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Stereoselective cyclopropyl phosphonate formation using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide. Unusual phosphoryl group migration

Wanda H. Midura *, Agata Sobczak, Piotr Paluch

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Lodz, Sienkiewicza 112, Poland

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ABSTRACT

Methylation of *t*-butyl-1-dimethylphosphono-2-*p*-tolylsulfinyl cyclopropanecarboxylic ester occurs with full inversion of the configuration, but the stereochemistry of carbanion formation is structure-dependent. Reaction of cyclopropyl sulfoxide with *i*-PrMgCl leads to unprecedented 1,2 migration of the phosphoryl group.

Cyclopropane-containing compounds exhibit a broad spectrum of biological properties[1] and are present in over 100 therapeutic agents.[2] Cyclopropane rings are found in a variety of natural products and biologically active compounds including terpenes, pheromones, fatty acid metabolites, and unusual amino acids. The synthetic utility and medicinal properties of enantioenriched cyclopropanes have inspired many investigations on their synthesis.[3] New and more efficient methods for the preparation of these entities in enantiomerically pure form are still evolving, many of which proceed via Michael addition initiated ring-closure sequences (MIRC).[4] In cyclopropanation reactions involving conjugate addition to an activated olefin, different ylides are used most often as nucleophiles.[5] Stereoselective formation of cyclopropanes can be accomplished either by reagent-controlled or substrate-controlled processes.

Continuing our work on the application of optically active sulfinyl compounds in asymmetric synthesis, we have designed a new type of a chiral sulfur ylide as a single enantiomer, containing a sulfinyl group bonded to the ylidic carbon atom. Our investigations proved the utility of sulfinylmethylide in asymmetric syntheses of the corresponding oxiranes and aziridines.[6] High facial stereoselectivity was also observed for cyclopropanation, where the stereoselectivity depends on the structure of the Michael acceptor.[7]

Our initial investigations concentrated on cyclopropanation of vinyl phosphonates, as an approach to the corresponding cyclopropanes, which are precursors of constrained phosphonic analogues of natural and non-natural amino acids of potential, and in some cases, documented biological and therapeutic activity.[8] The presence of a chiral sulfinyl substituent on the phosphoryl cyclopropane structure allows the possibility of additional functionalization under stereochemical control. In particular, cyclopropanation of *t*-butyl 2-dimethoxyphosphoryl acrylate (**2**) using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide (**1**) and K_2CO_3 as the base, afforded a separable mixture of three diastereomers **3a–c** in a 65:21:14 ratio (Scheme 1A).[9] The relative configuration was determined by ^{1}H NMR spectroscopy, where the coupling constant values, $^3J_{HP}$ provided conclusive evidence for the assignment of the *cis–trans* geometry in the substituted cyclopropylphosphonates. The absolute stereochemistry of the cyclopropane ring in **3a** was assumed to be (1*R*,2*S*), based on a preferential approach to the most stable conformer B of ylide **1** (Fig. 1) as assigned by DFT calculations.[6c]

To introduce an additional substituent onto the cyclopropane ring, at the carbon α to the sulfinyl substituent, LiHMDS was used as the base. The carbanion generated from **3** at −78 °C was quenched with methyl iodide (as an electrophile). Methylation of the *trans* diastereomer of cyclopropyl sulfoxide **3a** afforded the corresponding methylated cyclopropane **4a**[10] as the only product (Scheme 1B). The stereochemistry of this process was determined by a NOESY experiment: based on $^3J_{HP}$ coupling constant values, the hydrogens bonded to the cyclopropane ring were assigned as H*cis* and H*trans* with respect to the phosphorus atom. Since the methyl group interacted with H*trans* (signal enhancement interaction with H*trans* was observed), (Fig. 2) the sulfinyl

* Corresponding author. Tel./fax: +48 42680 3216.
E-mail address: whmidura@bilbo.cbmm.lodz.pl (W.H. Midura).

