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Nucleophilic Additions to Alkylidene Bis(sulfoxides)—Stereoelectronic Effects in Vinyl Sulfoxides

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Dedicated to Professor Dr. Dr. h. c. Dieter Seebach on the occasion of his 70th birthday

Abstract: Conjugate additions of nucleophiles (e.g. enolates, amines and malonate anions) to bis(*p*-tolylsulfinyl)alkenes, alkylidene-1,3-dithiane-1,3-dioxides and alkylidene-1,3-dithiolane-1,3-dioxides have recently been published. Reasons for different selectivities and reaction rates will be discussed by consideration of steric and electronic effects. The preferred mode of attack can be explained by stereoelectronic effects (hyperconjugation) in the primarily carbanion, which is stabilized by n→S-O-σ* interaction with an antiperiplanar S=O group. Calculation of the transition states [BP86/aug-TZVP] for the addition of acetone enolate to the dithiane-derived alkylidene bis(sulfoxide) revealed that 6.6–7.3 kJ mol^{-1} more energy is needed for an attack leading to a less-stabilized carbanion. Two axial S=O groups in dithiolane-derived alkylidene bis(sulfoxides) lead to a higher reactivity towards nucleophiles.

Keywords: density functional calculations · diastereoselectivity · nucleophilic addition · stereoelectronic effects · sulfur heterocycles

Introduction

A multitude of information has been published on the addition of nucleophiles to carbonyl compounds and α,β-unsaturated carbonyl compounds. The frontier orbitals in these reactions are well known to every chemist[1] and special modes of attack, like the Zimmerman–Traxler transition state, can be handled by 3rd year students.[2] Even very sophisticated stereoelectronic effects are—though possibly not commonly known—at least understood by specialists in this field.[3] While sulfoxides behave in some aspects similarly to carbonyl compounds, much less is published or commonly known about sulfoxides and especially about vinyl-substituted sulfoxides.[4] During the examination of nucleophilic additions to dithiane-derived alkylidene bis(sulfoxides),[5,6] we were confronted with some fundamental questions which have hardly been addressed in the literature.

Alkylidene bis(sulfoxides)[4] have repeatedly been used in organic synthesis due to their electron-deficient double bond.[8] Since non-symmetrically substituted sulfoxides are chiral and configurationally stable, these reactions can be led diastereoselectively. Aggarwal and co-workers very successfully used dithiane- and dithiolane-derived bis(sulfoxides) of type **2** and **3** in epoxidations, cyclopropanations, and cycloadditions (Figure 1).[9] The cleavage of the auxiliary, for instance with the Pummerer reaction, releases a carbonyl group.[4,9b,10] Fensterbank, Malacria, and co-workers reported on nucleophilic additions to ditolyl-substituted alkylidene bis(sulfoxides) **1** (Figure 1) and observed excellent selectivities and a high reactivity in the addition of *C*-, *N*-, and *O*-nucleophiles.[11,12] They argued that a steric hindrance arising from the π-stacked tolyl groups is responsible for these selectivities. We found that dithiane-derived substrates **2** gave somewhat poorer selectivities and are not as reactive. For example, a nucleophilic attack of secondary amines is achieved only with a high excess (amine used as solvent), with

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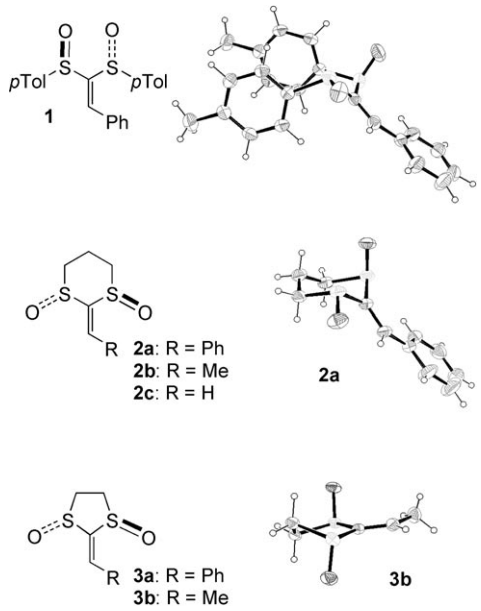


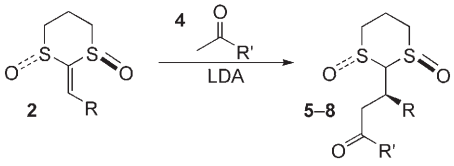
Figure 1. Alkylidene bis(sulfoxides) and their crystal structures.[7] top;[11a] middle;[5] bottom.[6]

a significantly lower rate and with a poor yield. Nevertheless, steric hindrance should be essentially the same in **2** as in substrates **1**. In contrast, we observed a significantly higher reactivity in additions to dithiolane-derived alkylidene bis(sulfoxides) **3**. Addition of piperidine as a secondary amine proceeded fast, even at −78 °C and with only a slight excess of the amine.[6] Though substrates **1**–**3** are quite similar on a first glance, they behave very differently in terms of reactivity and selectivity.

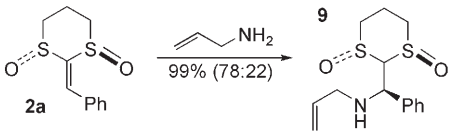
To understand and to be able to influence the stereochemical outcome in the nucleophilic addition to vinyl sulfoxides, it seems to be essential to know about the stereoelectronic effects arising from the S=O double bond. These effects compete with possible steric effects or with a putative pre-complexation as present in the Zimmerman–Traxler transition state. Though stereoelectronic effects of sulfoxides have occasionally been investigated,[13,14] much less is known about orbital interactions in vinyl sulfoxides.[15] The systems used up to now were either not in a fixed (or otherwise unambiguously known) conformation and thus did not allow a concise treatment[11,16] or were present together with interfering carbonyl groups,[8a,17] which did not allow an independent examination of the sulfoxide's influence. Herein we discuss stereoelectronic effects in the reactions of vinyl sulfoxides.

