Asymmetric Cyclopropanation of Optically Active (1-Diethoxyphosphoryl)vinyl *p*-Tolyl Sulfoxide with Sulfur Ylides: A Rationale for Diastereoselectivity

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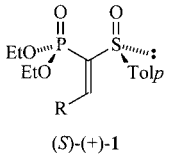
Dedicated to Professor Mieczysław Makosza on the occasion of his 70th birthday

Keywords: Asymmetric synthesis / Cyclopropanes / Density functional calculations / Diastereoselectivity / Vinyl sulfoxides

The title sulfoxide (*S*)-(+)-**1a** was found to react with sulfur ylides affording the corresponding cyclopropanes in high yields. With fully deuterated dimethyl(oxo)sulfonium methylide, $(CD_3)_2S(O)CD_2$, the cyclopropanation reaction occurred in a highly diastereoselective manner producing the cyclopropane **4a**-d_2 as a major diastereomer in which the newly formed quaternary α-carbon atom is chiral due to isotopic substitution (CH_2 vs. CD_2). The diastereomer **4b**-d_2, having the opposite configuration at the α-carbon atom, was obtained starting form the 2,2-dideuterio substituted vinyl sulfoxide, (*S*)-(+)-**1a**-d_2, and the nondeuterated ylide. The diastereomeric ratio in both reactions was found to be ca. 10:1. The reaction of (*S*)-(+)-**1a** with diphenylsulfonium isopropylide yielded the cyclopropane (+)-**7** as a single diastereomer. X-ray structural studies of the crystalline 1-phosphorylvinyl sulfoxide **9** as well as density functional calculations (B3LYP/6-31G*) on (1-phosphoryl)vinyl sulfoxides revealed the origin of the experimentally observed diastereoselectivities and allowed us to propose a transition state model for the cyclopropanation reaction of chiral 1-phosphorylvinyl sulfoxides.

Introduction

The sulfinyl group has proved to be one of the most efficient chiral auxiliaries because of its extraordinary ability to control the stereoselectivity of asymmetric processes.[1−3] Among a great number of optically active sulfinyl compounds, chiral enantiomerically pure vinyl sulfoxides, which have recently found a wide application in numerous asymmetric reactions, are especially important. However, the use of simple, unsubstituted enantiopure vinyl sulfoxides in asymmetric synthesis is restricted due to their low reactivity and moderate stereoselectivity. The reactivity of a sulfinylethylene can be increased by introduction of electron-withdrawing group(s) at the α- and/or β-positions of the carbon−carbon double bond, the carbonyl and alkoxycarbonyl groups having been most frequently used for this purpose.[4] In fact, many asymmetric Diels−Alder reactions of such vinyl sulfoxides have been described and have been found to occur efficiently and with high stereoselectivity.[5] Recently, chiral alkylidene bis(sulfoxides) have been demonstrated as excellent acceptors in totally diastereoselective Michael additions.[6]



(*S*)-(+)-**1**

1a, R = H **1b**, R = Ph
1c, R = Me **1d**, R = *n*Bu

In the course of our studies on the applications of chiral vinyl sulfoxides in asymmetric synthesis, we designed a new group of activated enantiomerically pure vinyl sulfoxides, namely (1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **1a** and its β-substituted analogues.[7,8] The presence of the electron-withdrawing phosphoryl group increases not only the reactivity of the carbon-carbon double bond in **1** but also the degree of stereocontrol because of the bulky, tetrahedral structure of the diethoxyphosphoryl group. The optically pure sulfoxide **1a** and its analogues were found to be good Michael acceptors and reactive Diels−Alder dienophiles. Moreover, they could also be used as key reagents for the

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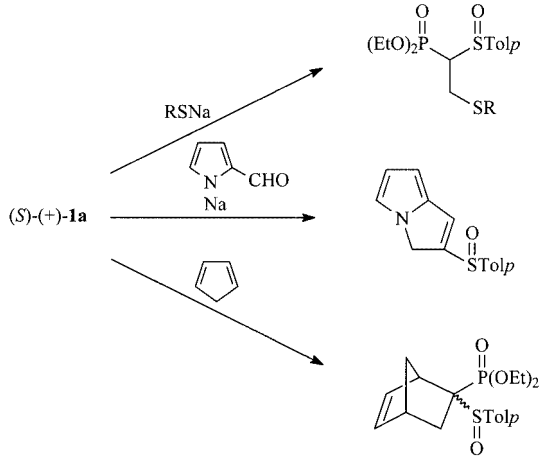
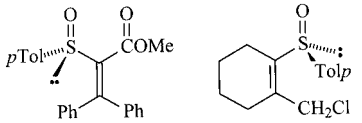
construction of monocyclic compounds and condensed carbo- and heterocycles via tandem Michael addition/intramolecular Horner−Wittig reactions. Scheme 1 shows selected reactions of **1a** illustrating its typical reactivity.



Scheme 1. Examples of typical reactions of (*S*)-(+)-(1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxides **1**

In this paper we wish to disclose the results of the reactions of (*S*)-(+)-**1a** with sulfur ylides which afford the corresponding cyclopropanes in a highly or fully diastereoselective way.[9] Herein we also report the results of X-ray structural studies and theoretical calculations of α-phosphorylvinyl sulfoxides which corroborate the transition state model proposed by us in our preliminary communication for the asymmetric cyclopropanation reaction of (*S*)-(+)-**1a** with diphenyldiazomethane.[9,10]

Our interest in this new asymmetric cyclopropanation reaction was stimulated by two facts. The first was that a wide variety of natural products and currently used insecticides contain the chiral cyclopropane unit.[11] Secondly, at the beginning of this study, there were only two reports describing asymmetric cyclopropanation using the enantiopure vinyl sulfoxides **2** and **3** as chiral reagents.[12,13]



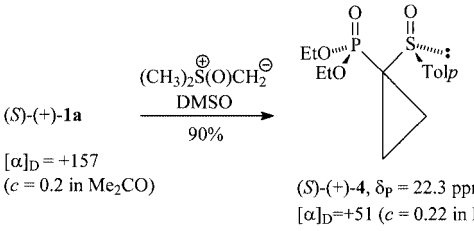
2 **3**

In the meantime, we reported the highly diastereoselective cyclopropanation reactions of (*S*)-(+)-**1a** and (*S*)-(+)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide with ethyl (dimethylsulfuranylidene)acetate (EDSA) which paved the way to enantiopure cyclopropylphosphonate analogues of nucleotides and 2-amino-3-phenylcyclopropylphosphonic acid (a constrained analogue of phaclofen), respectively.[14,15]

Results and Discussion

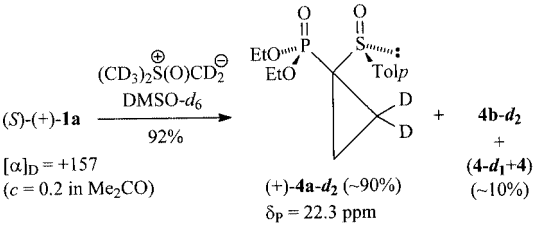
Reaction of (*S*)-(+)-(1-Diethoxyphosphoryl)vinyl *p*-Tolyl Sulfoxide 1a with Sulfur Ylides

Initially, the reactivity of our sulfoxide towards a sulfur ylide was examined. Thus, (*S*)-(+)-**1a** was treated with an excess of dimethyl(oxo)sulfonium methylide in DMSO at room temperature. After ca. 3 hours this reaction afforded the expected cyclopropane (*S*)-(+)-**4** as the only product which was isolated by flash chromatography on silica gel in 90% yield [Equation (1)].



