)-butenyl Sulfone (1a). Ethyl methyl sulfide (0.500 g, 6.60 mmol) was dissolved in dichloromethane (66.0 mL) in a 100 mL round-bottom flask. 3-Chloroperoxybenzoic acid (*m*-CPBA; 70% in H_2O, 3.90 g, 15.8 mmol) and sodium bicarbonate (0.550 g, 6.60 mmol) were added. The reaction was stirred for 16 h, at which time the starting material was consumed. The reaction was quenched with saturated sodium bicarbonate (50 mL) and extracted with methylene chloride (3 × 50 mL). The organic layers were combined and washed with concentrated sodium bicarbonate (3 × 50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to give a pure white solid in 75% yield (0.540 g).

2,6-Dimethylpyridine (DMP; 0.110 g, 0.940 mmol) was dissolved in tetrahydrofuran (6 mL) in a 25 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The reaction mixture was cooled to −78 °C, and 1.6 M *n*-BuLi (0.588 mL, 0.940 mmol) was added dropwise. The reaction mixture was stirred for 30 min, at which time ethyl methyl sulfone (0.090 g, 0.832 mmol) was added in tetrahydrofuran (2.5 mL) via cannula. The reaction was stirred for 30 min, at which time hydrocinnamaldehyde (0.110 g, 0.820 mmol) was added by syringe. The reaction was stirred overnight at −60 °C. Upon consumption of starting material, the reaction was quenched with H_2O (10 mL), extracted with ethyl acetate (3 × 20 mL), and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the crude product. The crude mixture was purified by flash silica chromatography (50% hexanes/50% ethyl acetate) to give 0.107 g of the desired β-hydroxy sulfone as an oil in 52% yield.

The β-hydroxy sulfone (0.107 g, 0.442 mmol) was dissolved in methylene chloride (8.0 mL) in a 100 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The reaction flask was cooled to 0 °C, and triethylamine (0.718 g, 7.10 mmol) and methanesulfonyl chloride (0.370 g, 3.20 mmol) were added. The reaction was stirred for 1 h, at which time 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU; 0.250 g, 1.60 mmol) was added. The reaction was stirred for 1 h at 0 °C and 1 h at room temperature. The reaction was diluted with brine and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by flash silica chromatography (50% hexanes/50% ethyl acetate) to give 0.790 g of ethyl 4-phenyl-1-butenyl sulfone as an oil in 80% yield of 5.3:1 *E*/*Z* isomers. Data for the *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.28 (m, 2H), 7.24−7.17 (m,3H), 6.92 (ddd, 1H, J = 14.8, 14.0, 7.2 Hz), 6.15 (dt, 1H, J = 15.2, 1.6 Hz), 2.91 (m, 2H), 2.85−2.79 (m, 2H), 2.64−2.59 (m, 2H), 1.14 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.4, 139.8, 128.4, 128.2, 127.8, 126.3, 48.8, 33.7, 33.0, 7.0; IR (thin film, cm^{-1}) 3054-(m), 3034(m), 2996(m), 2928(m), 2851(m), 1625(m), 1606(m), 1496(m), 1452(m), 1423(w), 1297(s), 1287(s), 1210(m), 1123(s), 1056(w), 950(m), 921(m), 901(w), 824(m), 757(s), 689(m); HRMS *m*/*z* calcd for $C_{12}H_{16}O_2S$ 225.0949, found 225.0944.

(ii) Isopropropyl 4-Phenyl-1(*E*)-butenyl Sulfone (1b). Diisopropylamine (1.00 g, 9.84 mmol) was dissolved in tetrahydrofuran (10 mL) in an oven-dried 50 mL round-bottom flask charged with argon and a magnetic stir bar. The solution was cooled to −78 °C, and 1.6 M *n*-BuLi (6.15 mL, 9.84 mmol) was added dropwise. The reaction was stirred for 30 min, at which time methyl isopropyl sulfone (0.600 g, 4.90 mmol) was added in via cannula in tetrahydrofuran (5 mL). The reaction was stirred for 30 min, at which time diethyl chlorophosphonate (0.850 g, 4.90 mmol) was added via syringe. After the resulting solution was stirred for 1 h, hydrocinnamaldehyde (0.548 g, 4.08 mmol) was added and the reaction stirred at −78 °C for 16 h. The reaction was quenched with H_2O (20 mL), extracted with diethyl ether (3 × 20 mL), and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the crude product. The crude mixture was purified by flash silica chromatography (80% hexanes/20% ethyl acetate) to give 0.464 g