Results and Discussion

Dithiane-derived alkylidene bis(sulfoxides): Dithiane-derived alkylidene bis(sulfoxides) were prepared by slight modification of a procedure presented by Aggarwal et al.[18] They were obtained in two steps from 1,3-dithiane by Peterson olefination and subsequent enantio- and diastereoselective *S*-oxidation. Addition of enolates to bis(sulfoxide) **2a** proceeded with selectivities better than 85:15 and with close to quantitative yields,[5] in which a single recrystallization gave pure products (Scheme 1). Yields and selectivities were



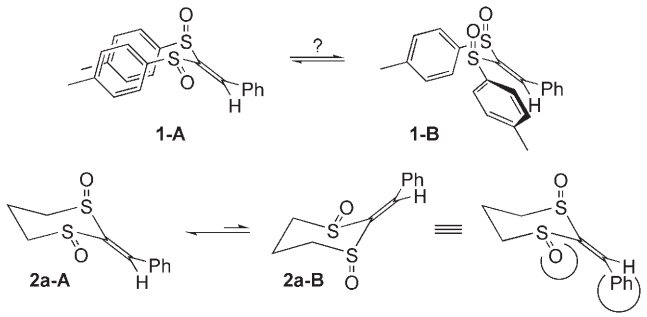
Starting material	R	R'	Product	Yield [%]	d.r.
2a	Ph	Ph	**5**	82[a]	96:4
2a	Ph	Me	**6**	68[a]	86:14
2a	Ph	OEt	**7**	75[a]	89:11
2b	Me	Ph	**8**	88[b]	25:75[c]



Scheme 1. Nucleophilic attack to dithiane-derived substrates **2**. [a] Purified major isomer. [b] Mixture of isomers. [c] Isomers could not be separated. LDA = lithium diisopropylamide.

similar when allylamine was added, though the resulting diastereoisomers (78:22) were not separable, either by chromatography or by crystallization. The attack is assumed to proceed generally from the *Re* side. Evidence for this comes from X-ray crystallographic analyses.[5]

In a mechanistic investigation on diastereoselectivities, the conformational space and its population by preferred conformations is of special importance. In the open-chain bis(sulfoxides) **1** several conformations should be considered, even though it has been claimed that the π-stacked conformation **1-A** is solely relevant in nucleophilic additions (Scheme 2).[11a] Dithiane-derived bis(sulfoxide) **2** is less flexible. At least for bulky substituents (R = Ph), only conformation **2a-A** is significantly populated because of allylic strain



Scheme 2. Conformations in alkylidene bis(sulfoxides).

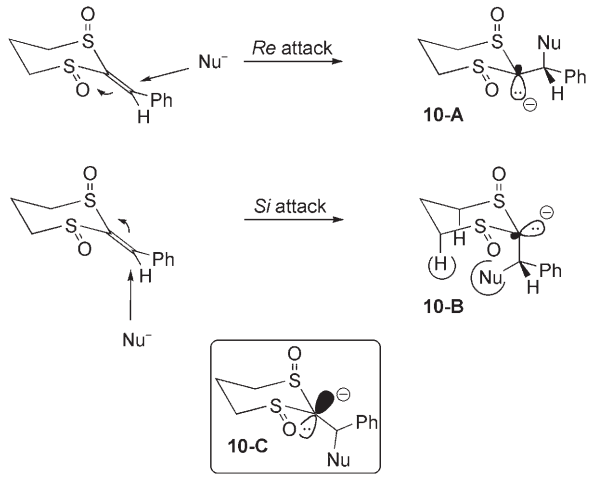
($A^{1,3}$ strain)[19] and a (admittedly weak) hydrogen bond between the equatorial S=O oxygen and the vinylic hydrogen.[20] We calculated that the energy of conformation **2a-B** (R = Ph) is about 15.9 kJ mol^{-1} higher than for conformation **2a-A** [BP86/aug-TZVP]. The Curtin–Hammett principle allows for energy-rich conformations in mechanistic pathways;[21] nevertheless, conformation **2a-B** will not be considered in the further discussions when a bulky phenyl group (R = Ph) is present in the molecule.

Several reasons might be responsible for the observed diastereoselectivity in this reaction. A prerequisite for an appropriate consideration of possible steric reasons is a sufficient knowledge of the assumable trajectory. Nucleophilic additions to Michael-type systems proceed very similar[22] to additions to carbonyl double bonds in which the trajectory angle (O=C···Nu) has been determined by Bürgi, Dunitz, and Shefter to be about 109°.[23] Consequently, in conjugated systems, an approaching nucleophile should be far away from steric influences beyond the electron-deficient double bond as present in alkylidene bis(sulfoxides) **1**–**3**.

Besides this steric reasoning, diastereoselectivities might be ruled by a pre-complexation of the incoming nucleophile through the S=O oxygen. This seems not to be very likely in the reactions discussed here, since no influence of the counterion was observed by us in the addition of enolates. Even enolates released from silyl enol ethers with tetrabutylammonium fluoride (TBAF) were added with virtually identical selectivities.[5] Pre-complexation in the addition of cuprates is widely accepted in additions to α,β-unsaturated carbonyl compounds.[24] Nevertheless, the addition of cuprates to tolyl-substituted substrates **1** proceeded antiperiplanar to the axial S=O group,[11a] making a pre-complexation of the incoming cuprate very unlikely.[25]

The primary product in a conjugate addition of nucleophiles is a stabilized carbanion where the reasons for the stabilization should already work during the reaction and thus should have an impact on the nature of the transition state. While in a classical Michael addition (i.e., addition to an α,β-unsaturated carbonyl) a planar enolate is formed in which the negative charge and the counterion are predominantly located at the oxygen, this is not necessarily valid for vinyl sulfoxides (Scheme 3). The structure of α-sulfinyl carbanions has occasionally been studied. While NMR spectroscopic investigations suggested a planar structure (compare to the putative structure **10-C**),[26] more meaningful X-ray crystallographic analyses proved that the carbon atom is significantly pyramidalized when no further stabilizing substituent (e.g., an α-phenyl group) is present. The counterion is usually located in the vicinity of the carbon atom.[27] The high kinetic acidity of α-sulfinyl alkanes gives further evidence for a pyramidalized structure of the respective anions. No re-hybridization and thus no overcoming of an intrinsic barrier is necessary.[28,29]

The simultaneous formation of an antiperiplanar carbanionic lone pair by attack of a nucleophile should have far-reaching consequences. The concomitant change in hybridization at the α-carbon and consequently the change of the bonding angle from 120° to about 109° force the former alkylidene group towards the incoming nucleophile (Scheme 3). This structural change should lead to a significant increase in steric repulsion if the nucleophile approaches from the *Si* side (→ **10-B**). This effect would in fact favor an attack from the unhindered *Re* side, although it becomes operative only in an advanced state of the reaction (compare the structures of the transition states in Figure 3).



Scheme 3. Carbanion formation through nucleophilic attack to alkylidene bis(sulfoxides).

A second effect should have an even higher impact on selectivities during nucleophilic attack. An evolved axial lone pair is stabilized through antiperiplanar S=O bonds.[30] Contrary to α-carbonyl carbanions, which are stabilized through interaction with the π* orbital, here, it is an S–O σ* orbital in an appropriate orientation which leads to interaction and thus to stabilization of the n orbital by hyperconjugation (Figure 2, top row). A comparable interaction is not possible for an equatorial lone pair (though it should be stabilized to some extent through an antiperiplanar C–S σ* orbital[13b,31]). A similar, though less favorable interaction should be possible with a synperiplanar S=O bond (see below), but it should be negligible for clinal oriented S=O bonds.