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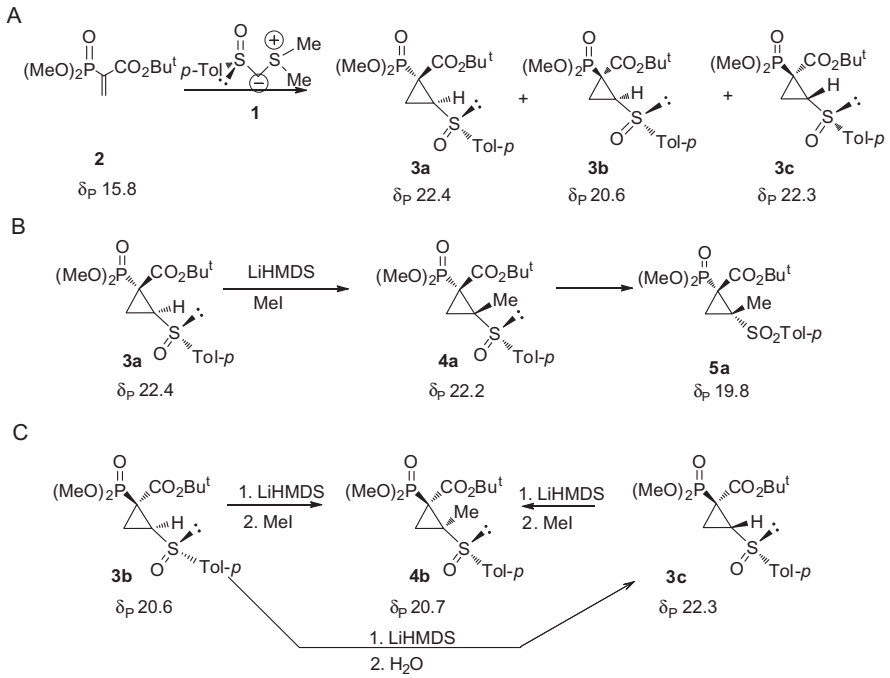


Scheme 1. Formation of cyclopropyl sulfoxides **3** and their subsequent alkylation.

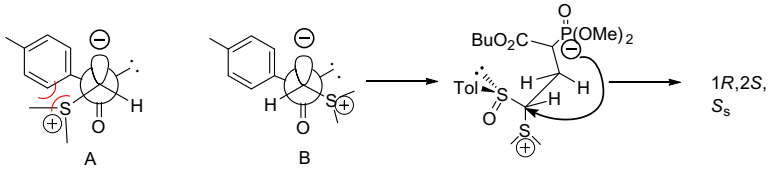


Figure 1.

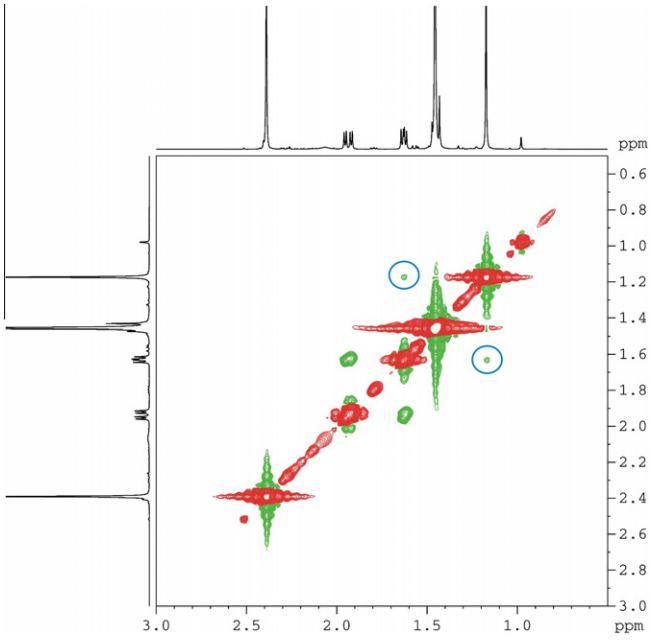
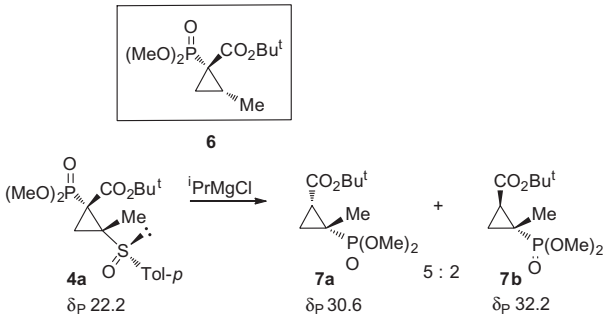


Figure 2. NOESY spectrum of **4a**. The key NOEs between the methyl group signals and H*trans* with respect to the phosphorus atom are marked with blue circles.

