

The Oxidative Michael Reaction. A Highly Diastereoselective
Synthesis of 5-Oxocarboxylic Acid Derivatives

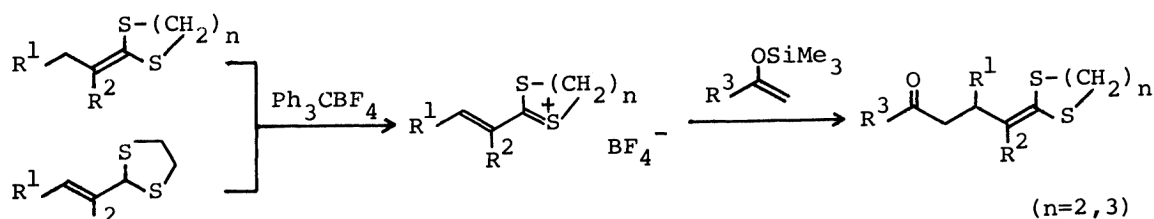
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Methyldiphenylsilyl enol ethers react with an allylic cation
stabilized by two sulfur atoms in a highly anti-selective manner to
afford 5-oxocarboxylic acid derivatives.

The Michael reaction¹⁾ is a fundamental method for carbon-carbon bond formation and, recently, growing interests have been paid to investigate the diastereoselectivity of this addition reaction.²⁻⁶⁾ However, at the present time, there are much less studies on the diastereoselection of the Michael reaction (1,4-addition) compared with that of the aldol type reaction (1,2-addition).⁷⁾ Concerning the stereochemical control of the Michael reaction, Yamaguchi and coworkers⁴⁾ have demonstrated that lithium enolates of esters and amides react with α,β -unsaturated esters in a highly diastereoselective manner, and Seebach and coworkers⁵⁾ have shown highly syn-selective addition of enamines to nitroolefins. Further, it was found in our laboratory that the trityl perchlorate catalyzed Michael reaction of silyl enol ethers to α,β -unsaturated ketones forming 1,5-diketones proceeds in a good anti-selectivity.⁶⁾

In the previous paper,⁸⁾ we have shown that ketene dithioacetals or α,β -unsaturated aldehyde ethylene dithioacetals can be oxidatively coupled with silylated carbon nucleophiles through the intermediate salts formed by the hydride abstraction of the acetals with trityl tetrafluoroborate (Scheme 1). This reaction is considered to be equivalent to the Michael reaction because a ketene dithioacetal function behaves as the Michael acceptor, synthetically equivalent to an ester function. Consequently, we turned our attention to investigate the diastereoselection of this oxidative Michael reaction and, in this communication, we wish to describe highly anti-selective coupling between silyl enol ethers and an allylic cation stabilized by two adjacent sulfur atoms.



Scheme 1.

The reaction between 2-styryl-1,3-dithiolan-2-ylum salt (1)⁸ and 1-siloxycyclohexene (2) was examined in detail. After the screening of the reaction conditions, particularly in respects of solvents, the substituents on the silicon atom of the silyl enol ether 2, and the counter anion of the salt 1, it was found that diastereoselectivities are fairly dependent on the substituents on the silicon of the enolate 2 (see Table 1). For example, almost all the silyl enol ethers 2 gave anti-adduct 3 as a major diastereomer,⁹ while syn-adduct 4 was predominant from 1-*t*-butyldimethylsiloxycyclohexene (2c) with low selectivity (entry 3). Among the silyl enol ethers examined, methyldiphenylsilyl enol ether 2e gave the highest anti-selectivity and it is noted that trifluoromethanesulfonate anion is the most suitable as the counter anion of the salt 1 (entry 6).

