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

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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

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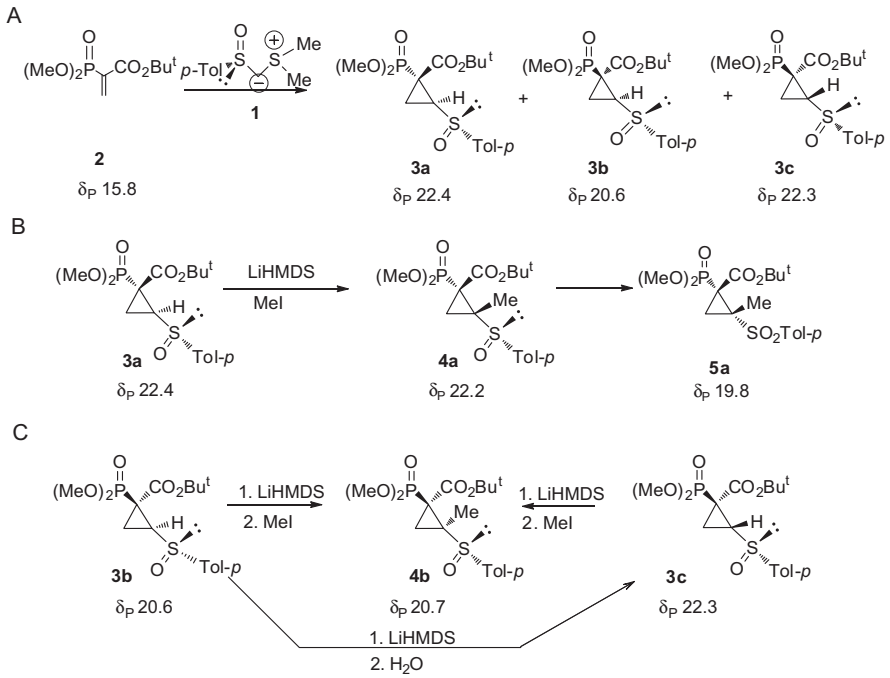

Scheme 1. Formation of cyclopropyl sulfoxides **3** and their subsequent alkylation.

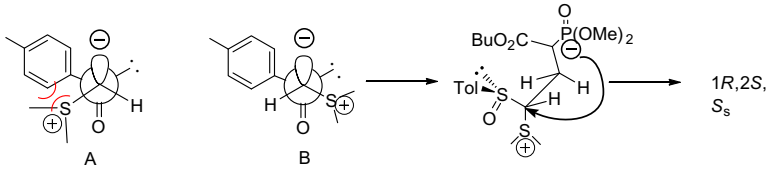

Figure 1.

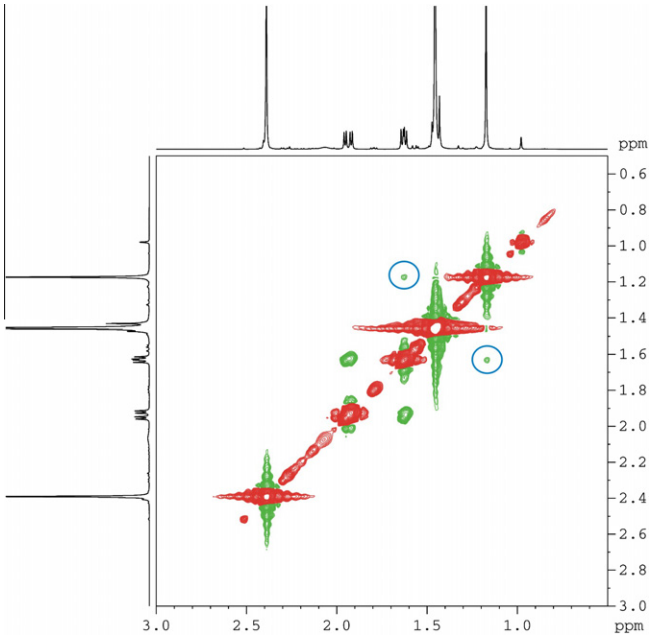

Figure 2. NOESY spectrum of **4a**. The key NOEs between the methyl group signals and H*trans* with respect to the phosphorus atom are marked with blue circles.

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.