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of the desired isopropyl 4-phenyl-1(*E*)-butenyl sulfone as an oil in 50% yield as a 5.7:1 *E*/*Z* mixture of isomers. Data for the *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.24 (m, 2H), 7.19−7.12 (m,3H), 6.84 (ddd, 1H, J = 15.2, 13.6, 6.8 Hz), 6.15 (dt, 1H, J = 15.2, 3.2 Hz), 2.91 (m, 2H), 2.97−2.88 (m, 1H), 2.83−2.74 (m, 2H), 2.60−2.55 (m, 2H), 1.20 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 139.6, 128.2, 127.9, 126.0, 125.9, 55.7, 33.4, 32.7, 15.0; IR (thin film, cm^{-1}) 3054(m), 3025(m), 2996-(m), 2938(m), 2870(m), 1625(m), 1606(m), 1500(m), 1471(m), 1442(s), 1384(w), 1365(w), 1297(s), 1249(s), 1172(m), 1123(s), 1075(w), 1046(m), 1027(w), 969(m), 930(w), 872(m), 815(s), 747-(s), 699 (s), 660(s), 602(w), 593(w), 573(m); HRMS *m*/*z* calcd for $C_{13}H_{18}O_2S$ 239.1106, found 239.1107.

(iii) *tert*-Butyl 4-Phenyl-1(*E*)-butenyl Sulfone (1c). Oxone (8.85 g, 14.4 mmol) was dissolved in water (16.0 mL) in a 50 mL round-bottom flask and cooled to 0 °C. *tert*-Butyl methyl sulfide (0.500 g, 4.80 mmol) in methanol (8.00 mL) was added to the oxone solution via cannula. After the resulting solution was stirred for 16 h, the oxone was filtered off to give methyl *tert*-butyl sulfone, which was purified by recrystallization to give 0.520 g of a white solid in 79% yield.

tert-Butyl methyl sulfone (0.252 g, 1.85 mmol) was dissolved in tetrahydrofuran (25 mL) in a 50 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The reaction mixture was cooled to −78 °C, and 1.56 M *n*-BuLi (1.31 mL, 2.05 mmol) was added dropwise. The reaction was stirred for 30 min, at which time hydrocinnamaldehyde (0.125 g, 0.931 mmol) was added by syringe. The reaction was stirred overnight at −60 °C. Upon consumption of starting material, the reaction was quenched with H_2O (10 mL), extracted with ethyl acetate (3 × 20 mL), and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the crude product. The crude mixture was purified by flash silica chromatography (70% hexanes/30% ethyl acetate) to give 0.235 g of the desired β-hydroxy sulfone as an oil in 91% yield.

The β-hydroxy sulfone (0.235 g, 0.869 mmol) was dissolved in methylene chloride (50 mL) in a 100 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The reaction flask was cooled to 0 °C, and triethylamine (1.41 g, 13.9 mmol) and methane sulfonyl chloride (0.727 g, 6.34 mmol) were added. The reaction was stirred for 1 h, at which time it was concentrated, dissolved in brine (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mesylate was brought on to the next step.