(1)

Since the above reaction does not generate a new stereogenic carbon centre, the optical activity of the cyclopropane **4** is due to the chiral sulfoxide moiety. However, by using the fully deuterated dimethyl(oxo)sulfonium methylide as the CD_2 transfer reagent it should be possible to carry out the asymmetric version of this reaction. In such a case the newly formed quaternary α-carbon atom is stereogenic due to isotopic substitution (CH_2 vs. CD_2). As expected, under comparable reaction conditions, (*S*)-(+)-**1a** gave the corresponding cyclopropane in 92% isolated yield upon treatment with the deuterated sulfur ylide [Equation (2)].



(2)

The ^{31}P NMR spectrum of the crude product revealed only one sharp signal at $\delta_P = 22.3$ ppm. The ^1H NMR spectrum (500 MHz, C_6D_6) of the isolated product showed high intensity signals for the methylene protons which appeared in the spectrum as doublets of doublets at $\delta = 1.18$ ppm ($^2J_{H,H} = 4.9$ and $^3J_{H,P} = 14.0$ Hz) and 1.30 ppm ($^2J_{H,H} = 4.9$ and $^3J_{H,P} = 9.9$ Hz) (Figure 1, a). These signals have been ascribed to the methylene protons of the expected cyclopropane **4a**-d_2. However, at lower field at ca. 1.4 and 1.6 ppm, some signals of low intensity (ca. 10%) were observed which could indicate the presence of the second, minor diastereomer, **4b**-d_2, having the opposite configuration at the α-carbon atom. To identify these signals and to solve the problem of the diastereoselectivity of this reaction, we decided to synthesise **4b**-d_2 from the cyclopropanation

reaction between dimethyl(oxo)sulfonium methylide and the 2,2-dideuterio-substituted vinyl sulfoxide, (*S*)-(+)-**1a**-d_2. In accord with the established approach of E. Fischer for inversion of configuration at the tetrahedral asymmetric carbon atom,[16] the use of the latter reagent should lead to the cyclopropane **4b**-d_2 with reversed positions of the CH_2 and CD_2 groups compared with **4a**-d_2. The required vinyl sulfoxide **1a**-d_2 was obtained by the sequence of reactions outlined in Scheme 2.

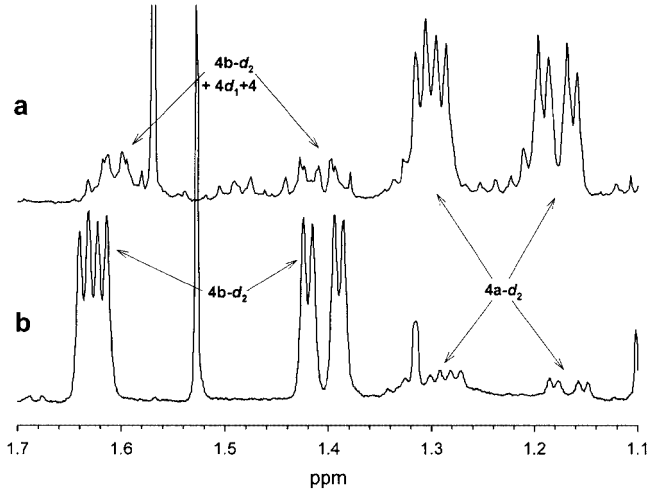
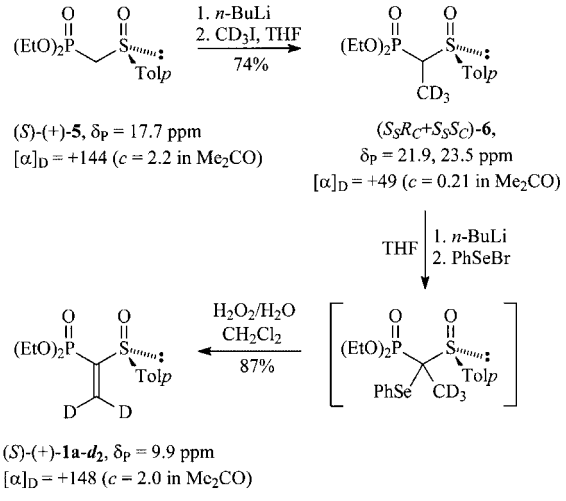


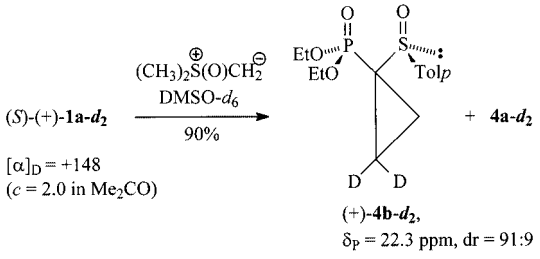
Figure 1. Cyclopropyl methylene proton signals in the ^{1}H NMR spectrum of (a) the cyclopropanation product of reaction 2 (**4a**-d_2-major) and (b) the cyclopropanation product of reaction 3 (**4b**-d_2-major



Scheme 2. Synthesis of (*S*)-(+)-(1-diethoxyphosphoryl-2,2-dideuterio)vinyl *p*-tolyl sulfoxide **1a**-d_2

In the first step, (*S*)-(+)-diethoxyphosphorylmethyl *p*-tolyl sulfoxide (**5**) was subjected to alkylation with trideuteriomethyl iodide to give the corresponding monoalkylation product **6** in 74% yield as a mixture of two diastereomers. Then, in a one-pot reaction involving selenenylation of **6** with phenylselenenyl bromide and subsequent oxidative benzeneselenenic acid elimination, the desired deuterated vinyl sulfoxide (*S*)-(+)-**1a**-d_2 was produced. After purification by column chromatography it was isolated in 87% yield.

The reaction of (*S*)-(+)-**1a**-d_2, obtained as above, with dimethyl(oxo)sulfonium methylide in [D_6]DMSO gave the corresponding cyclopropane in 90% yield [Equation (3)].



