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The Stereoselective Synthesis of Trisubstituted Olefins by the Reaction of (2-Phenylthiocyclobutyl)methyl Benzoates and Methyl Ethers with Silyl Nucleophiles

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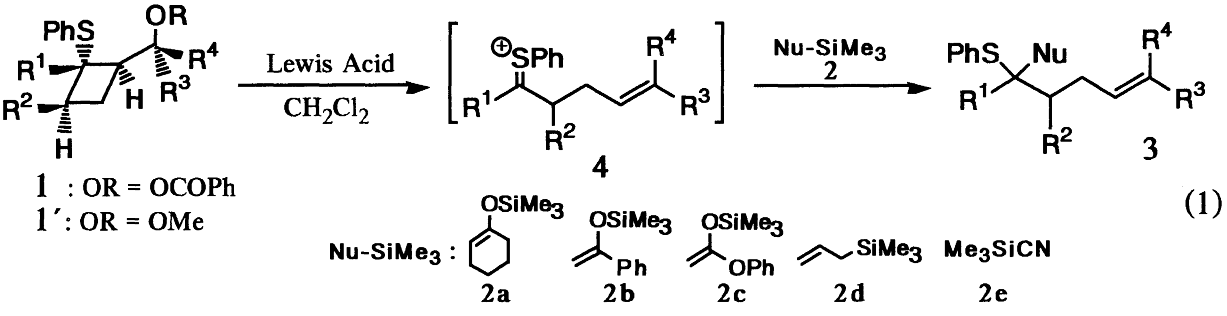
The Lewis acid-promoted reaction of 2-phenylthiocyclobutanemethanol derivatives with silyl nucleophiles gave the corresponding trisubstituted olefins with high stereoselectivity in good yields. It is suggested that the reaction proceeds via the thionium ion intermediate.

The carbon-carbon bond forming reactions via α-thio carbocations (thionium ions) have been extensively studied, and various methods for the generation of such active species, which included the treatments of thioacetals or α-chloro sulfides with Lewis acids,1) dimethyl(methylthio)sulfonium tetrafluoroborate,2) and trityl tetrafluoroborate,3) were reported. We also reported that thionium ions are formed by the protonation of alkenyl sulfides4) and the treatment of γ-phenylthioallyl and allenylstannanes with copper(II) or tin(IV) salt.5)

In the preceding paper,6) we showed that γ,δ-unsaturated ketones were obtained with high stereoselectivity by the reaction of methyl (2-phenylthiocyclobutyl)methyl ethers **1**′ with trimethylsilyl phenyl sulfide, followed by hydrolysis. It is reasonable to assume that the thionium ion intermediate **4** is formed on the fission of the carbon-carbon bond of cyclobutane ring in the above reaction. Therefore, we expected that trisubstituted olefins with various functional groups and carbon skeletons could be stereoselectively synthesized by the treatment of thionium ion intermediates **4** derived from 2-phenylthiocyclobutanemethanol derivatives **1** and **1**′ with carbon nuclephiles **2** (Eq. 1).



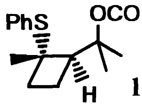
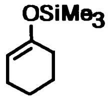
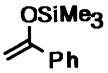
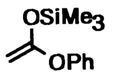
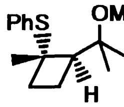
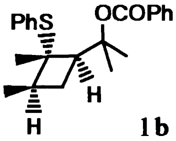
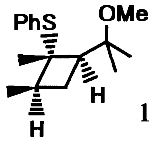
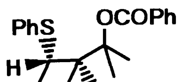
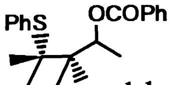
1 : OR = OCOPh
1′: OR = OMe

(1)

The starting materials **1** and **1**′ were stereoselectively synthesized in good yields by the reaction of 2-phenylthiocyclobutyl ketones with Grignard reagents in the presence of Ce(III) chloride6) or with MeLi, followed by the benzoylation or methylation.7)

First we studied the reaction of 2-phenylthiocyclobutanemethanol derivatives **1** and **1**′ with various silyl nucleophiles **2**. Although the homoallyl sulfide **3d-I** was obtained by the $TiCl_3(O^{i}Pr)$-promoted reaction of the methyl ether **1a**′ with allyltrimethylsilane (**2d**) (run 7, Table 1), it was found that the reaction of **1a**′ with the

Table 1. The reaction of silyl nucleophiles with (2-phenylthiocyclobutyl)methyl benzoates 1 and methyl ethers 1′a)