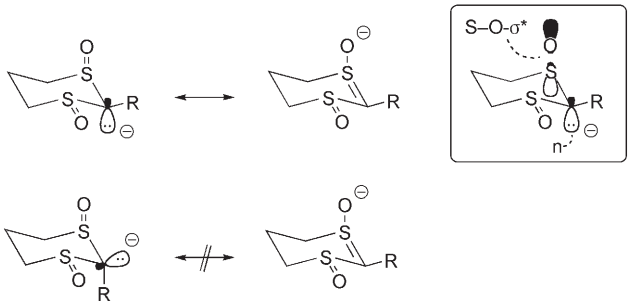


Figure 2. Stereoelectronic effects in sulfinyl carbanions.

This reasoning is strongly supported by calculations performed by us. The negatively charged disulfinyl-substituted carbon in **10** is perspicuously pyramidalized with an angular sum[32] of 338.4° proving that an n→S-O-σ* interaction is working to a significant extent. Calculations of the transition states of the competing diastereotopic modes of attack showed that this stabilizing interaction is already evident during the reaction. The transition state emerging from *Re* attack of the acetone enolate is 7.3 kJ mol^{-1} lower than that of a *Si* attack (Figure 3, Table 1). On the other hand, enolate

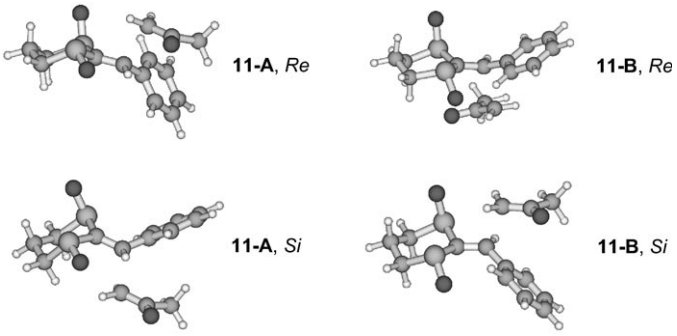


Figure 3. Calculated transitions states for attack of acetone enolate to alkylidene bis(sulfoxide) **2a**.[7]

Table 1. Energy differences between transition states and ground states of the reactants.

Entry	Transition state	Mode of attack[a]	Transition state energy [kJ mol^{-1}][b]
1	**11-A**	*Re* (top)	43.4
2	**11-A**	*Si* (bottom)	50.7
3	**11-B**	*Re* (bottom)	46.1
4	**11-B**	*Si* (top)	50.3

[a] Orientation of acceptor **11** as depicted in Scheme 3 and Figure 3. [b] BP86/aug-TZVP.

addition to the high-energy conformer **2a-B** is preferred from the *Re* side (i.e. from the bottom). The activation barrier for the *Si* attack to **2a-B** was calculated to be 4.2 kJ mol^{-1} higher than that of the *Re* attack.[33] Obviously the n→S-O-σ* interaction here is exceeded by other effects. Detailed inspection of the transition state geometries revealed that in the more favored transition state **11-B, *Re*** the enolate is closer to the acceptor (229.6 pm) than in transition state **11-B, *Si*** (234.1 pm). Furthermore, in **11-B, *Re*** the phenyl's *ortho* proton is closer to the equatorial oxygen (218.7 pm) than in transition state **11-B, *Si*** (247.4 pm), possibly allowing a weak but significantly stabilizing hydrogen bond. Nucleophilic attack to methyl-substituted alkylidene bis(sulfoxide) **2b** as a system without perturbing steric effects is discussed below.

While nucleophilic additions to sulfinylmethyl sulfides **12** are possible in open-chain substrates,[34] the cyclic, conformationally constrained substrate **13** (R = Ph)[14] does not react with enolates at all (Figure 4). NMR spectroscopic in-

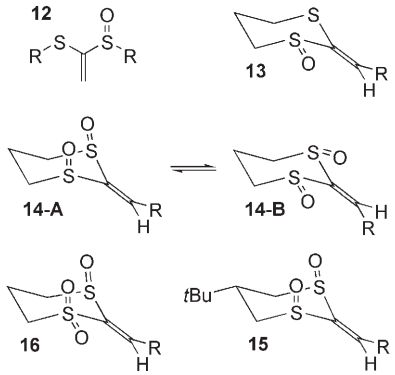
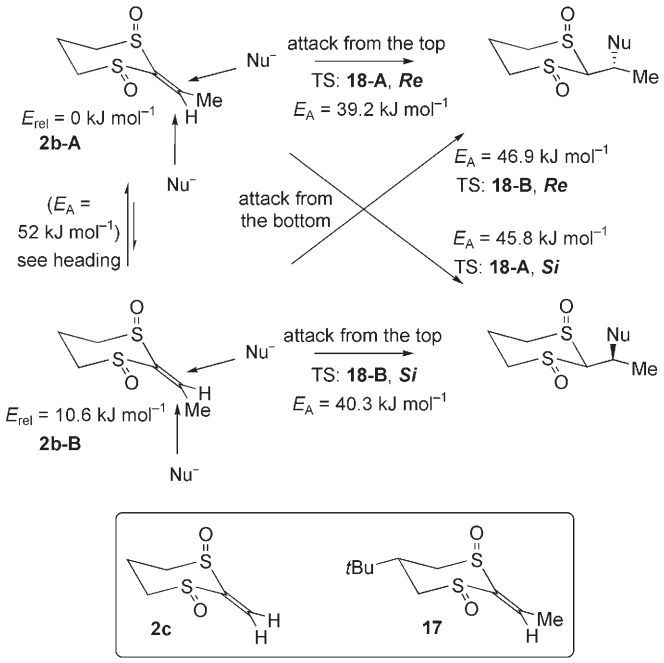


Figure 4. Sulfinylmethyl sulfides and axially chiral bis(sulfoxides).

vestigations revealed that the S=O bond is in a sterically and stereoelectronically favored equatorial position.[35] Obviously, the electron-withdrawing tendency of a sulfinyl group is not sufficiently active when the S=O bond is not co-planar with the evolving carbanionic lone pair.

If this reasoning applies, the presence of two S=O bonds antiperiplanar to an evolving lone pair should have an even higher impact. Reactivity of the alkylidene bis(sulfoxides) should increase and the diastereoselectivities should be even better. This might be a valid scenario in the reaction of bis-(tolylsulfinyl)-substituted substrates **1**. Though X-ray crystallographic analysis suggests the presence of conformation **1-A** with only one S=O group axial in the crystal (Figure 1), conformation **1-B** containing two axial S=O groups should be more reactive and thus might be susceptible towards the addition of nucleophiles (Scheme 2). Further evidence for the commanding influence of the axial S=O groups could possibly be supplied through the reaction outcome with substrate **14**. Unfortunately, up to now, no synthesis, either of the parent bis(sulfoxide) **14** or of its conformationally constrained derivative **15**, is known. The sulfinyl-sulfone **16** (R = Ph) bearing two axial S=O bonds could be prepared for comparison by oxidation of bis(sulfoxide) **2a**.[14] It reacted much faster with enolates than the parent bis(sulfoxide) **2a**, though the formation of 2:1 adducts (two equivalents of the sulfone reacted with one equivalent of the enolate in spite of a substantial steric hindrance for the second attack[36]) led to non-separable mixtures, which made a determination of the product's configurations impossible.

