Diastereoselective asymmetric cyclopropanation of (*S*)-(+)-α-(diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide

Wanda H. Midura,[a] Jerzy A. Krysiak,[a] Michał W. Wieczorek,[b] Wiesław R. Majzner[b] and Marian Mikołajczyk*[a]†

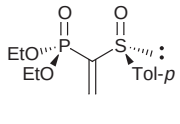
[a] *Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-363 Łódź, Sienkiewicza 112, Poland*

[b] *Institute of General Food Chemistry, Technical University of Łódź, 90-924 Łódź, Stefanowskiego 4/10, Poland*

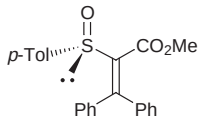
The title sulfoxide 1 reacts with fully deuterated dimethylsulfoxonium methylide, diphenylsulfonium isopropylide and diphenyldiazomethane to form the corresponding cyclopropanes 4 as single diastereoisomers; the chirality of the cyclopropane (+)-4c obtained from 1 and diphenyldiazomethane is (S_S,S_C) as determined by X-ray diffraction analysis; based on experimental data, the steric course of the asymmetric cyclopropanation is proposed.

α,β-Unsaturated sulfoxides have been widely used in asymmetric synthesis as versatile chiral reagents with the sulfinyl group playing the role of a chiral auxiliary.[1,2] Since α,β-unsaturated sulfoxides having no additional electron-withdrawing substituents on the double bond exhibit low reactivity, we recently designed a new type of activated chiral vinyl sulfoxides, namely α-phosphorylvinyl *p*-tolyl sulfoxide **1** and its β-substituted (Me, Ph, Bu^n) analogues.[3,4] The phosphoryl group in **1** activates not only the C=C bond but also makes possible further reactions such as, for instance, the Horner–Wittig reaction. The chiral sulfoxides **1** were found to be good Michael acceptors as well as Diels–Alder dienophiles. They were also used as key reagents for the construction of monocyclic- and condensed carbo- and hetero-cycles *via* tandem Michael addition/intramolecular Horner–Wittig reaction. However, the asymmetric induction in these reactions was not very high.

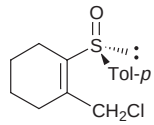
Now we extend our work in this area by reporting a fully diastereoselective, asymmetric cyclopropanation of the sulfoxide (*S*)-(+)-**1**. The present study on asymmetric cyclopropanation was stimulated by the fact that a wide variety of natural products and currently-used insecticides contain the cyclopropane ring in a chiral environment.[5] Moreover, to the best of our knowledge, there are only two reports describing asymmetric cyclopropanation using enantiopure vinylic sulfoxides as chiral reagents.[6,7] Thus, Hamdouchi[6] reacted the sulfoxide (*S*)-(+)-**2** with dimethyl(oxo)sulfonium methylide and obtained a mixture of two diastereoisomeric cyclopropanation products in a 5.9 : 1 ratio. On the other hand, the reaction of the cyclic vinylic sulfoxide **3** with allylmagnesium bromide was found by Iwata[7] to give the corresponding cyclopropane as a single diastereoisomer, however, accompanied by the side coupling product.



1

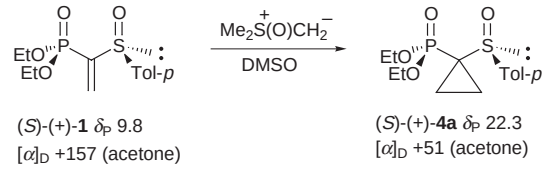


2



3

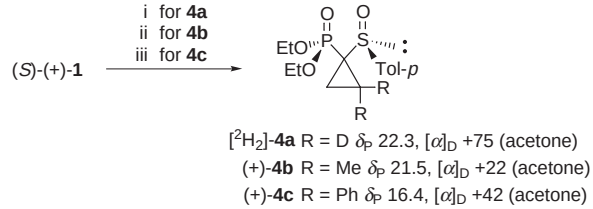
In our preliminary experiment (*S*)-(+)-α-(diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **1** was treated with an excess of dimethyl(oxo)sulfonium methylide in DMSO at room temperature and gave the expected cyclopropane (*S*)-(+)-**4a** as the only product [eqn. (1)], isolated by flash chromatography on silica gel in 90% yield. The asymmetric version of the reaction was realized by using fully deuterated dimethyl(oxo)sulfonium methylide as the CD_2 transfer agent (Scheme 1). Although the chirality at the newly formed quaternary α-carbon atom is due to isotopic substitution (CH_2 *vs.* CD_2), the ^{31}P NMR spectrum of the crude cyclopropane [$^2H_2$]-**4a** formed revealed only one sharp signal at δ_P 22.3, strongly suggesting that only one diastereoisomer was formed. The deuterium decoupled ^{1}H NMR spectra (500 MHz) of the pure product isolated in 92% yield confirmed its full diastereoisomeric purity (the cyclopropane methylene protons appeared in the spectrum as doublets of doublets at δ 1.26 and 1.38 with $^2J_{H–H}$ = 4.8 and $^3J_{H–H}$ = 9.8 and 14.0 Hz).