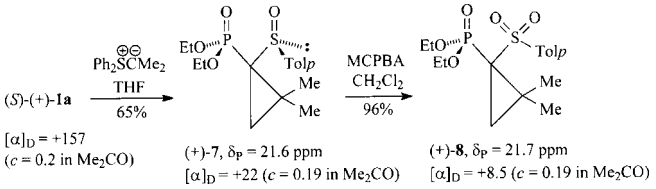
(3)

An analysis of its ^{1}H NMR spectrum (500 MHz, C_6D_6) revealed the presence of high intensity signals for the methylene protons of **4b**-d_2 at δ = 1.43 ppm ($^2J_{H,H}$ = 4.3 and $^3J_{H,P}$ = 15.1 Hz) and 1.65 ppm ($^2J_{H,H}$ = 4.3 and $^3J_{H,P}$ = 8.8 Hz). Moreover, the low intensity doublets of doublets appearing in the spectrum at δ = 1.18 and 1.30 ppm were found to be identical to those of **4a**-d_2 (Figure 1, b). Hence, in this cyclopropanation reaction, two diastereomeric cyclopropanes **4b**-d_2 and **4a**-d_2 were produced in a 91:9 ratio as determined by integration of the above discussed CH_2 signals.

Most probably, the major diastereomer **4a**-d_2 formed in the reaction between (*S*)-(+)-**1a** and deuterated sulfonium ylide [Equation (2)] also contains **4b**-d_2 as a minor isomer. However, the exact determination of the diastereomeric ratio in this case is difficult because the methylene protons of the latter are obscured by other signals most likely due to the mono- and nondeuterated cyclopropane **4** which was also present in the reaction product in small amounts. In fact, the mass spectrum of the reaction product showed, in addition to the molecular peak ([M + H]$^+$, *m*/*z*: 319) for **4a**-d_2, two other [M + H]$^+$ peaks for the monodeuterated cyclopropane **4**-d_1 (*m*/*z*: 318) and nondeuterated cyclopropane **4** (*m*/*z*: 317).

Encouraged by the high diastereoselectivity observed in the cyclopropanation reaction discussed above, we carried out the reaction of (*S*)-(+)-**1** with diphenylsulfonium isopropylide[17] under the standard reaction conditions (THF, −70 °C, 3 h) (Scheme 3). It was gratifying to find that the cyclopropane (+)-**7** formed in this reaction and isolated in 65% yield was a single diastereomer as indicated by its ^{31}P and ^{1}H NMR spectra. Thus, the ^{1}H NMR spectrum of (+)-**7** displayed two sharp singlets for the cyclopropyl methyl protons at δ = 1.48 and 1.63 ppm, and two doublets of doublets at δ = 1.77 ppm ($^2J_{H,H}$ = 5.6, $^3J_{H,P}$ = 8.9 Hz) and 1.99 ppm ($^2J_{H,H}$ = 5.6 and $^3J_{H,P}$ = 16.3 Hz) characteristic of the cyclopropyl methylene protons. In order to additionally confirm the full diastereomeric purity of (+)-**7**, it was oxidised to the optically active sulfone (+)-**8** in which the only stereogenic atom was the newly formed quaternary α-

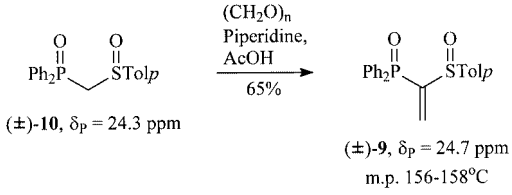
carbon atom. The ^{1}H NMR spectrum of the sulfone (+)-**9** recorded in the presence of (*R*)-(+)-*tert*-butylphenylphosphinothioic acid as a chiral solvating agent[18] did not show a typical doubling of the cyclopropyl methyl and methylene protons thereby providing unequivocal evidence of the full enantiomeric purity of (+)-**8** and, consequently, of the full diastereomeric purity of its precursor i.e. the cyclopropane (+)-**7**.



Scheme 3. Synthesis of cyclopropane (+)-**7** and sulfone (+)-**8**

Synthesis, Crystal and Molecular Structures of Racemic (1-Diphenylphosphinoyl)vinyl *p*-Tolyl Sulfoxide 9

To understand the origin of the observed diastereoselectivities in the cyclopropanation reaction of (*S*)-(+)-**1a**, we decided firstly to determine the structures and conformations of (1-phosphoryl)vinyl sulfoxides. Since our reagent (*S*)-(+)-**1a** is a liquid, our study started with the synthesis of the closely structurally related crystalline sulfoxide (1-diphenylphosphinoyl)vinyl *p*-tolyl sulfoxide **9**. It was easily obtained from racemic (diphenylphosphinoyl)methyl *p*-tolyl sulfoxide **10**[19] and formaldehyde in the presence of piperidine and acetic acid [Equation (4)]. The crude product was purified by column chromatography and suitable crystals for X-ray analysis were obtained by slow crystallisation from benzene.



(4)

A three-dimensional view of the molecule of **9** and the atom numberings are shown in Figure 2. Selected bond lengths are also shown. An analysis of the structural parameters obtained for **9** indicates that the sulfinyl oxygen atom O1 is located almost in the plane formed by the ethylenic carbon atoms and both heteroatoms, i.e. phosphorus and sulfur. Its distance from this plane is 0.128 Å and the torsional angle C2−C1−S1−O1 is equal to −3.2°. The phosphoryl oxygen atom was found to be deflected from this plane by 0.658 Å. The torsional angle C2−C1−P1−O11 is equal to 150.2°. Moreover, both polar sulfinyl and phosphoryl groups adopt an *anti* orientation in the crystalline state (the torsional angle P1−O11···S1−O1 is equal to 153.4°), the former being *syn*-coplanar with the carbon−carbon double bond. Such a conformation of the reactive fragment of 1-phosphorylvinyl sulfoxide **9** is stabilised by an intramolecular hydrogen bond formed by the sulfinyl oxygen atom O1 and the vinylic proton at C2 [*d*(H···O1) = 2.305 Å]. It is interesting to point out that a similar intramolecular hydrogen contact of 2.257 Å has also been found in the solid-state conformation of (*E*)-(1-methylsulfenyl-2-phenyl)vinyl *p*-tolyl sulfoxide.[20] A recent X-ray analysis of (*S*,*S*)-1,1-bis(*p*-tolylsulfinyl)-2-phenylethylene also revealed a short contact of 2.28 Å between the vinylic hydrogen and the sulfinyl oxygen.[6]

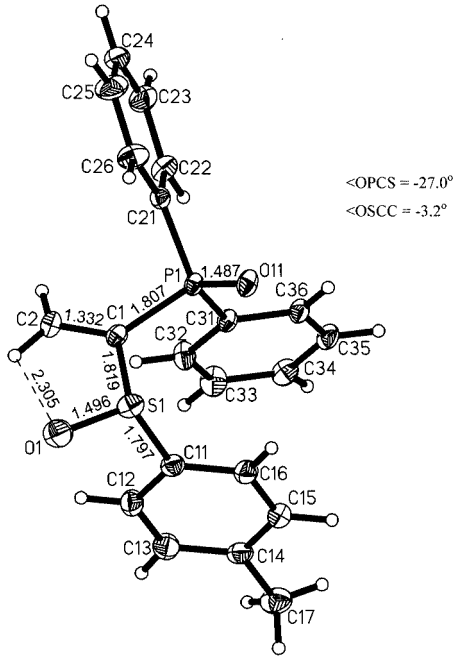


Figure 2. Solid state structure of (±)-**9** with selected bond lengths (thermal ellipsoids drawn at 50% probability for non-hydrogen atoms; hydrogen atoms are shown as spheres with arbitrary radii)

The crystal packing of the molecules of **9** in the unit cell is presented in Figure 3 in which intermolecular short contacts are depicted. In the crystalline state, the molecules of **9** are held together by two intermolecular hydrogen bonds (2.460 Å) between the sulfinyl oxygen atom O1 and the *p*-tolyl methyl hydrogen atom at C17 forming a linear structure. Such arrays of **9** then form a pleasingly ordered supramolecular structure via two intermolecular hydrogen bonds of 2.420 Å in length between the phosphoryl oxygen atom O11 and the aromatic ring hydrogen atom at C34.