The poor and even inverted selectivity in the addition of the acetophenone enolate to ethylidene-1,3-dithiane-1,3-dioxide (**2b-A**) can be explained by comparison of calculated transition-state energies (Scheme 1 and Scheme 4).[33] An attack from the top is again favored over an attack from the bottom (6.6 kJ mol^{-1}). Nevertheless, here we have to consider a reaction of the high-energy isomer **2b-B**, which is only 10.6 kJ mol^{-1} less stable and thus significantly populated. Reaction of this conformer leads to permuted diastereoisomers, in which attack from the top again is 6.6 kJ mol^{-1} less expensive than attack from the bottom. The activation barrier for the ring-flipping between conformers **2-A** and **2-B** was measured for the parent alkylidene bis(sulfoxide) **2c**



Scheme 4. Nucleophilic attacks to substrates bearing a small methyl group (Nu$^-$ = acetone enolate). All values were calculated (BP86/aug-TZVP) except for the activation barrier for the conformational interchange between **2b-A** and **2b-B** which was measured by NMR spectroscopy for the parent compound **2c**.

(R = H)[37] by determination of the coalescence in deuterated methanol at 500 MHz.[38,33] The coalescence temperature was found to be −67 °C, corresponding to a free energy of activation of 40 kJ mol^{-1} and an activation barrier of 52 kJ mol^{-1} at this temperature.[39,40,41] It is reasonable to assume that this value is similar for the methyl-substituted substrate **2b**. These findings explain that none of the diastereoisomers is formed preferentially with this substrate. Investigations with conformationally locked substrates, for example 5-*tert*-butyl-substituted **17**, which should give further evidence for this explanation, are in progress.

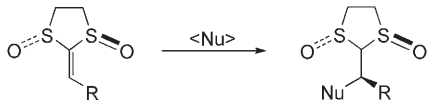
A generally applied tool for the quantification of hyperconjugative interactions is the natural bond orbital method (NBO) developed by Weinhold and co-workers,[42,43] transforming the canonical delocalized Hartree–Fock molecular orbitals (MOs) into localized hybrid orbitals (NBOs). The interactions between filled and antibonding orbitals quantify the energetic contribution of a distinct hyperconjugation. We calculated selected energy contributions of these delocalizations by deletion of the corresponding off-diagonal elements of the Fock matrix in the NBO basis.[33] These calculations were performed for transition states **18**. The energy contribution for the interaction of the alkylidene π bond (donor) with the axial S=O σ* orbital (acceptor) are 41.9 (**18-B**, ***Si***) and 41.5 kJ mol^{-1} (**18-A**, ***Re***), respectively, when attack of the enolate comes from the top (as depicted in Figure 3). They are only 25.4 (**18-B**, ***Re***) and 25.9 kJ mol^{-1} (**18-A**, ***Si***), respectively, when the enolate approaches from the lower side. Apparently, this hyperconjugation significantly contributes to the transition states energy difference between attack from the top and attack from the bottom, but it has to be kept in mind that this is only one stereoelectronic effect in a plethora of interactions which stabilize a molecule. The interaction of the alkylidene π bond with the equatorial S=O σ* orbital is worth less than 4 kJ mol^{-1} for all considered transition states. Evidently, this is a negligible hyperconjugation.

Dithiolane-derived Alkylidene bis(sulfoxides): In the corresponding dithiolane derived alkylidene bis(sulfoxides) **3** both the S=O groups are approximately co-planar and stretching in antipodal directions (Figure 1).[6] These compounds are significantly more reactive than dithiane derived substrates **2** which caused some problems during the workup process. Chromatography with dichloromethane and methanol on silica gel led to a distinct addition of methanol to the electron deficient double bond. We assume that not only the antiperiplanar S=O group but also—though possibly less effective—the synperiplanar S=O group stabilizes the carbanionic lone pair (Figure 5). Due to this stabilization in both

Figure 5. Conceivable structures of carbanions formed during nucleophilic attack to bis(sulfoxides) **3**.

directions, a sp^2 hybridization of the carbanion can no longer be excluded. As a matter of fact, the angular sum of the primarily formed carbanion was calculated to be 359.6°, the 2-substituent forms an angle of only 7° with the plane spanned by S1, C2, and S3.

The addition of the acetophenone enolate to phenyl-substituted bis(sulfoxide) **3a** led to only one diastereomer (≥98:2, Scheme 5, Table 2), in which a top approach is preferred (orientation of the substrate as seen in Scheme 5). This could be proven by two X-ray crystallographic analyses of the addition products.[6] The further tested piperidine and the malonate anion added to the bissulfoxide **3a** with high yields and selectivities (Table 2, entries 2 and 3). This finding again proved the high reactivity of the herein presented substrates. Whereas the dithiane derived compound **2a** (R = Ph) gave only a poor 20% yield when reacted for 48 h in piperidine as the solvent, bis(sulfoxide) **3a** cleanly gave the adduct **20** with only two equivalents of piperidine at −78 °C



Scheme 5. Addition of nucleophiles to dithiolane-derived bis(sulfoxides) **3**.

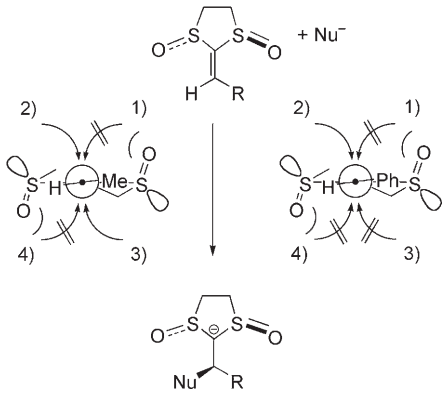
Table 2. Nucleophilic attack to dithiolane-derived substrates **3**.

Entry	Bis(sulfoxide)	Nucleophile	Product	Yield [%]	d.r.
1	**3a**, R = Ph		**19**	80	≥98:2
2	**3a**, R = Ph		**20**	quant.	92:8
3	**3a**, R = Ph		**21**	92	94:6
4	**3b**, R = Me		**22**	81	55:45[a]

[a] Isomers could not be separated.

for 30 min (Table 2, entry 2). With a smaller methyl group present in the bis(sulfoxide), selectivity of an enolate addition virtually vanished to 55:45.