(1)

Similarly, treatment of (*S*)-(+)-**1** with diphenylsulfonium isopropylide (prepared according to the procedure described by Corey[8]) in THF at room temperature yielded the corresponding cyclopropane (+)-**4b** which was isolated in a pure state by flash chromatography in 65% yield. To our delight, also in this case the cyclopropanation reaction resulted in the formation of a single diastereoisomer, as evidenced by the ^{1}H and ^{31}P NMR spectra of the product.

In addition to sulfur ylides, in the course of these studies the behaviour of the vinylic sulfoxide (*S*)-(+)-**1** towards diazomethane and diphenyldiazomethane was investigated. Whereas the reaction of the former dipole was found to give rise to 3-diethoxyphosphorylpyrazole *via* transient formation of the corresponding 1,3-cycloadduct, elimination of toluene-*p*-sulfenic acid and tautomerization,‡ the latter reacted with (*S*)-(+)-**1** affording a single diastereoisomeric cyclopropane (+)-**4c** as indicated by the ^{1}H and ^{31}P NMR spectral analysis of the crude product.§ After flash chromatography, pure (+)-**4c** (mp 89–91 °C) was obtained in 86% yield. To provide an unequivocal proof of the full asymmetric induction occuring in this reaction, the cyclopropane (+)-**4c** was oxidized by MCPBA to the



Scheme 1 *Reagents and conditions*: i, $(CD_3)_2S(O)CD_2$, [$^2H_6$]DMSO; ii, Ph_2SCMe_2, THF; iii, Ph_2CN_2, Et_2O

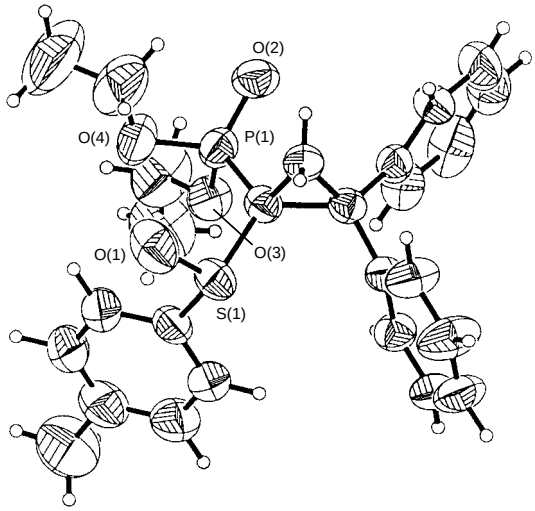
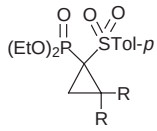


Fig. 1 X-Ray structure of (+)-**4c**. Ellipsoids are shown at the 50% probability level

optically active sulfone (+)-**5c**. Its ^{1}H NMR spectrum recorded in the absence and in the presence of (*R*)-(+)-*tert*-butylphenylphosphinothioic acid as a chiral solvating agent[9] showed only two doublets of doublets for the cyclopropyl methylene protons (δ 2.67 and 2.83; $^2J_{H–H}$ = 6 and $^3J_{P–H}$ = 7.1 and 8.4 Hz, respectively), while in the spectrum of the racemic sulfone (±)-**5c** prepared in an independent way in the presence of a



(+)-**5b** R = Me δ_P 21.7, $[\alpha]_D$ 8.5 (acetone)
(+)-**5c** R = Ph δ_P 15.1, $[\alpha]_D$ 25.0 (acetone)

chiral phosphinothioic acid, all the signals of the appropriate protons were doubled. In a similar way, the full enantiomeric purity of the sulfone (+)-**5b** obtained from (+)-**4b** was also confirmed.