Theoretical Calculations

To gain a deeper understanding of the factors controlling the stereoselectivity of the cyclopropanation reactions of 1-phosphorylvinyl sulfoxides **1** and especially to determine the gas phase conformation of **1**, calculations using density functional theory (DFT) at the B3LYP/6-31G* level were carried out. In this context, it is interesting to note that Tietze and co-workers[21] have recently described the results of DFT calculations on 1-carbonyl-substituted vinyl sulfoxides. However, since there is a distinct difference between

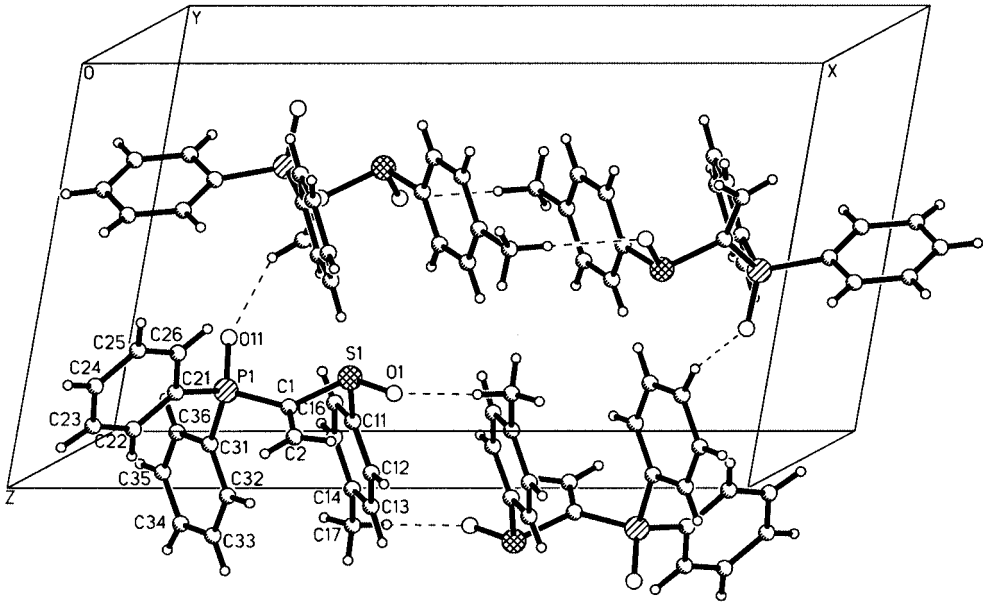
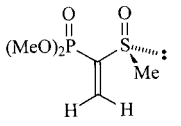


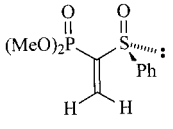
Figure 3. Crystal packing diagram for **9**

the phosphoryl and carbonyl groups with regards to steric and electronic effects, our computational studies on 1-phosphoryl-substituted vinyl sulfoxides were additionally justified.

The model compounds (dimethoxyphosphoryl)vinyl methyl sulfoxide **11** and (dimethoxyphosphoryl)vinyl phenyl sulfoxide **12** were chosen, both having the (*S*) configuration at the sulfur atom. These vinyl sulfoxides closely resemble the sulfoxide (*S*)-(+)-**1a** used in our experimental studies but due to smaller sizes of the models, the cost of the calculations was more reasonable.



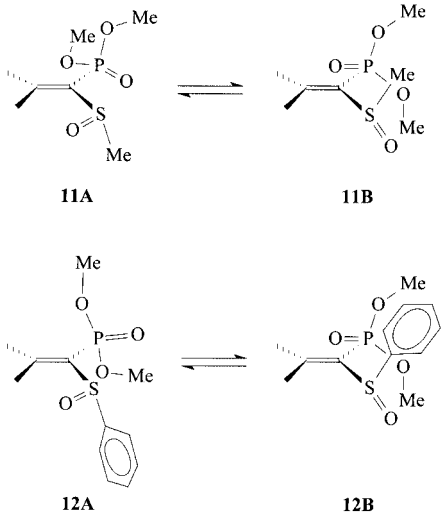
11



12

For both model sulfoxides, the conformational search was performed at the AM1 semiempirical level. The four most stable conformations were further optimised at the B3LYP/6-31G* level. For the two most stable conformations of **11**, the intermediate products of addition of the isopropylide anion and the final products of cyclopropanation were also constructed and optimised. Depending on the direction of a nucleophilic attack of the carbanion, two diastereomeric products were generated. The calculations were performed to compare the energetics of the reactions involving various conformations of the starting reagent and different directions of the approach of a nucleophile.

The two most stable conformations of **11** and **12** are presented in Scheme 4. The calculated energies (in Hartrees) and relative enthalpies at 298 K (in kcal/mol) are given in Table 1. The most stable conformations are, in both cases, very similar and closely analogous to the X-ray structure of the 1-phosphorylvinyl sulfoxide **9** (see Figure 4). The S=O bond is almost syncoplanar with the vinyl group (the torsional angle C−C−S−O = 1° and 5.7° for **11** and **12**, respectively) resulting in a high anisotropy of the steric hindrance around the vinyl group. The next stable conformations for both models are higher in energy by ca. 2 kcal/mol (Scheme 4, Table 1). The concentrations of the most stable conformation **A** in equilibrium with **B** were estimated from the equation $K = e^{-\Delta G/RT}$ and were found to be 98−99% and 96−97% for the sulfoxides **11** and **12**, respectively.



11A **11B**

12A **12B**

Scheme 4. Calculated most stable conformations for vinyl sulfoxides **11** and **12**

Table 1. Total electronic energies, corrections for enthalpy and Gibbs free energy at 298 K and relative enthalpies for model species obtained from the DFT calculations

	-E (a.u.)	ΔH^{298} (a.u.)	ΔG^{298} (a.u.)	ΔH_{rel} (kcal/mol)
11A	1237.82311	0.18022	0.12138	0
11B	1237.81977	0.18041	0.12283	2.2
12A	1429.60589	0.23538	0.16868	0
12B	1429.60269	0.23549	0.16879	2.1
13A	1355.78359	0.26801	0.20253	2.1
13B	1355.78275	0.26800	0.20255	2.6
13C	1355.78339	0.26798	0.20278	2.2
13D	1355.78693	0.26804	0.20349	0