Since these substrates (**3**) are quasi-C_2 symmetric, both trajectories of a nucleophilic attack should be favored through similar stereoelectronic effects. Nevertheless, with a bulky phenyl substituent present in the substrate attack is highly selective leading predominantly to one diastereoisomer. Our preliminary rational for this observation is that a second effect due to steric constrains becomes dominant. With respect to the plane of the double bond, four trajectories are possible (Scheme 6): attack 1) from the top right, 2) from the top left, 3) from the bottom right and 4) from the bottom left. Attacks 1 and 4 are possibly hindered through the axial oxygen atoms since these are much closer to the assumed trajectory than in substrates **2**. Attacks from the right (1 and 3) should be less favorable because of the interfering substituent R. This hindrance is negligible with a small methyl group giving rise to a poor selectivity (55:45) but becomes dominant with a bulky phenyl group allowing an attack only from direction 2, which would explain the observed selectivity of 98:2.



Scheme 6. Nucleophilic attack to dithiolane-derived alkylidene bis(sulfoxides). See text for details.

Conclusion

A sulfoxide is an electron-withdrawing functional group establishing electrophilic properties in its vicinity. From the stereochemistry in the addition of nucleophiles to vinyl sulfoxides and from theoretical investigations we concluded that a stabilizing stereoelectronic effect works favorably when a donor orbital (e.g. a lone pair) is antiperiplanar to an S=O group. This innovative finding should be an important foundation for the development of stereoselective reactions involving sulfoxides and related compounds.

Experimental Section

Computational methods: Quantum-chemical calculations were performed with the program package TURBOMOLE[44] using the DFT level of theory in combination with the RI-J approximation,[45] the BP functional,[46] and an aug-TZVP basis set (a TZVP basis set,[47] augmented with diffusive s, p, d, and f functions from Dunning's aug-cc-pVTZ basis[48]). The geometries of the starting materials, transition states and products were optimized at the BP86/aug-TZVP level and their nature was confirmed by vibrational analyses. To recover the influence of the solvent we used the COSMO module employing an infinite ε and optimized radii.[49] The NBO 3.1 program[42,43] was used as interfaced to the Gaussian 03 program package.[50]

General: The synthesis of compounds **2a**,[5] **2c**,[37] **3a**,[6] **5–7**,[5] **13**,[14] **16**,[14] and **19**[6] was published elsewhere. Tetrahydrofuran (THF) was distilled over a sodium benzophenone ketyl radical and CH_2Cl_2 was distilled over CaH_2. All moisture-sensitive reactions were carried out in oxygen-free argon using oven-dried glassware and a vacuum line. Flash column chromatography[51] was carried out using Merck silica gel 60 (230–400 mesh) and thin layer chromatography was carried out using commercially available Merck F_{254} pre-coated sheets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Cryospek WM-250, AM-400 and DRX 500. Chemical shifts are given in ppm downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments. Melting points were measured on a Büchi apparatus and were not corrected. IR spectra were recorded on a Bruker IFS-88 spectrometer. Elemental analyses were performed on a Heraeus, CHN-O-rapid. Electrical ionization and high resolution mass spectra were recorded on a Finnigan MAT-90. Optical rotations were recorded on a Perkin Elmer 241 polarimeter and specific optical rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.

***(R,R)*-2-Ethylidene-1,3-dithiane-1,3-dioxide (2b)**: The procedure is a slightly modified procedure from Aggarwal et al.[18] 1,3-Dithiane (2.40 g, 20.0 mmol) was suspended in THF (60 mL) under argon with stirring. The suspension was cooled to −78 °C and *n*BuLi (2.5 M solution in hexane, 8.3 mL, 21 mmol) was added over 15 min. The solution was allowed to warm to 0 °C over 1 h. The solution was re-cooled to −78 °C and TMS-Cl (2.64 mL, 20.8 mmol) dissolved in THF (80 mL) was added within 15 min. The solution was allowed to warm to room temperature over a period of 1 h. The solution was re-cooled to −78 °C and *n*BuLi (2.5 M solution in hexane, 8.3 mL, 21 mmol) was added within 15 min. The solution was allowed to warm to 0 °C within 1 h. The solution was re-cooled to −78 °C and freshly distilled ethanal (916 mg, 20.8 mmol) dissolved in THF (8 mL) was added within 15 min. The solution was warmed to room temperature overnight. The solution was poured in a saturated NH_4Cl solution (60 mL), extracted with ethyl acetate (3 × 60 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. Purification via bulb-to-bulb distillation (bath temperature of up to 120 °C, 1.5×10^{-2} mbar) afforded the desired crude ketene dithioacetal as a pale viscous oil (2.9 g).

(+)-Diethyl tartrate (4.12 g, 40 mmol, traces of water were removed by azeotropic distillation with toluene) and freshly distilled Ti(O*i*Pr)$_4$

(3.0 mL, 10 mmol) were dissolved in CH_2Cl_2 (90 mL) at room temperature under argon and stirred for 30 min. The solution became yellow. The crude ketene dithioacetal (prepared as described above) was dissolved in CH_2Cl_2 (12 mL) and added to the reaction mixture, which was then cooled to −45 °C and stirred for 2 h. Cumene hydroperoxide (80 %; 15 mL, 80 mmol) in CH_2Cl_2 (8 mL) was added over a period of 1 h, while the solution was allowed to warm to −20 °C. The mixture was stored for 24 h in a freezer (about −23 °C). Distilled water (7.2 mL, 0.4 mol) was added and the reaction mixture was stirred vigorously for 1 h. The resulting gel was placed in an ultrasonic bath for 1 h to afford a filterable suspension, which was suction-filtered through a large sintered glass funnel filled with celite (1.5 cm height). The celite pad was washed with CH_2Cl_2 (≈10×5 mL). The filtrate was then stirred for 1 h with a mixture of 2N NaOH (60 mL) and brine (32 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated to leave about 18 g of an oily material. Pure bis(sulfoxide) **2b** was obtained by chromatography (SiO_2, CH_2Cl_2/MeOH 50:1) (2.35 g, 13.2 mmol, 66 % over three steps) as a yellowish wax: softening range about 40 °C; R_f = 0.16 (CH_2Cl_2/acetone 2:1); $[\alpha]_D^{20}$ = +4.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (d, ^3J = 7.3 Hz, 3H; CH_3), 2.38 (ddddd, ^2J = 15.9 Hz, ^3J = 5.4 Hz, ^3J = 3.9 Hz, ^3J = 3.1 Hz, ^3J = 2.7 Hz, 1H; 5-H_{eq}), 2.67 (ddd, ^2J = 14.1 Hz, ^3J = 12.9 Hz, ^3J = 3.1 Hz, 1H; 6-H_{ax}), 2.80 (ddd, ^3J = 13.2 Hz, ^2J = 11.9 Hz, ^3J = 2.7 Hz, 1H; 4-H_{ax}), 3.09 (ddddd, ^2J = 15.9 Hz, ^3J = 13.2 Hz, ^3J = 12.9 Hz, ^3J = 2.7 Hz, ^3J = 2.4 Hz, 1H; 5-H_{ax}), 3.23 (dddd, ^2J = 14.1 Hz, ^3J = 3.9 Hz, ^3J = 2.7 Hz, ^4J = 1.3 Hz, 1H; 6-H_{eq}), 3.63 (dddd, ^2J = 11.9 Hz, ^3J = 5.4 Hz, ^3J = 2.4 Hz, ^4J = 1.3 Hz, 1H; 4-H_{eq}), 6.76 ppm (q, ^3J = 7.3 Hz, 1H; =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (t), 15.0 (q), 48.6 (t), 55.2 (t), 136.6 (d), 144.7 ppm (s); IR (DRIFT): $\tilde{\nu}$ = 2920 (s), 1740 (s), 1433 (m), 1050 (s, S=O), 867 cm^{-1} (m); MS (EI, 60 °C): m/z (%): 178 (12) [M^+], 130 (100) [$(M-SO)^+$], 106 (19), 104 (19), 90 (19), 89 (22), 72 (38), 71 (38), 57 (41), 43 (67); HRMS (EI) calcd for $C_6H_{10}O_2S_2$: 178.0122, found 178.0126.