In order to rationalize the steric course of the above described fully diastereoselective cyclopropanations of the sulfoxide (*S*)-(+)-**1**, we determined the crystal and molecular structure of the cyclopropane (+)-**4c** by X-ray diffraction (Fig. 1).¶ It turned out that the absolute configuration of the newly formed chiral centre at the α-carbon atom is *S*. Moreover, both polar sulfinyl

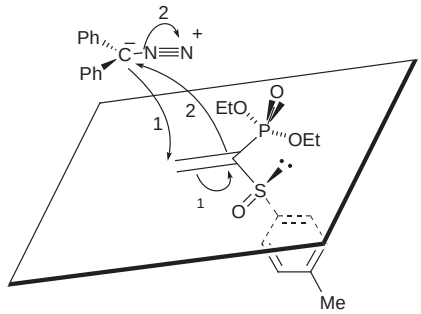
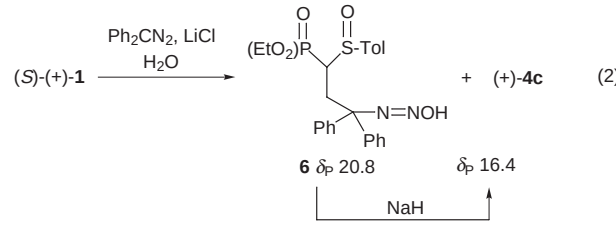


Fig. 2 The proposed steric course of the reaction of Ph_2CN_2 with the sulfoxide (*S*)-(+)-**1**

and phosphoryl groups in **4c** are in *anti*-like orientation [the torsional angle S(1)–O(1)···P(1)–O(2) is equal to 93.3 (±0.1)°]. Therefore, it is reasonable to assume that (*S*)-(+)-**1** adopts a similar conformation, and nucleophilic addition of diphenyldiazomethane to the vinylic β-carbon atom of **1** (step 1) and subsequent ring closure (step 2) occur exclusively from the less-hindered diastereotopic face occupied by the electron lone pair at sulfur, as schematically depicted in Fig. 2.

A two-step mechanism for cyclopropanation was supported by isolation of the intermediate adduct **6** which was formed together with the cyclopropane (+)-**4c** when the reaction was carried out in the presence of LiCl [eqn. (2)]. Its subsequent



cyclization to (+)-**4c** was found to occur in the presence of NaH.

In summary, we have described the fully diastereoselective asymmetric synthesis of a new type of optically active cyclopropane **4** which is geminally substituted with two different heteroatoms. The specific reactivity of each heteroatomic centre provides interesting possibilities for further transformations of the cyclopropane **4** into optically active cyclic and acyclic derivatives.

Notes and References

† E-mail: marmikol@bilbo.cbmm.lodz.pl

‡ The results of the reaction of diazomethane with sulfoxide **1** and its β-substituted analogues will be published elswhere.

§ The formation (10%) of the corresponding 3-phosphorylpyrazoline (δ_P 19.3) was observed.

¶ *Crystal data* for (+)-**4c**; $C_{26}H_{29}O_4PS$, M = 468.52, orthorhombic, space group $P2_12_12_1$; a = 9.301 (7), b = 16.209 (7), c = 16.755 (6) Å; V = 2526 (2) Å^3; Z = 4; D_C = 1.232 g cm^{-3}; μ = 19.67 cm^{-1} (Cu-Kα). A total of 5042 unique reflections were collected in the conventional $\omega/2\theta$ scan mode, of which 4817 observed reflections [$I > 2\sigma(I)$] were used in the structure solution (direct methods) and refinement (full-matrix least-squares) to give final R = 0.0429 for 339 refined parameters and ωR = 0.1107. The absolute configuration was established by the Flack parameter, 0.001 (16). CCDC 182/835.

1 M. Mikołajczyk, J. Drabowicz and P. Kiełbasiński, *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*, CRC Press, Boca Raton, 1997.
2 A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341.
3 M. Mikołajczyk and W. H. Midura, *Tetrahedron: Asymmetry*, 1992, **3**, 1515.
4 W. H. Midura and M. Mikołajczyk, *Phosphorus, Sulfur, Silicon*, 1994, **95**–**96**, 397.
5 H. U. Reissig, in *The Chemistry of Cyclopropyl Group*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1987, ch. 8; H. W. Liu and C. T. Walsh, *idem*, ch. 16; J. Salaün, M. S. Baird, *Curr. Med. Chem.*, 1995, **2**, 511.
6 Ch. Hamdouchi, *Tetrahedron Lett.*, 1992, **33**, 1701.
7 T. Imanishi, T. Ohara, K. Sugiyama, Y. Ueda, Y. Takemoto and C. Iwata, *J. Chem. Soc., Chem. Commun.*, 1992, 296.
8 E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, 1967, **89**, 3912.
9 J. Drabowicz, B. Dudziński, M. Mikołajczyk, S. Colonna and N. Gaggero, *Tetrahedron: Asymmetry*, 1997, **13**, 2267 and references cited therein.

Received in Cambridge, UK, 16th February 1998; 8/01299G