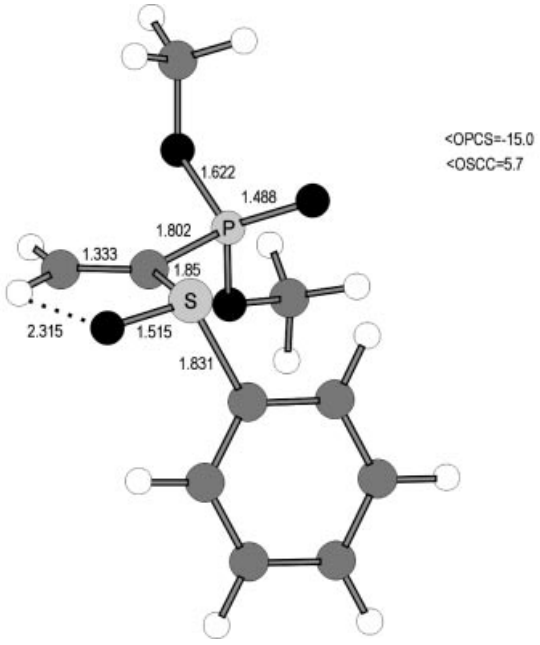


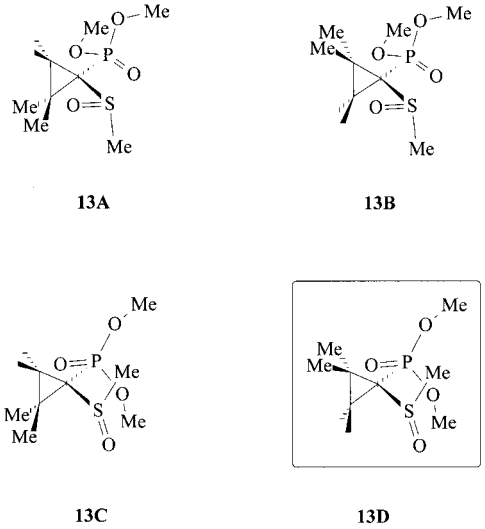
Figure 4. Calculated structure of **12** with the selected bond lengths

Stabilisation of the conformations **11A** and **12A** arises, at least in part, from electronic effects. The NBO analysis indicates that the "planar" CCSO arrangement is stabilised by the $n_S \rightarrow \sigma^*_{C=C}$, $n_S \rightarrow \pi^*_{C=C}$, $\sigma_{S-C} \rightarrow \pi^*_{C=C}$ and $\pi_{C=C} \rightarrow \sigma^*_{S-C}$ delocalisation interactions. The overall energy of these interactions estimated by the NBO deletion procedure is 10.9 kcal/mol. The energy of the interactions stabilising the conformations **11B** and **12B**, i.e., $\pi_{C=C} \rightarrow \sigma^*_{S-O}$, $\pi_{C=C} \rightarrow \sigma^*_{S-C}$ and $\sigma_{S-C} \rightarrow \sigma^*_{C=C}$, is 6.8 kcal/mol. Additional stabilisation of the conformations **11A** and **12A** may be due to the intramolecular hydrogen bonding between the sulfinyl oxygen atom and the vinyl hydrogen atom. The distances between interacting atoms are 2.342 and 2.315 Å in **11A** and **12A**, respectively, and the Wiberg bond order is 0.015 for both species. According to NBO deletion analysis, stabilisation resulting from this interaction ranges from 1.1 kcal/mol for the sulfoxide **11** to 2.0 kcal/mol for the sulfoxide **12**. Based on NBO analysis, a similar stabilisation mechanism was postulated by Tietze to explain the stability of the "coplanar" conformation of methyl vinyl sulfoxide.[21]

It should be pointed out that the role of the phosphoryl group in preferential stabilisation of any conformation is insignificant. Total energies of electronic interactions of the phosphoryl group with the C=C bond estimated by the NBO deletion procedure are very similar, i.e. 23.0 and 24.2 kcal/mol for the conformers **11A** and **11B**, respectively. Thus, the phosphoryl group shows mainly the steric effect directing the nucleophilic attack on the β-carbon atom. It also shows the inductive effect which causes diversification of atomic charges on both vinyl carbon atoms. Thus, the charges are −0.72 e and −0.35 e on the α- and β-carbon atoms, respectively, in **11** (the differences between conformations **A** and **B** being insignificant), while they are −0.49 e (α-carbon atom) and −0.41 e (β-carbon atom) in methyl vinyl sulfoxide where the phosphoryl group has been replaced by hydrogen. Hence, the phosphoryl group reduces the negative NBO charge on the β-carbon atom making it more electron-deficient and more susceptible towards nucleophilic attack.

All isomers of the intermediate product generated by addition of the isopropylide anion to the sulfoxide **11** molecule are very close in energy. Their enthalpies at 298 K differ by less than 0.8 kcal/mol. This result suggests that the thermodynamics of the intermediate product formation are probably not the factor determining the steric course of the reaction.

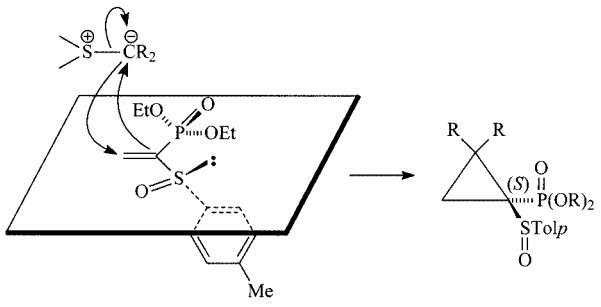
A comparison of the energies of the diastereomers **13** formed by cyclopropane ring closure shows that the most stable is the isomer **13D** obtained by the attack of a nucleophile on the less hindered side occupied by the electron lone pair at sulfur (Scheme 5, the most stable isomer is shown in a frame; Table 1). The geometry of the most stable cyclopropane isomer **13D** is in qualitative agreement with the X-ray structure reported for 1-diethoxyphosphoryl-2,2-diphenyl-1-(*p*-tolylsulfinyl)cyclopropane.[10]



Scheme 5. Calculated most stable conformations of diastereomeric cyclopropanes **13**

Transition State Model for Cyclopropanation of 1-Phosphorylvinyl Sulfoxides

Although some simplifications were assumed in our calculations (simple, less hindered structures of vinyl sulfoxides, the use of the isopropylide anion as a model for the sulfur ylide, neglecting the solvent effect), the results obtained are in very good agreement with the experimental observations. First of all, the crystalline state and gas phase conformations of 1-phosphorylvinyl sulfoxides were found to be almost identical. In both conformations there are two sterically different diastereotopic faces, the less hindered being occupied by the lone pairs of electrons on the sulfur atom and the phosphoryl oxygen atom. Then, the role of hydrogen bonding in stabilising the syncoplanar arrangement of the carbon−carbon double bond and sulfinyl group was confirmed. Moreover, the calculations revealed that steric and not thermodynamic factors are responsible for the observed stereoselectivity of the cyclopropanation reaction. If we make the very reasonable assumption that the conformation of 1-phosphorylvinyl sulfoxide in solution is the same as that in the solid-state and in the gas phase, all these observations may then be explained in terms of the transition state model of the cyclopropanation reaction shown below (Scheme 6) where steric approach control is a decisive factor. Hence, the approach of a sulfur ylide to the carbon−carbon double bond in (*S*)-(+)-**1a** takes place preferentially or exclusively from the less hindered diastereotopic face occupied by the lone pairs of electrons on the sulfur atom and the phosphoryl oxygen atom (top-face attack). The bottom-face attack of a sulfur ylide is much less probable due to steric hindrance exerted by the *p*-tolyl function and the two alkoxy groups.