(*R*,*R*)-2-Ethylidene-1,3-dithiolane-1,3-dioxide (3b): Ethane-1,2-dithiol (4.72 g, 50.0 mmol) was added dropwise at 0 °C to propionyl chloride (4.62 g, 50.0 mmol) and stirred for 30 min at this temperature. Perchloric acid (70 %, 5.2 mL, 60 mmol) was carefully added dropwise. An exothermic reaction started after 0.5–5 min. The mixture was stirred for 30 min at room temperature, then cooled to 0 °C and freshly distilled Ac_2O (35 mL) was carefully added dropwise. The dithiolanylium salt was precipitated with anhydrous Et_2O (80 mL) and filtrated under argon. The red needles were washed with Et_2O (3×30 mL) and dissolved in anhydrous MeCN (50 mL). Et_3N was added until the red color disappeared and the solvents were removed at reduced pressure. The resulting oil was dissolved in saturated aqueous NH_4Cl solution (70 mL) and the solution was extracted with EtOAc (3×30 mL). The combined organic layers were dried (Na_2SO_4 and K_2CO_3), the solvents were removed and the residue was distilled by bulb-to-bulb distillation yielding 2-ethylidene-1,3-dithiolane (2.90 g, 22.0 mmol, 44 %) as a yellowish oil. Spectroscopic data were in full agreement with published information.[52]

(+)-Diethyl tartrate (9.1 g, 44 mmol, traces of water were removed by azeotropic distillation with toluene) and freshly distilled Ti(O*i*Pr)$_4$ (3.13 g, 11.0 mmol) were dissolved at room temperature under argon in anhydrous CH_2Cl_2 (5 mL per mmol) and stirred for 30 min. 2-Ethylidene-1,3-dithiolane (2.90 g, 22.0 mmol) in CH_2Cl_2 (22 mL) was added, and the mixture was cooled to −40 °C and stirred for 2 h. Cumene hydroperoxide (technical grade, 80 %, 16.7 g, 88.0 mmol) in CH_2Cl_2 (9 mL) was added within 1 h. The solution was warmed to −20 °C and stored for 15 h in a freezer (< −20 °C). H_2O (8 mL) was added, and the mixture was stirred vigorously for 1 h at room temperature. The slurry was kept for 1 h in an ultrasonic bath, and the resulting suspension was filtered through a sinter glass (G2) covered with a celite pad (1.5 cm). The filter cake was washed repeatedly with small amounts of CH_2Cl_2. The solvents were removed and chromatography on SiO_2 (CH_2Cl_2/acetone 2:1) yielded bis(sulfoxide) **3b** (1.80 g, 11.0 mmol, 50 %) as a yellowish highly viscous oil, which solidified upon standing. R_f = 0.18 (CH_2Cl_2/acetone 2:1); $[\alpha]_D^{20}$ = −82.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (d, ^3J = 7.2 Hz, 3H; CH_3), 3.61–3.83 (m, 4H; 4-H_2, 5-H_2), 7.44 ppm (q, ^3J = 7.2 Hz, 3H; =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (q), 50.6 (t), 50.7 (t), 151.3 (d), 157.7 ppm (s); IR (film): $\tilde{\nu}$ = 2980 (m), 1610 (m), 1399 (m), 1017 cm^{-1} (s, S=O); MS (EI, 25 °C): m/z (%): 164 (80) [M^+], 136 (74), 108 (80), 87 (71), 72 (100), 71 (84); HRMS (EI) calcd for $C_5H_8O_2S_2$: 163.9966, found 163.9964.

(3*R*,1′*R*,3′*R*)-3-(1,3-Dioxo-1,3-dithian-2-yl)-1-phenyl-1-butanone (8): NaHMDS (2 M solution in hexane, 600 μL, 1.2. mmol) was added at −78 °C to a solution of acetophenone (168 mg, 1.4 mmol) in THF (10 mL). After 45 min at −78 °C, this mixture was transferred via a cannula to a −78 °C solution of bis(sulfoxide) **2b** (178 mg, 1 mmol) in THF (15 mL). The reaction mixture was stirred for 5 h and was then quenched by addition of MeOH (0.5 mL) at −78 °C. The solution was poured into a saturated NH_4Cl solution (25 mL), extracted with ethyl acetate (3× 15 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. A slurry of the hardly soluble residue and SiO_2 (2 g) in CH_2Cl_2 was carefully evaporated and the remnant was filled on top of a loaded column (SiO_2). Chromatography (CH_2Cl_2/MeOH 20:1) yielded a mixture of isomers (266 mg, 0.891 mmol, 89 %) which were recrystallized twice (50 mL MeOH) to give diastereomerically pure **8** as colorless prisms (80 mg, 0.268 mmol, 27 %): m.p. 224 °C (decomp); $[\alpha]_D^{20}$ = −23.2 (c = 0.19 in $CHCl_3$); ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.28 (d, ^3J = 7.1 Hz, 3H; 4-H), 2.24–2.29 (m, 1H; 5′-H_{eq}), 2.51–2.2.61 (m, 1H), 3.00–3.11 (m, 3H), 3.21–3.26 (m, 1H), 3.34–3.39 (m, 2H; 3′-H_2), 3.44–3.61 (m, 1H; 4′-H_{eq}), 3.97 (d, ^3J = 3.9 Hz, 1H; 2′-H), 7.53–7.77 (m, 2H; arom.), 7.65–7.68 (m, 1H; arom.), 8.99–8.01 ppm (m, 2H; arom.); ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.7 (t), 17.1 (q), 27.7 (d), 42.8 (t), 46.3 (t), 53.3 (t), 76.9 (d), 128.4 (d, 2 C), 129.3 (d, 2 C), 133.8 (d), 137.0 (s), 198.3 ppm (s); IR (DRIFT): $\tilde{\nu}$ = 2979 (m), 1684 (s), 1362 (m), 1225 (m), 1030 (s, S=O), 775 (m), 695 cm^{-1} (m); elemental analysis calcd (%) for $C_{14}H_{18}O_3S_2$: C 56.35, H 6.08; found: C 56.33, H 6.26.