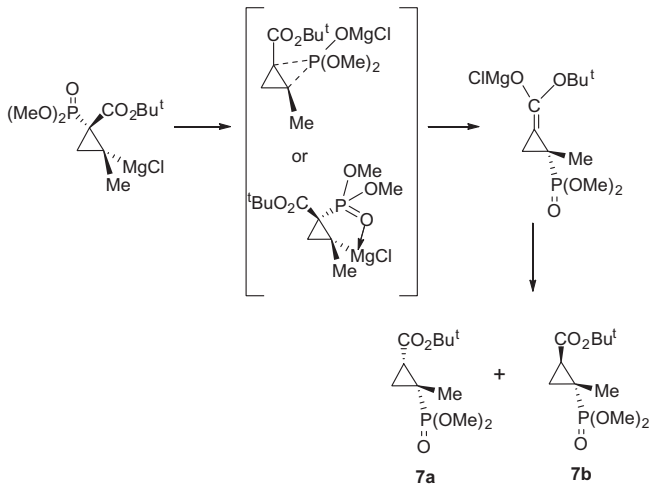
substituent must be on the same side as the phosphoryl group, which revealed that the alkylation process proceeded with inversion of configuration.

On the other hand, under the same reaction conditions, *cis* diastereomer **3b** gave the product of retention of configuration; the same product was formed by methylation of the second *trans* diastereomer **3c** (Scheme 1C). Loss of the chirality on sulfur by simple oxidation of both cyclopropyl sulfoxides **4a** and **4b** gave only one sulfone **5a**, thus establishing the same relative configuration for both.

It is generally accepted that the stereochemistry of the reactions of α-lithiosulfoxides with electrophilic reagents depends upon the nature of the latter. Thus, electrophiles containing oxygen atoms (H_2O, D_2O, and CH_2O) react in THF with retention of configuration, whereas CH_3I reacts with inversion.[11] Albeit recently, retention of configuration for both types of electrophiles was found to occur during cyclopropyl sulfoxide exchange,[12] we thus assumed that the typical steric course of the reaction takes place in the examples presented here. The different stereochemistry observed for *cis* isomer **3b** results probably via inversion of its corresponding carbanion to the more stable *trans* form. Since subsequent alkylation also occurs with inversion of configuration, the overall stereochemical outcome is retention. This assumption was confirmed by an additional experiment where the carbanion formed from *cis* isomer **3b** was reacted with H_2O affording **3c** (Scheme 1C). Similar high *syn* selectivity of carbanion formation was observed during sulfoxide/lithium exchange of bis(*p*-tolylsulfinyl)cyclopropanes.[12b] Based on these observations, the alkylation of **3** was performed without prior separation of diastereomers, affording **4a** and **4b** in a 2:1 ratio. Simple recrystallization from diethyl ether gave the major diastereomer **4a** in pure form.



Scheme 2. Sulfinyl exchange.



Scheme 3. 1,2-Migration of a phosphoryl group.

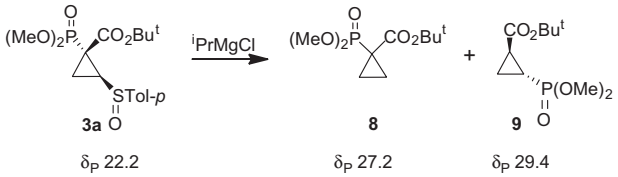
For further functionalization, mono-methylated cyclopropanes **4** were subjected to sulfoxide/metal exchange, a reaction that has been widely applied to the synthesis of enantiomerically pure sulfoxides, and also as a method to generate the corresponding carbanions. Although a variety of bases was used for this purpose,[13,14] due to the presence of other reactive centers in cyclopropyl sulfoxide **4**, isopropylmagnesium chloride was used as the reagent of choice in our preliminary investigations.