Scheme 6. The preferred steric course of the reaction of (*S*)-(+)-**1a** with sulfur ylides

Based on this model it is possible to assign the absolute configuration to the cyclopropanes **4a**-d_2, **4b**-d_2 and **7** obtained in the context of this work as (1*S*,S_S), (1*R*,S_S) and (1*S*,S_S), respectively.

Experimental Section

General Remarks: NMR spectra were recorded with Bruker instruments at 200 MHz and 500 MHz for ^{1}H, 81 MHz for ^{31}P and 50.3 MHz for ^{13}C. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to Me_4Si as an external standard. ^{31}P NMR downfield chemical shifts are expressed with a positive sign, in ppm, relative to an external standard of 85% H_3PO_4. High resolution mass spectra were recorded on a Finnigan MAT 95 apparatus. IR spectra were measured on an ATI Mattson spectrometer. Optical rotations were measured on a Perkin−Elmer 241 MC photopolarimeter at 20 °C. Reactions were monitored by TLC chromatography (Merck Kieselgel 60_{254}). Column chromatography was performed using Merck silica gel (70−230 mesh).

(*S*)-(+)-1-Diethoxyphosphoryl-1-(*p*-tolylsulfinyl)cyclopropane (4): To a solution of DMSO (2 mL) and THF (5 mL) was added NaH (48 mg, 2 mmol) and the mixture was heated for 30 min at 70 °C. After this time, it was cooled to 0 °C and trimethyl(oxo)sulfonium iodide (240 mg, 1.2 mmol) was added. The reaction mixture was stirred for 10 min at 0 °C and sulfoxide (*S*)-(+)-**1a** (300 mg,1 mmol) dissolved in THF (5 mL) was then added. After stirring at room temperature for 3 h, the reaction mixture was quenched with an aqueous solution of ammonium chloride (10 mL), extracted with $CHCl_3$ (2 × 20 mL) and the $CHCl_3$ solution was dried with anhydrous $MgSO_4$. The solvents were removed under vacuum (30 °C/0.05 Torr). The crude product was purified by column chromatography (petroleum ether/acetone, 10:1, R_f = 0.37) and isolated as a colourless oil (285 mg) in 90% yield. $[\alpha]_D^{20}$ = +51 (*c* = 0.22 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.3 ppm. ^{1}H NMR (500 MHz, C_6D_6): δ = 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 0.95 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 1.17−1.35 (m, 2 H, CH_2), 1.40−1.69 (m, 2 H, CH_2), 1.98 (s, 3 H, CH_3Ph), 3.61-3.74 (m, 1 H, CH_2O), 3.75−3.83 (m, 3 H, CH_2O), 6.89 and 7.65 ppm (A_2B_2, 4 H, aromatic). IR (film): $\tilde{\nu}$ = 2982, 2960, 1260, 1230, 1042, 1023 cm^{-1}. $C_{14}H_{21}O_4PS$ (316.3): calcd. C 53.11, H 6.63, P 9.80, S 10.12; found C 53.24, H 6.72, P 9.68, S 9.98.

(*S*)-(+)-2,2,2-Trideuterio-1-(diethoxyphosphoryl)ethyl *p*-Tolyl Sulfoxide (6): To a solution of sulfoxide (*S*)-(+)-**5** (1.06 g, 4 mmol) in THF (20 mL) was added a solution of *n*-butyllithium (1.8 mL, 4.2 mmol) in hexane at −78 °C. The reaction mixture was stirred at this temperature for 10 min and a solution of trideuteriomethyl iodide (0.86 g, 6 mmol) in THF (5 mL) was then added. The mixture was warmed slowly to room temperature and quenched with aqueous ammonium chloride. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The chloroform solution was dried with anhydrous $MgSO_4$ and the solvents were evaporated to give the crude product which was purified by chromatography (hexane/acetone, 2:1) and isolated as a pale yellow oil (0.91 g) in 74% yield. $[\alpha]_D^{20}$ = +49 (*c* = 0.21 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.9 and 23.5 ppm (1:3 ratio). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 2.39 (s, 3 H, CH_3Ph), 2.86 (d, $^2J_{H,P}$ = 17.7 Hz, 1 H, CH), 4.00−4.25 (m, 4 H, CH_2O), 7.29−7.55 ppm (m, 4 H, aromatic) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (d, $^1J_{C,P}$ = 5.7 Hz), 22.3, 56.7, 59.6, 63.6, 125.2, 129.9, 130.9, 142.5 ppm. HRMS (EI): calcd. for $C_{13}H_{18}D_3O_4PS$: 307.10929; found 307.10865.

(*S*)-(+)-2,2-Dideuterio-1-(diethoxyphosphoryl)vinyl *p*-Tolyl Sulfoxide (1a-d_2): To a stirred THF solution (15 mL) of sulfoxide (+)-**6** (0.91 g, 3 mmol) was added a solution of *n*BuLi (1.45 mL, 3.3 mmol) at −78 °C. After 5 min, a solution of phenylselenenyl bromide (3 mmol), prepared by addition of an equimolar amount of bromine to a solution of diphenyl diselenide in THF (5 mL), was added at once. The reaction mixture was stirred for 2−3 min and then poured into a 1:1 mixture (15 mL) of diethyl ether and aqueous solution of sodium carbonate at 0 °C. The organic layer was separated, dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and treated with

a solution of H_2O_2 and water (1:1 mixture, 3 mL). The reaction mixture was stirred for 30 min and the solvents were evaporated. The crude sulfoxide **1a-d_2** was then purified by column chromatography and isolated as a pale yellow oil (0.79 g) in 87% yield. $[\alpha]_D^{20}$ = +148 (c = 2.0 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 9.9 ppm. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_3CH_2O), 2.40 (s, 3 H, CH_3Ph), 3.81−4.11 (m, 4 H, CH_2O), 7.32−7.59 (m, 4 H, aromatic) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7 (d, $^1J_{C,P}$ = 7.9 Hz), 21.2, 63.1 (d, $^2J_{C,P}$ = 5.1 Hz), 126.2, 129.3, 132.1, 138.64, 142.2 ppm. $C_{13}H_{17}D_2O_4PS$ (304.3): calcd. C 51.31, H 6.95; found C 51.36, H 6.73.