(1*R*,3*R*,1′*R*)- and (1*R*,3*R*,1′*S*)-2-[Phenyl(prop-2-en-1-ylamino)methyl]-1,3-dithiane-1,3-dioxide (9a,b): A solution of bis(sulfoxide) **2a** (60 mg, 0.25 mmol) and allyl amine (100 μL, 1.33 mmol) in CH_2Cl_2 (1 mL) were stirred at room temperature for 24 h. Volatile components were removed in vacuo and the residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH 10:1) to yield **9** (77 mg, 0.25 mmol, 99 %) as a mixture of isomers (78:22). Major isomer **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25–2.33 (m, 1H; 5′-H_{eq}), 2.51 (ddd, ^2J = 14.4 Hz, ^3J = 12.3 Hz, ^3J = 3.5 Hz, 1H; 6′-H_{ax}), 2.87 (ddd, ^3J = 12.3 Hz, ^2J = 11.9 Hz, ^3J = 2.3 Hz, 1H; 4′-H_{ax}), 2.93–3.07 (m, partly covered, 4H; 5′-H_{ax}, CH_2NH), 3.27 (dddd, ^2J = 14.4 Hz, ^3J = 5.1 Hz, ^3J = 2.3 Hz, ^4J = 1.2 Hz, 1H; 6′-H_{eq},), 3.31 (d, ^3J = 4.0 Hz, 1H; 2′-H), 3.61 (dddd, ^2J = 11.9 Hz, ^3J = 5.8 Hz, ^3J = 2.4 Hz, ^4J = 1.2 Hz, 1H; 4′-H_{eq}), 4.84 (m_{br}, 1H; 1-H), 5.01 (dddd, ^3J = 10.2 Hz, ^4J = 1.4 Hz, ^4J = 1.4 Hz, ^2J = 1.4 Hz, 1H; =CH_aH_b), 5.07 (dddd, ^3J = 17.2 Hz, ^4J = 1.8 Hz, ^4J = 1.5 Hz, ^2J = 1.4 Hz, 1H; =CH_aH_b), 5.82 (dddd, ^3J = 17.2 Hz, ^3J = 10.2 Hz, ^3J = 6.3 Hz, ^3J = 5.4 Hz, 1H; -CH=CH_2), 7.26–7.46 ppm (m, 5H; arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (t), 46.0 (t), 49.7 (t), 50.5 (t), 58.4 (d), 80.6 (d), 116.4 (t), 127.7 (d, 2 C), 128.2 (d), 129.0 (d, 2 C), 136.0 (d), 137.9 ppm (s). Minor isomer **9b** (selected data): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (ddd, ^2J = 14.6 Hz, ^3J = 12.2 Hz, ^3J = 3.5 Hz, 1H; 6′-H), 3.55 (dddd, ^2J = 12.9 Hz, ^3J = 6.3 Hz, ^3J = 2.9 Hz, ^4J = 1.1 Hz, 1H; 4′-H_{eq}), 3.38 (d, ^3J = 8.4 Hz, 1H; 2′-H), 4.70 (d, ^3J = 8.4 Hz, 1H; 1-H), 5.76 ppm (dddd, ^3J = 17.2 Hz, ^3J = 10.3 Hz, ^3J = 6.9 Hz, ^3J = 5.0 Hz, 1H; -CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (t), 45.6 (t), 49.5 (t), 50.9 (t), 62.4 (d), 79.6 (d), 116.5 (t), 128.5 (d, 2 C), 128.7 (d), 129.0 (d, 2 C), 136.0 (d), 137.9 ppm (s); IR (DRIFT): $\tilde{\nu}$ = 3335 (s, NH), 3069 (m), 2901 (s), 1643 (m), 1421 (m), 1027 (s, S=O), 917 (m), 871 cm^{-1} (m); MS (EI, 110 °C): m/z (%): 297 (10) [M^+], 280 (20), 242 (56), 206 (21), 192 (59), 175 (29), 146 (100), 134 (55), 118 (25), 102 (26), 91 (37), 77 (18), 56 (14), 41 (34); HRMS (EI) calcd for $C_{14}H_{19}NO_2S_2$: 297.0857, found 297.0853.

(1′*R*,1″*R*,3″*R*)-1-[(1,3-Dioxo-1,3-dithiolan-2-yl)phenylmethyl]piperidine (20): Freshly distilled piperidine (40 μL, 34 mg, 0.40 mmol) was added at −78 °C to the bis(sulfoxide) **3a** (45 mg, 0.20 mmol) in THF (2 mL). The mixture was stirred for 30 min at −78 °C (monitored by TLC) and allowed to warm to room temperature over 30 min. Excess piperidine was removed by rotary evaporation using azeotropic distillation with benzene (2×10 mL) and the residue was dissolved in CH_2Cl_2 (ca. 400 μL). Hexane (10 mL) was added and the precipitate, colorless crystals (mixture of isomers **20**, 92:8), was collected by filtration (62 mg, 0.20 mmol, quant.): ^{1}H NMR (500 MHz, $CDCl_3$, major isomer): δ = 1.30–1.35 (m, 2H; CH_2), 1.53–1.60 (m, 2H; CH_2), 1.62–1.69 (m, 2H; CH_2), 2.25–2.33 (m, 2H;

CH_2), 2.58–2.61 (m, 2H; CH_2), 3.58 (dddd, ^2J=13.7 Hz, ^3J=4.1 Hz, ^3J=1.4 Hz, ^5J=1.0 Hz, 1H), 3.65 (ddd, ^3J=13.8 Hz, ^2J=13.5 Hz, ^3J=4.1 Hz, 1H), 3.75 (ddd, ^2J=13.5 Hz, ^3J=4.3 Hz, ^3J=1.4 Hz, 1H), 3.85 (ddd, ^3J=13.8 Hz, ^2J=13.7 Hz, ^3J=4.3 Hz, 1H), 4.58 (d, ^3J=13.6 Hz, 1H; CH), 4.11 (d, ^3J=13.6 Hz, 1H; CH), 7.28–7.30, 7.40–7.48 ppm (2 m, 5H; Ph); ^{1}H NMR (500 MHz, $CDCl_3$, minor isomer, selected data): δ=4.08 (d, ^3J=13.4 Hz, 1H), 4.49 ppm (d, ^3J=13.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, major isomer): δ=24.3 (t), 26.3 (t), 49.6 (t), 50.3 (bt), 51.2 (t), 95.9 (d), 128.6 (d), 129.2 (d), 130.7 (d), 132.6 ppm (s); IR (DRIFT): $\tilde{\nu}$=2935 (m), 1028 cm^{-1} (s, S=O); MS (FAB): *m/z* (%): 312 (100) [M^+]; HRMS (FAB) calcd for $C_{15}H_{22}NO_2S_2$: 312.1092, found: 312.1098; elemental analysis calcd (%) for $C_{15}H_{21}NO_2S_2$: C 57.84, H 6.80, N 4.50; found: C 57.46, H 6.84, N 4.54.