The mesylate was dissolved in benzene (40 mL) in an oven-dried 100 mL round-bottom flask charged with argon and a magnetic stir bar. DBU (0.489 g, 3.22 mmol) was added, and the reaction was refluxed for 1 h. The reaction was cooled to room temperature, diluted with brine, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by flash silica chromatography (70% hexanes/30% ethyl acetate) to give 0.219 g of the desired *tert*-butyl 4-phenyl-1(*E*)-butenyl sulfone as a white solid in 94% yield as a 10:1 *E*/*Z* mixture of isomers, mp 88−90 °C. Data for the *E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.27 (m, 2H), 7.22−7.16 (m, 3H), 6.88 (ddd, 1H, J = 15.2, 13.6, 6.8 Hz), 6.20 (dt, 1H, J = 15.2, 1.6 Hz), 2.85−2.81 (m, 2H), 2.67−2.61 (m, 2H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.7, 139.7, 128.4, 128.1, 126.2, 124.3, 58.0, 33.6, 33.0, 22.9; IR (thin film, cm^{-1}) 3044(w), 3034(w), 2967(m), 2938(m), 2870(w), 1628(m), 1606(m), 1500(m), 1461(m), 1403-(w), 1355(w), 1278(s), 1258(s), 1191(w), 1114(s), 1027(m), 805-(s), 786(s), 728(m), 879(m), 850(m); HRMS *m*/*z* calcd for $C_{14}H_{20}O_2S$ 253.1262, found 253.1256.

Isopropyl Vinyl Sulfoxide (2b). (i) 2-(1-Methylethyl)thioethanol. The β-hydroxy sulfide was prepared according to the experiment of Clive.[15] 1-Methylethyl thiol (3.14 g, 41.3 mmol) was added dropwise to a solution of sodium (0.950 g, 41.3 mmol) in absolute ethanol (65.0 mL) in a 100 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The solution was stirred for 15 min, at which time 2-chloroethanol (3.33 g, 41.3 mmol) was added slowly. After the solution was refluxed for 1 h, the solvent was removed slowly by distillation. The residue was cooled, and solid NaBr was filtered off to yield 4.5 g of the desired 2-(1-methylethyl)thioethanol as an oil in 91% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74−3.64 (m, 2H), 2.98−2.90 (m, 1H), 2.77−2.73 (m, 2H), 1.26 (d, 6H, J = 7.8 Hz).

(ii) Isopropyl Vinyl Sulfide. The vinyl sulfide was prepared according to Jenks.[16] A 20 mL oven-dried two-neck round-bottom flask was equipped with two condensers. One condenser led to a short-path distillation head. The other was used as an inlet for 2-(1-methylethyl)thioethanol and argon. The distillation head was equipped with a round-bottom flask used for the sulfide trap, cooled to −78 °C. Argon was used to control the flow of sulfide gas to the trap. KOH (0.467 g, 8.33 mmol) was added to the two-neck round-bottom flask, which was then heated to 320 °C using a heating mantle and sand bath. After the KOH turned to a molten liquid, 2-(1-Methylethyl)thioethanol (1.00 g, 8.33 mmol) was added dropwise directly onto the KOH, resulting in evolution of gas which was collected as a liquid in the trap. The reaction was stirred until the evolution of gas stopped. The product was pure by ^{1}H NMR, yielding 48% of the desired material: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.35 (dd, 1H, J = 16.8, 9.90 Hz), 5.22 (d, 1H, J = 2.4 Hz), 5.18 (d, 1H, J = 8.7 Hz), 2.74−2.65 (m, 1H), 3.18−3.09 (m, 1H), 1.29 (d, 6H, J = 10.8 Hz).

(iii) Isopropyl Vinyl Sulfoxide. The vinyl sulfoxide was prepared according to Jenks.[16] 2-Propyl vinyl sulfide (0.384 g, 3.80 mmol) was placed in a 10 mL round-bottom flask charged with a magnetic stir bar and argon. Acetic acid (1.50 mL) was added, and the reaction was cooled to 0 °C. Hydrogen peroxide (30%, 0.430 mL, 3.80 mmol) was added, and the reaction was stirred for 2.5 h, at which time the reaction was quenched dropwise with sodium carbonate until a pH of 7 was reached. The organics were extracted with CH_2Cl_2, washed with water, dried over magnesium sulfate, and concentrated. The concentrated product (0.21 g, 46% yield) was pure by ^{1}H NMR: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 6.29 (dd, 1H, J = 15.9, 9.90 Hz), 5.68 (d, 1H, J = 16.2), 5.60 (d, 1H, J = 6.6 Hz), 2.54−2.40 (m, 1H), 0.92 (d, 3H, J = 6.9 Hz), 0.85 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 123.3, 51.5, 15.3, 14.2; IR (thin film, cm^{-1}) 2938(m), 2861(m), 1702(m), 1635(m), 1587(m), 1558(m), 1461(m), 1384(w), 1316(w), 1278-(m), 1230(s), 1181(w), 1114(m), 959(w), 853(w), 757(s), 728(m), 679(m); HRMS *m*/*z* calcd for $C_5H_{10}OS$ 119.0531, found 119.0521.