Cyclopropanation Reaction of (*S*)-(+)-1a with $(CD_3)_2S(O)CD_2$: Sodium hydride (16 mg) was added to a solution of [D$_6$]DMSO (1 mL) and THF (2 mL). The mixture was heated at 70 °C for 30 min, then cooled to 0 °C and deuterated trimethylsulfoxonium iodide (80 mg, 4 mmol) [prepared by addition of CD_3I to $(CD_3)_2SO$] was added. After stirring at 0 °C for 10 min, sulfoxide (*S*)-(+)-**1a** (0.1 g 0.33 mmol) dissolved in THF (2 mL) was added. The reaction mixture was stirred at room temperature for 3 h and then quenched with aqueous ammonium chloride solution (3 mL). The organic layer was extracted with $CHCl_3$ (3 × 5 mL) and dried with $MgSO_4$. The solvent was removed under vacuum and the crude product purified by column chromatography (hexane/acetone 10:1) to give the cyclopropane **4a-d_2** (90%) contaminated with **4b-d_2**, **4-d_1** and **4** (ca. 10%) (96 mg) in 92% yield. $[\alpha]_D^{20}$ = +49 (c = 0.21 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.3 ppm; **4a-d_2:** ^{1}H NMR (500 MHz, C_6D_6): δ = 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 0.95 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 1.18 (dd, $^2J_{H,H}$ = 4.9, $^3J_{H,P}$ = 14.0 Hz, 1 H, CH_2), 1.30 (dd, $^2J_{H,H}$ = 4.9, $^3J_{H,P}$ = 9.9 Hz, 1 H, CH_2), 1.98 (s, 3 H, CH_3Ph), 3.61−3.74 (m, 1 H, CH_2O), 3.75-3.83 (m, 3 H, CH_2O), 6.89 and 7.65 ppm (A_2B_2, 4 H, aromatic) ppm. HRMS (CI) $[M + H]^+$: calcd. for $C_{14}H_{19}D_2O_4PS$: 319.1102; found 319.1106.

Oxidation to the Sulfone: The cyclopropane prepared as above (100 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (10 mL) and *m*-chloroperbenzoic acid (156 mg, 1 mmol) was added. The mixture was stirred vigorously for 6 h. It was then washed with a saturated aqueous solution of sodium carbonate (2 × 10 mL), the solvent evaporated and the crude product purified by column chromatography (hexane/acetone, 10:1, R_f = 0.42) giving the sulfone (100 mg) as a colourless oil in 97% yield. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 18.5 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H, CH_3CH_2O), 1.51−1.64 (m, 2 H, CH_2), 1.75−1.85 (m, 2 H, CH_2), 2.44 (s, 3 H, CH_3Ph), 3.96−4.08 (q, 4 H, CH_2O), 7.26, 7.75 ppm (A_2B_2, 4 H, aromatic). $C_{14}H_{19}D_2O_5PS$ (334.36): calcd. C 50.24, H 6.88, P 9.27, S 9.57; found C 50.21, H 7.08, P 9.39, S 9.37.

Cyclopropanation Reaction of (*S*)-(+)-1a-d_2 with $(CH_3)_2S(O)CH_2$: To a solution of [D$_6$]DMSO (2 mL) and THF (5 mL) was added NaH (48 mg, 2 mmol) and the mixture was heated at 70 °C for 30 min. After this time, the mixture was cooled to 0 °C and trimethylsulfoxonium iodide (240 mg 12 mmol) was added. After stirring at 0 °C for 10 min, sulfoxide (*S*)-(+)-**1a-d_2** (300 mg, 1 mmol) dissolved in THF (5 mL) was added. The reaction mixture was kept at room temperature for 3 h and was then quenched with aqueous ammonium chloride solution (10 mL). The water layer was extracted with $CHCl_3$ (3 × 10 mL). The chloroform extract was dried with anhydrous $MgSO_4$ and the solvents were evaporated under vacuum (30 °C/0.05 Torr) The crude product was purified by column chromatography (petroleum ether/acetone, 10:1; R_f = 0.37) affording a mixture of **4b-d_2** and **4a-d_2** (91:9) as a colourless oil (286 mg) in 90% yield. $[\alpha]_D^{20}$ = +52 (c = 0.19 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ 22.3 ppm. HRMS (CI) $[M + H]^+$: calcd. for $C_{14}H_{19}D_2O_4PS$: 319.1102; found 319.1103. **4b-d_2:** ^{1}H NMR (500 MHz, C_6D_6): δ 0.86 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 0.95 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3CH_2O), 1.43 (dd, $^2J_{H,H}$ = 4.3, $^3J_{H,P}$ = 15.1 Hz, 1 H, CH_2), 1.65 (dd, $^2J_{H,H}$ = 4.3, $^3J_{H,P}$ = 8.8 Hz, 1 H, CH_2), 1.96 (s, 3 H, CH_3Ph), 3.61-3.68 (m, 1 H, CH_2O), 3.77−3.85 (m, 3 H, CH_2O), 6.88 and 7.69 ppm (A_2B_2, 4 H, aromatic).

(+)-1-Diethoxyphosphoryl-2,2-dimethyl-1-(*p*-tolylsulfinyl)cyclopropane (7): To a stirred solution of ethyldiphenylsulfonium tetrafluoroborate (484 mg 1.7 mmol) [prepared by addition of diphenyl sulfide to an equimolar amount of triethyloxonium tetrafluoroborate in dichloromethane, room temp., 24 h] in dry dichloromethane (0.165 mL, 1.7 mmol) and freshly distilled DME (15 mL) was added LDA (1.8 mmol) under argon at −78 °C. The mixture was stirred at −78 °C for 30 min and methyl iodide (passed through basic alumina immediately prior to use) (0.115 mL, 1.7 mmol) was added. This caused the yellow-green colour to fade and formation of a colourless precipitate after 5 min. After stirring between −70 and −50 °C for 2 h, an additional amount of LDA (1.8 mmol) was added. The bright orange-coloured solution was stirred at −70 °C for 1.5 h and sulfoxide (*S*)-(+)-**1a** (270 mg 0.9 mmol) was added in DME (2 mL). The solution was stirred between −70 and −20 °C for 3 h. The colourless mixture was quenched with aqueous saturated ammonium chloride (10 mL), allowed to warm to ambient temperature and extracted with diethyl ether (3 × 15 mL). The organic layer was dried with anhydrous $MgSO_4$ and the solvent evaporated. Purification by column chromatography (hexane/acetone, 12:1; R_f = 0.34) gave the cyclopropane **7** (200 mg) as a colourless oil in 65% yield; $[\alpha]_D^{20}$ = +22.0 (c = 0.19 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.6 ppm. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 and 1.34 (2 × t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3CH_2O), 1.48 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 1.77 (dd, $^2J_{H,H}$ = 5.6, $^3J_{H,P}$ = 8.9 Hz, 1 H, CH_2), 1.99 (dd, $^2J_{H,H}$ = 5.6, $^3J_{H,P}$ = 16.3 Hz, 1 H, CH_2), 2.42 (s, 3 H, CH_3Ph), 3.40−3.68 (m, 2 H, CH_2O), 4.15 (m, 2 H, CH_2O), 7.28 and 7.47 ppm (A_2B_2, $^3J_{H,H}$ = 8.0 Hz, 4 H, aromatic). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.5, 16.1, 21.3, 22.6, 24.4, 27.2, 28.6, 61.1, 63.6, 125.2, 128.9, 138.9, 140.4 ppm. IR (neat): $\tilde{\nu}$ = 2980, 2926 (CH_3), 1260 (OCH_3), 1160 (P=O), 1026 cm^{-1} (S=O). HRMS(CI) $[M + H]^+$: calcd. for $C_{16}H_{26}O_4PS$: 345.12869; found 345.1276.