In the reaction of **4a** with isopropylmagnesium chloride performed at −10 °C in diethyl ether for 20 min the expected isopropyl *p*-tolyl sulfoxide was formed. Although ^{31}P and ^{1}H NMR spectra revealed the presence of two compounds in a 2:5 ratio, now lacking a sulfur substituent, these spectroscopic data were inconsistent with the expected product structure **6**. Large coupling constants (hydrogen–phosphorus with the methyl group), 12.45 Hz and 11.0 Hz, suggested a close proximity between the phosphoryl and methyl substituents. The new products were identified as *cis* and *trans* diastereomers of *t*-butyl-2-methyl-2-dimethylphosphonocyclopropanecarboxylates *cis*-**7a**[15] and *trans*-**7b** (Scheme 2). The reaction, repeated under the same conditions, of the mixture of diastereomers **4a**/**4b** occurred in a similar manner affording a mixture of *cis*/*trans* diastereomers **7** in the same ratio 5:2.

The formation of cyclopropanes **7** can be explained via 1,2-migration of a phosphoryl group. Taking into account that **7a** and **7b** are optically active, this process seems to occur in a concerted manner (Scheme 3). Predominant formation of **7a**, where the two bulky (phosphoryl and carbobutoxy) groups are in a *cis* relationship, suggests preferential protonation of the enolate from the less hindered face.

We investigated further whether the phosphoryl group 1,2-migration was general and would occur for cyclopropanecarboxylic ester **3**. Initial experiments were performed on *trans* isomers of **3**. The application of various conditions (Table 1) showed that this reaction was temperature dependent. At low temperature (−50 °C) desulfinylated cyclopropane **8** was observed as the only product (entries 1–3), whereas increasing the temperature and extending the reaction time caused the formation of regioisomer **9**. However, increasing the time to 2 h did not improve the **9**/**8** ratio, but resulted in partial decomposition (entry 8). There was no significant difference between diethyl ether and CH_2Cl_2, but more polar THF inhibited the rearrangement (entry 7). According to the plausible mechanism presented in Scheme 3, to accomplish phosphoryl group 1,2-migration, the magnesium-bearing carbon

Table 1
Reaction of **3** with ^{i}PrMgCl



Entry	Cyclopro pane	Reaction conditions			Regioisomer ratio[a]	
		i-PrMgCl	Solvent	Temp/time	8	9
1	**3a/3c**	1.5 equiv	CH_2Cl_2	−50 °C/10 min	>99%[b]	–
2	**3a/3c**	3 equiv	CH_2Cl_2	−50 °C/10 min	>99%	–
3	**3a**	3 equiv	Et_2O	−50 °C/10 min	>99%	–
4	**3a/3c**	3 equiv	CH_2Cl_2	−10 °C/20 min	40%	60%
5	**3a**	3 equiv	Et_2O	−10 °C/20 min	62%	38%[c]
6	**3a**	3 equiv	Et_2O	0 °C—rt/30 min	32%	68%
7	**3a**	3 equiv	THF	0 °C/30 min	90%	10%
8	**3a**	3 equiv	Et_2O	rt/2 h [d]	30%	70%
9	**3b**	3 equiv	Et_2O	−10 °C/30 min	75%	25%[c]
10	**3b**	3 equiv	Et_2O	0 °C/1 h	30%	70%

[a] Product ratios measured by ^{31}P and ^{1}H NMR spectroscopy.
[b] 50% Conversion.
[c] A trace of *cis*-**9** was detected.
[d] 10% of by-products were formed.

atom should be in the appropriate configuration. Surprisingly, although the required relationship should be easily accessible from *cis*-**3b**, we did not observe a significant increase in the amount of regioisomer **9** (entries 9 and 10). In the absence of an anion-stabilizing group the magnesium derivative is quite unstable. Therefore, the only possibility of its stabilization is by coordination with the phosphoryl group which is, however, accessible only from one side. This probably reduces the barrier of inversion for the *trans*-magnesium derivative and similar reactivity for both isomers was observed. The crucial element of the structure under investigations is the presence of two electron-withdrawing substituents on carbon 2, which makes the 1,2 migration of the phosphoryl group possible.

The migration product **9** was formed as the *trans* isomer, only traces of the *cis* isomer[16] were detected in two cases (entries 5 and 9). Evidently, in the case of cyclopropane **3** only a thermodynamically controlled product could be obtained.

To the best of our knowledge, the migration of a phosphoryl group on a cyclopropane ring, as described above, has not been previously reported. It can be compared to [1,2]anionic rearrangement in *N*-Boc and *N*-phosphonate terminal aziridines providing an access to the corresponding aziridinyl esters and aziridinyl phosphonates.[17] Relevant base-induced migrations of a phosphoryl group between a heteroatom and carbon have been the subject of investigations in different laboratories.[18] In the case presented here, rearrangement takes place between carbon atoms in different electronic environments, being electron deficient due to the presence of electron-withdrawing substituents and a carbanion. Further studies of this reactivity pattern are currently underway in our laboratory.