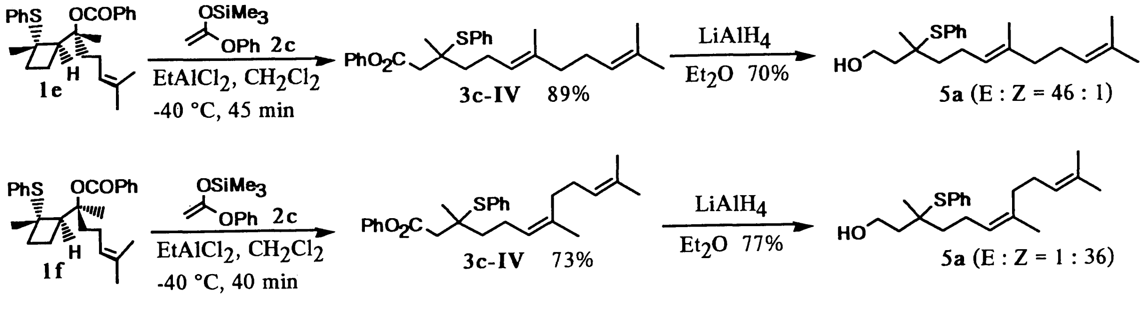
Run	Cyclobutane 1 or 1′	Me$_3$SiNu 2	Lewis Acid	Temp °C	Time h	Product 3b) (Yield/%)
1	 1a	 2a	(PhO)AlCl$_2$	-78	2	3a-I (55)c)d)
2		 2b	(PhO)AlCl$_2$	-78	1.5	3b-I (82)
3		 2c	EtAlCl$_2$	-40	1.5	3c-I (80)
4		 2d	EtAlCl$_2$	-78	7	3d-I (51)
5		Me$_3$SiCN 2e	Et$_2$AlCl	-78 - 0	3.5	3e-I (89)
6	 1a′	2a	TiCl$_3$(O^{i}Pr)	-78 - r.t.	48	none
7		2d	TiCl$_3$(O^{i}Pr)e)	-40	1	3d-I (64)
8	 1b	2c	EtAlCl$_2$	-40	1.5	3c-II (87)c)f)
9		2e	EtAlCl$_2$	-40	14	3e-II (78)c)
10	 1b′	2d	TiCl$_3$(O^{i}Pr)e)	-40	1	3d-II (46)c)g)
11	 1c	2b	(PhO)AlCl$_2$	-40	2	3b-II (73)
12		2c	EtAlCl$_2$	r.t.	0.25	3c-III (89)
13		2e	EtAlCl$_2$	r.t.	15.5	3e-III (77)
14	 1d	2c	AlCl$_3$	-78 - r.t.	19	no reaction

a) All reactions were performed with a similar procedure as described in the text, unless otherwise noted. b) The structures of these compounds were supported by IR and NMR spectra. c) Obtained as a mixture of diastereomers. d) The diastereomers were in the ratio 1.9 : 1. e) 1.2 equiv. of TiCl$_3$(O^{i}Pr) were used. f) The diastereomers were in the ratio 2.7 : 1. g) The diastereomers were in the ratio 1.6 : 1.

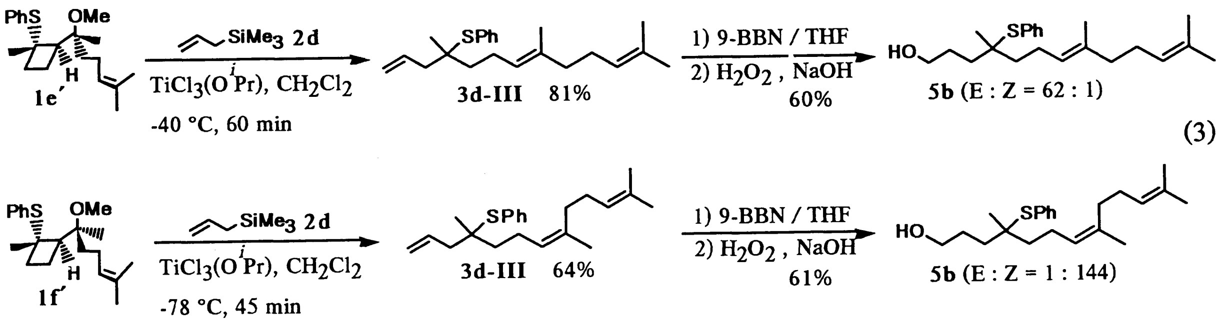
enol silyl ether **2a** was complicated and the expected product **3a-I** was not formed (run 6). This difficulty, however, was overcome by the use of the corresponding benzoate **1a** (runs 1 and 2). Using suitable Lewis acids, (2-phenylthiocyclobutyl)methyl benzoates **1a**, **1b**, and **1c** reacted with silyl nucleophiles to give the corresponding olefinic compounds **3** in good yields. On the other hand, no reaction was observed when the secondary alcohol derivative **1d** was treated with the ketene silyl acetal **2c** in the presence of $AlCl_3$, $EtAlCl_2$, or $TiCl_3(O^iPr)$ (run 14).