Isopropyl 5-Phenyl-2(*E*)-pentenoate (3b). Diisopropylamine (0.506 g, 5.00 mmol) was dissolved in tetrahydrofuran (26 mL) in an oven-dried 50 mL round-bottom flask charged with argon and a magnetic stir bar. The solution was cooled to −78 °C, and 1.5 M *n*-BuLi (3.33 mL, 5.00 mmol) was added dropwise. The reaction was stirred for 30 min, at which time isopropyl acetate (0.441 g, 5.00 mmol) was added. After the solution was stirred for 30 min more, hydrocinnamaldehyde (0.560 g, 4.17 mmol) was added by syringe. The reaction was stirred overnight at −60 °C. Upon consumption of starting material, the reaction was quenched with H_2O (10 mL), extracted with ethyl acetate (3 × 20 mL), and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to give the crude product. The crude mixture was purified by flash silica chromatography (90% hexanes/10% ethyl acetate) to give 0.754 g of the desired β-hydroxy ester as an oil in 82% yield.

The β-hydroxy ester (0.508 g, 2.31 mmol) was dissolved in methylene chloride (18 mL) in a 100 mL oven-dried round-bottom flask charged with argon and a magnetic stir bar. The reaction flask was cooled to 0 °C, and triethylamine (3.74 g, 37.0 mmol) and methanesulfonyl chloride (1.93 g, 16.9 mmol) were added. The reaction was stirred for 1 h, at which time DBU (1.30 g, 8.55 mmol) was added. After being stirred for 1 h more, the reaction was quenched with H_2O, diluted with brine, and extracted with ethyl

acetate (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by flash silica chromatography (90% hexanes/10% ethyl acetate) to give 0.349 g of the desired isopropyl ester as an oil in 75% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.31 (m, 2H), 7.26−7.21 (m, 3H), 7.04 (ddd, 1H, J = 15.6, 13.6, 6.8 Hz), 5.88 (d, 1H, J = 15.6 Hz), 5.14−5.08 (m, 1H), 2.81 (t, 2H, J = 7.6 Hz), 2.57−2.52 (m, 2H), 1.30 (d, 6H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 147.5, 140.7, 128.3, 128.2, 126.0, 122.2, 67.2, 34.2, 33.7, 21.7; IR (cm^{-1}) 3025(w), 3005(m), 2967-(m), 2947(m), 1712(s), 1654(m), 1480(m), 1471(m(, 1452(m), 1365-(m), 1355(m), 1307(m), 1268(s), 1210(m), 1181(m), 1152(m), 1104(s), 998(m), 974(m), 930(w), 911(w), 843(w), 737(m), 689-(m).

General Competition Experiment. Benzyl mercaptan (1 equiv) was dissolved in methanol (0.5 M) in an oven-dried round-bottom flask charged with argon and equipped with a magnetic stir bar. Triethylamine (1.1 equiv), distilled over calcium hydride, was added dropwise, and the reaction was stirred for 30 min. One equivalent of each of two of the unsaturated compounds was dissolved in methanol and added via cannula to the benzylmercaptan solution. Upon consumption of benzyl mercaptan as determined by TLC, the reaction was quenched with H_2O, extracted with Et_2O, dried over magnesium sulfate, filtered, and concentrated. The crude material was then analyzed by GC to obtain a ratio of products formed or starting materials consumed.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and GC traces of the reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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