Acknowledgement

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9. *Procedure for cyclopropanation*: to a round-bottomed flask equipped with a magnetic stir bar were added 2 mmol (0.47 g) of *t*-butyl-1-dimethylphosphonoacrylate and 2 mmol (0.6 g) of (*S*)-dimethyl sulfonium-(*p*-tolylsulfinyl) methyl tetrafluoroborate in 10 mL of CH_2Cl_2. To this suspension was added 0.3 g of K_2CO_3 and the mixture stirred vigorously overnight. Filtration and evaporation of the solvent afforded a crude residue, which was purified by chromatography. Separation of the diastereomers was achieved by chromatography on silica (hexane/acetone 2:1).
10. (+)-(1*R*,2*R*,*Ss*)-*t*-Butyl-1-dimethylphosphono-2-*p*-tolylsulfinyl-2-methylcyclopropane-carboxylate (**4a**): $[\alpha]_D^{20}$ + 28.8 (*c* 3.9, acetone); mp 133–135 °C; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 22.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (s, 3H, CH_3–C(SO)), 1.45 (s, 9H, COC(CH_3)$_3$), 1.63 (dd, 1H, J_{HH} = 6.2, J_{PH} = 9.1 Hz), 1.93 (dd, 1H, J_{HH} = 6.2, J_{PH} = 16.6 Hz), 2.39 (s, 3H, $C_6H_4CH_3$), 3.84 (d, 3H, POCH_3, J_{PH} = 11.2 Hz), 3.96 (d, 3H, POCH_3, J_{PH} = 11.4 Hz), 7.29 and 7.50 (A_2B_2, 4H, $C_6H_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 9.15 (d, J_{CP} = 1.4 Hz), 20.1 (d, J_{CP} = 3.0 Hz), 21.3, 27.7, 35.7 (d, J_{CP} = 179.7 Hz), 47.8 (d, J_{CP} = 4.4 Hz), 53.4 (d, J_{CP} = 5.9 Hz), 53.8 (d, J_{CP} = 6.4 Hz), 83.2, 124.7, 129.6, 138.5, 141.6, 165.2 (d, J_{CP} = 4.3 Hz); MS (CI) *m*/*z* 403 [M+H]$^+$. Anal. Calcd. for $C_{18}H_{27}O_6PS$: C, 53.72, H, 6.76. Found: C, 53.84, H, 6.87.
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15. (+)-(1*S*,2*R*)-t-Butyl-2-methyl-2-dimethylphosphonocyclopropanecarboxylate **7a**: $[\alpha]_D^{20}$ + 19.4 (*c* 1.2, acetone) ^{31}P NMR (81 MHz, $CDCl_3$) δ: 30.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (ddd, 1H, *J* = 4.5, 7.75, J_{PH} = 9.37 Hz), 1.30 (d, 3H J_{PH} = 12.45 Hz, CH_3–CP), 1.47 (s, 9H, COC(CH_3)$_3$), 1.67 (ddd, 1H, J_{HH} = 4.5, 6.6, J_{PH} = 16.75 Hz)*, 1.72 (ddd, 1H, J_{HH} = 6.6, 7.75, J_{PH} = 9.33 Hz)*, 3.74 (d, 3H, POCH_3, *J* = 10.7 Hz), 3.76 (d, 3H, POCH_3, J_{PH} = 10.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 18.3 (*C*H_2C), 19.0 (d, J_{CP} = 194.0 Hz, CP), 21.8 (d, J_{CP} = 4.7 Hz), 27.9 (COC(CH_3)$_3$), 29.4 (d, J_{CP} = 2.9 Hz), 52.5 (d, J_{CP} = 6.3 Hz), 52.9 (d, J_{CP} = 6.2 Hz, POCH_3), 81.0 (*C*OC(CH$_3$)$_3$), 168.4 (d, J_{CP} = 7.1 Hz); MS (CI) *m*/*z* 265 [M+H]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{11}H_{22}O_5P$ [M+H]$^+$ 265.1205 Found 265.1211.
16. Cis-**9** (δ_P 28.8 ppm), was not separated in pure form.
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