The two possible pathways can be supposed for the present reaction. One is a two-step reaction via the thionium ion intermediate **4**, which we have expected. The other is a concerted reaction in which new carbon-carbon bond formation and cleavage of the cyclobutane ring take place simultaneously. It was found that the products **3** were obtained as mixtures of diastereomers in the reactions of cyclobutanemethanol derivatives **1b** and **1b′**, which had a substituent at the position β to the phenylthio group (runs 8, 9, and 10). Since it is reasonable to assume that the concerted reaction would be highly stereospecific process, these results suggest that the present reaction proceeds via the thionium ion intermediate **4**.

The typical experimental procedure is as follows: To a CH_2Cl_2 (6.5 ml) solution of 1-phenoxy-1-trimethylsiloxyethene (**2c**) (409 mg, 1.97 mmol) and (1R*, 2S*)-1-(1-benzoyloxy-1-methylethyl)-2-methyl-2-phenylthiocyclobutane (**1a**) (446 mg, 1.31 mmol) was added a hexane solution of $EtAlCl_2$ (2.1 ml, 1.97 mmol) dropwise at -40 °C. After being stirred for 1.5 h, the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ and the mixture was filtered through celite. The organic materials were extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica-gel chromatography (hexane : AcOEt = 95 : 5), and phenyl 3,7-dimethyl-3-phenylthio-6-octenoate (**3c-I**) (373 mg, 80%) was isolated.



(2)



(3)

The synthetic utility of the present reaction for the stereoselective preparation of trisubstituted olefins was demonstrated in the following experiments. The cyclobutylmethyl benzoate **1e** and its epimer **1f** were treated with the ketene silyl acetal **2c** to give the (*E*)- and (*Z*)-dienyl esters **3c-IV**, respectively (Eq. 2). Similarly, the reactions of the methyl ether **1e′** and its epimer **1f′** with allyltrimethylsilane (**2d**) gave the stereoisomers of triene **3d-III** with high selectivity (Eq. 3). The stereoisomeric purity of these compounds was determined by the HPLC analysis[8] after they were transformed to the hydroxy sulfides **5**.

The phenylthio group of **3** can be removed by reductive desulfurization or β-elimination after **3** are converted to the corresponding sulfoxides or sulfones.[9] Furthermore, 2-phenylthioalkanenitriles **3e** obtained by the reaction of **1** with trimethylsilyl cyanide can be transformed to 2,2-disubstituted alkanenitriles by the reductive lithiation using tributylstannyllithium followed by alkylation.[10] Therefore, it should be noted that the present reaction provides a versatile method for the stereoselective synthesis of trisubstituted olefins possessing a variety of functional groups.

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6) T. Fujiwara, T. Iwasaki, and T. Takeda, *Chem. Lett.*, **1993**, 1321.
7) The starting material **1a** was prepared by the reaction of methyl (1R*, 2S*)-2-methyl-2-phenylthio-1-cyclobutyl ketone with MeLi (1.5 equiv. / Et_2O / -20 °C / 92%) and the benzoylation of the resulting alcohol (*n*-BuLi, 1.1 equiv. / benzoyl chloride, 1.3 equiv. / THF / 0 °C - r.t. / 97%). In a similar manner, **1b** and **c** were prepared from the corresponding *trans*-2-phenylthiocyclobutyl ketones. The yields of each transformations were as follows; MeLi addition (**1b**: 93%, **1c**: 95%), benzoylation (**1b**: 95%, **1c**: 98%). The methyl ethers **1a′** and **1b′** were also obtained by the methylation of the alcohols (NaH, 4 equiv. / MeI, 3 equiv. / THF / 0 °C - r.t.) in 95% yields, respectively. The secondary benzoate **1d** was synthesized by the reduction of methyl (1R*, 2S*)-2-methyl-2-phenylthio-1-cyclobutyl ketone ($LiAlH_4$, 0.5 equiv. / Et_2O / 0 °C / 88%), followed by the benzoylation (93%). The benzoates **1e** and **1f** were prepared by the benzoylation of the corresponding alcohols[6] in 95% and 85% yields, respectively.
8) The stereoisomeric mixture of authentic hydroxy sulfide **5a** was synthesized from a mixture of geranylacetone and nerylacetone (6 : 4). The stereoisomeric mixture of ketones was transformed to the thioacetal with Me_3SiSPh,[a] which was treated with **2c** (1.5 equiv.) in the presence of $EtAlCl_2$ (1.1 equiv. / CH_2Cl_2 / 0 °C - r.t. / 1.3 h) to give **3c-IV** in 19% yield. The ester **3c-IV** was reduced with $LiAlH_4$ (0.5 equiv. / Et_2O / 0 °C) to give **5a** in 77% yield. The authentic hydroxy sulfide **5b** was also prepared by the reaction of the thioacetal with **2d** (2 equiv.) in the presence of $SnCl_4$ (1.1 equiv. / CH_2Cl_2 / -78°C / 40 min / 84%), followed by the hydroboration (9-BBN, 1.1 equiv. / THF / r.t. / 24 h) -oxidation in 64% yield. a) D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).
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