Dimethyl (1′*R*,1″*R*,3″*R*)-2-[(1,3-Dioxo-1,3-dithiolan-2-yl)phenylmethyl]-malonate (21): Dimethyl malonate (228 μL, 264 mg, 2.00 mmol) was added at 0°C to a slurry of NaH (suspension in mineral oil, 60%, 80.0 mg, 2.00 mmol) in THF (5 mL) and the mixture was stirred for 1 h at 0°C, cooled to −78°C and transferred via a cannula to a pre-cooled solution of **3a** (113 mg, 1.00 mmol) in THF (10 mL). The reaction was quenched after 5 min with MeOH (≈0.5 mL) and the mixture was poured into a saturated aqueous NH_4Cl solution, extracted with ethyl acetate (2×20 mL) and CH_2Cl_2 (2×20 mL), and dried (Na_2SO_4, K_2CO_3). After removal of the solvents in vacuo the diastereomeric ratio was determined to be 94:6 (^{1}H NMR, integration of the signals for 2″-H). The residue was purified by MPLC on SiO_2 (CH_2Cl_2/MeOH 50:1) to yield a mixture of isomers **20** (164 mg, 0.458 mmol, 92%) as a colorless solid: Major isomer **21a**: R_f=0.26 (CH_2Cl_2/acetone 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.48–3.53 (m, 2H; 4-H_2 or 5-H_2), 3.65 (s, 3H; Me), 3.70 (s, 3H; Me), 3.79–3.86 (m, 2H; 4-H_2 or 5-H_2), 4.12 (dd, ^3J=10.1 Hz, ^3J=5.8 Hz, 1H; 1′-H), 4.20 (d, ^3J=5.8 Hz, 1H; 2-H), 4.68 (d, ^3J=10.1 Hz, 1H; 2″-H), 7.30–7.39, 7.42–7.45 ppm (2 m, 5H; Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.1 (d), 50.7 (t), 52.1 (t), 52.8 (q), 52.9 (q), 55.1 (d), 94.7 (d), 128.7 (d), 128.9 (d), 129.3 (d), 136.6 (s), 167.6 (s), 167.7 ppm (s); IR (DRIFT): $\tilde{\nu}$=1749 (s, C=O), 1438 (m), 1154 (m), 1030 cm^{-1} (s, S=O); MS (EI, 160°C): *m/z* (%): 358 (13) [M^+], 327 (13), 326 (19), 298 (28), 234 (33), 233 (32), 232 (24), 222 (100), 218 (26), 205 (21), 202 (27), 198 (13), 190 (13), 189 (10), 175 (44), 173 (32), 163 (19), 162 (64), 135 (12), 134 (47), 131 (17), 121 (28), 116 (10), 115 (43), 108 (89), 43 (14); HRMS (EI) calcd for $C_{15}H_{18}O_6S_2$: 358.0544, found: 358.0540; Elemental analysis calcd (%) for $C_{15}H_{18}O_6S_2$: C 50.26, H 5.06; found: C 50.30, H 5.21. Minor isomer **21b**, selected data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.58 (dd, ^3J=11.9 Hz, ^4J=1.4 Hz, 1H; 2″-H) ppm.

(3*R*,1′*R*,3′*R*)-3-(1,3-Dioxo-1,3-dithiolan-2-yl)-1-phenylbutan-1-one (22): NaHMDS (2 M in hexane, 600 μL, 1.20 mmol) was added at −78°C to a solution of acetophenone (168 mg, 1.40 mmol) in THF (10 mL). After stirring for 45 min, this solution was transferred via a cannula to a pre-cooled (−78°C) solution of **3b** (164 mg, 1 mmol) in THF (15 mL per mmol). The reaction was quenched after 10 min with MeOH (ca. 0.5 mL) and the mixture was added to a saturated aqueous NH_4Cl solution (20 mL per mmol), extracted with EtOAc (2×20 mL) and CH_2Cl_2 (2×20 mL), and dried (Na_2SO_4, K_2CO_3). The solvents were removed in vacuo. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy (d.r. 55:45, integration of the signals of the *S*,*S*-acetalic hydrogens). The remnant was separated and purified by MPLC (SiO_2, CH_2Cl_2/MeOH 50:1) afforded **22** (231 mg, 0.812 mmol, 81%) as a non-separable mixture of isomers: R_f=0.26 (CH_2Cl_2/acetone 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers): δ=1.41 (d, ^3J=6.6 Hz, 3H; 4-H_3, major), 1.49 (d, ^3J=6.8 Hz, 3H; 4-H_3, minor), 2.99–3.17 (m, 2H; 3-H, both), 3.26 (dd, ^2J=17.0 Hz, ^3J=7.6 Hz, 1H; 2-CH_aH$_b$, minor), 3.29 (dd, ^2J=17.4 Hz, ^3J=7.8 Hz, 1H; 2-CH_aH$_b$, major), 3.46 (dd, ^2J=17.0 Hz, ^3J=4.6 Hz, 1H; 2-H$_a$H$_b$, minor), 3.64 (dd, ^2J=17.4 Hz, ^3J=4.0 Hz, 1H; 2-H$_a$H$_b$, major), 3.63–3.86 (m, 9H; 4′-H_2, 5′-H_2, both, 2′-H, major), 3.95 (dd, ^3J=8.8 Hz, ^4J=1.1 Hz, 1H; 2′-H, minor), 7.46–7.51, 7.57–7.61, 7.97–7.10 ppm (3 m, 5H; Ph, both); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers): δ=19.3 (q), 20.4 (q), 26.7 (d), 27.5 (d), 43.5 (t), 43.7 (t), 51.3 (t), 51.45 (t), 51.54 (t), 97.6 (d), 97.9 (d), 128.1 (d), 128.2 (d), 128.7 (d), 128.7 (d), 133.5 (d), 136.5 (s), 136.6 (s), 197.4 (s) 197.6 ppm (s); IR (DRIFT): $\tilde{\nu}$=2078 (m), 1681 (s, C=O), 1447 (m), 1223 (m), 1029 cm^{-1} (s, S=O); MS (EI, 160°C): *m/z* (%): 284 (3) [M^+], 267 (11), 159 (18), 148 (10), 145 (10), 108 (45), 105 (100) [$C_7H_5O^+$], 77 (50), 57 (14), 43 (14); HRMS (EI) calcd for $C_{13}H_{16}O_3S_2$: 284.0541, found 284.0535; elemental analysis calcd (%) for $C_{13}H_{16}O_3S_2$: C 54.90, H 5.67; found C 54.68, H 5.74.

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