(+)-1-Diethoxyphosphoryl-2,2-dimethyl-1-(*p*-tolylsulfonyl)cyclopropane (8): Cyclopropane **7** (150 mg, 0.4 mmol) was oxidised with *m*-chloroperbenzoic acid (180 mg, 1 mmol) in CH_2Cl_2 solution (5 mL) in the same way as described above. Purification by column chromatography (hexane/acetone, 12:1; R_f = 0.38) gave the sulfone **8** (150 mg) as a colourless oil in 96% yield. $[\alpha]_D^{20}$ = +8.5 (c = 0.19 in acetone). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 18.9 ppm. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.98 (dd, $^2J_{H,H}$ = 5.3, $^3J_{H,P}$ = 16.3 Hz, 1 H, CH_2), 2.08 (dd, $^2J_{H,H}$ = 5.3, $^3J_{H,P}$ = 9.5 Hz, 1 H, CH_2), 2.43 (s, 3 H, CH_3Ph), 3.40−3.68 (m, 2 H, CH_2O), 4.15 (m, 2 H, CH_2O), 7.30 and 7.52 ppm (A_2B_2, $^3J_{H,H}$ = 8.2 Hz, 4 H, aromatic). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 16.3 (d, $^1J_{C,P}$ = 5.2 Hz), 21.6, 22.6, 24.4, 29.6, 30.9, 63.39 (d, $^2J_{C,P}$ = 7.8 Hz), 128.9, 131.0, 136.7, 140.4 ppm. $C_{16}H_{25}O_5PS$ (360.4): calcd. C 53.32, H 6.94, P 8.60, S 8.79; found C 53.28, H 6.69, P 8.61, S 9.18.

(±)-1-(Diphenylphosphinoyl)vinyl *p*-Tolyl Sulfoxide (9): To a solution of paraformaldehyde (0.9 g, 15 mmol) in benzene (20 mL) was added piperidine (0.42 g, 5 mmol). The reaction mixture was heated to reflux for 3 h. Sulfoxide **10** (0.36 g, 6 mmol) and acetic acid were then added. The reaction mixture was kept at 30−40 °C for 48 h. After evaporation of the solvents, the residue was washed with diethyl ether (3 × 20 mL). The crude sulfoxide **9**, in the form of a

yellow oil, was purified by column chromatography (hexane/acetone, 1:3) and crystallised from diethyl ether to give white crystals of **9** (1.09 g) in 60% yield. For X-ray analysis **9** was recrystallised from benzene, m.p. 156−158 °C. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 24.7 ppm. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3Ph), 6.16 (dd, 1 H, $^2J_{H,H}$ = 0.6, $^3J_{H,P}$ = 16.1 Hz; CH_2), 7.03 (dd, 1 H, $^2J_{H,H}$ = 0.6, $^3J_{H,P}$ = 35.1 Hz; CH_2), 6.96 and 7.42 (A_2B_2, $^3J_{H,H}$ = 12.4 Hz, 4 H, Tol), 7.20−7.53 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3, 126.0, 128, 128.2, 128.5, 128.7, 129.4, 131.0, 131.3, 131.4, 132.5, 138.3, 152.1 (d, $^1J_{C,P}$ = 86.4 Hz) ppm. $C_{21}H_{19}O_2PS$ (366.4): calcd. C 68.78, H 5.19, P 8.46, S 8.73; found C 68.99, H 5.14, P 8.38, S 8.90.

Crystal Structure Determination: The crystal and molecular structures of the sulfoxide **9** were determined using data collected at low temperature on a KUMA (Oxford Instruments KM4) diffractometer[22] with graphite-monochromated Mo-K_α radiation. Compound **9** crystallises in the monoclinic system, space group $P2_1/c$, with the unit cell consisting of 4 molecules. Crystal data and experimental details are shown in Table 2. The lattice constants were refined by a least-squares fit of 5841 reflections in the θ range 3.68−35.60°. A total of 5809 independent reflections with $I > 0$ were used to solve the structure by direct methods and to refine it by full-matrix least-squares using F^2.[23,24] Hydrogen atoms were found from a difference Fourier map and refined isotropically. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to R = 0.0541 for 302 refined parameters and 5032 observed reflections with $I \geq 2\sigma(I)$. Data processing was carried out with the KM4CCD software.[22] The structure solution was carried out with SHELXS[23] and the structure refinement with SHELXL.[24] CCDC-229638 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Computational Method: For the DFT calculations, Becke's three parameter hybrid functional (B3)[25] together with the correlation functional of Lee, Yang and Parr (LYP)[26] with the 6-31G* basis set were employed. All calculations were performed for the gas phase conditions using the Gaussian 98 package.[27] Equilibrium geometries of model compounds were found at the B3LYP/6-31G* level. Stationary points were confirmed by frequency calculations. Vibrational components of the thermal energy were scaled by 0.98. All enthalpy and Gibbs free energy values were corrected to 298 K. Final single-point energies were calculated at the B3LYP/6-311+G(2d,p) level for the B3LYP/6-31G* geometries. Orbital populations, atomic charges and Wiberg bond indices were calculated with the NBO 3.0 program included in the Gaussian package using the HF/6-31G* method.[28] The energies of orbital interactions were calculated as the difference between the electronic energy, regarding a full orbital interaction pattern, and the energy for the molecular system with deletion of the Fock matrix elements corresponding to the particular interaction.[28]

Table 2. Crystal data for **9** and experimental details

Empirical formula	$C_{21}H_{19}O_2PS$
Formula mass	366.39
Crystal stem	monoclinic
Space group	$P2_1/c$
a (Å)	19.348(4)
b (Å)	8.839(3)
c (Å)	11.080(3)
β (°)	103.18(3)
V (Å^3)	1845.0(9)
Z	4
D_c (g/cm^3)	1.319
μ (mm^{-1})	0.273
Crystal dimensions (mm)	0.60 × 0.60 × 0.15
Maximum 2θ (°)	71.20
Radiation, λ (Å)	Mo-K_α, 0.71073
Scan mode	ω
hkl ranges	−25 to 24, −14to 11, −17 to 14
No. of runique eflections	5841
With $I > 0\sigma(I)$	5809
Obsd. with $I > 2\sigma(I)$	5032
No. of parameters refined	302
Largest diff. peak (e·Å^{-3})	0.584
Largest diff. hole (e·Å^{-3})	−0.648
Shift/esd. max.	0.001
$R_{obsd.}$	0.0541
$wR_{obsd.}$	0.1261
$S_{obsd.}$	1.082
Weighting coeff.[a]	0.0513, 1.9768
m, n	
R_{int}	0.0553
$T_{measd.}$	100(2)
$F(000)$	768

[a] Weighting scheme $w = [\sigma^2(F_o^2) + (mP)^2 + nP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$.

Acknowledgments

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