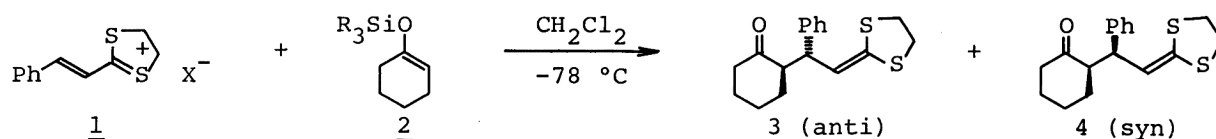


Table 1. Stereoselectivity in the Reaction of 1 with 2

Entry	R_3Si	X^-	Yield/%	anti : syn ^{a)}
1	Me_3Si (<u>2a</u>)	BF_4^- (<u>1a</u>)	84	65 : 35 ^{b)}
2	Et_3Si (<u>2b</u>)	BF_4^-	89	78 : 22
3	$t\text{-BuMe}_2\text{Si}$ (<u>2c</u>)	BF_4^-	86	40 : 60
4	PhMe_2Si (<u>2d</u>)	BF_4^-	88	84 : 16
5	Ph_2MeSi (<u>2e</u>)	BF_4^-	83	88 : 12
6	Ph_2MeSi	CF_3SO_3^- (<u>1b</u>)	74	91 : 9
7	Ph_3Si (<u>2f</u>)	BF_4^-	84	85 : 15 c)

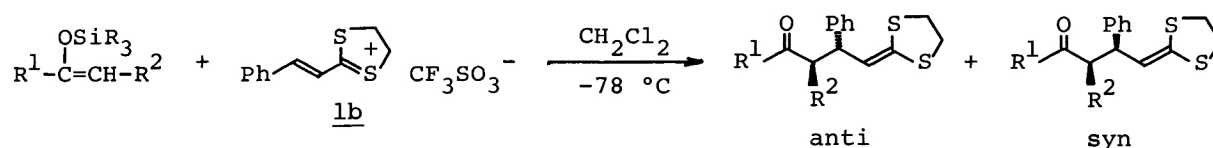
a) Determined by HPLC analysis unless otherwise stated.

b) Determined by NMR analysis.

c) Reaction temperature $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$.

Thus, the reaction with various silyl enol ethers or a ketene silyl acetal was carried out by using 2-styryl-1,3-dithiolan-2-ylum trifluoromethanesulfonate (1b)¹⁰ and the results are summarized in Table 2. As can be seen in Table 2, a ketene silyl acetal also reacts with the salt 1b in a good selectivity (entry 6). However, in the case of 3-siloxy-2-pentene almost no selectivity was realized in the corresponding adduct (entries 4,5).

The following experimental procedure is representative: To a stirred suspension of 2-styryl-1,3-dithiolan-2-ylum trifluoromethanesulfonate (1b, 59 mg, 0.17 mmol) in 1 ml of dichloromethane is added a dichloromethane (2 ml) solution of 1-methyldiphenylsiloxycyclohexene (2e, 103 mg, 0.35 mmol) at -78°C . The reaction mixture is stirred at the same temperature for 31 h. The reaction is worked up by adding aqueous sodium hydrogencarbonate and organic materials are extracted with dichloromethane. After the organic layer is dried and evaporated, the residue is purified by thin layer chromatography to give 2-[2-(2-oxocyclohexyl)-2-phenylethylidene]-1,3-dithiolane (3 and 4) in 74% yield (38 mg, 0.12 mmol). The HPLC analysis indicates that diastereomer ratio is 91:9.⁹

Table 2. Stereoselective Preparation of Keto Ketene Dithioacetals^{a)}

Entry	Silyl Enol Ether	Yield/%	anti : syn ^{b)}
1		74	91 : 9
2		86	92 : 8
3		74	92 : 8
4		90	53 : 47 c,d)
5		85	51 : 49 c,e)
6		83	94 : 6

a) All new compounds gave satisfactory spectroscopic data.

b) Determined by HPLC analysis.

c) The tetrafluoroborate salt 1a was used instead of 1b.

d) Silyl enol ether prepared in THF according to Ref. 11 was used.

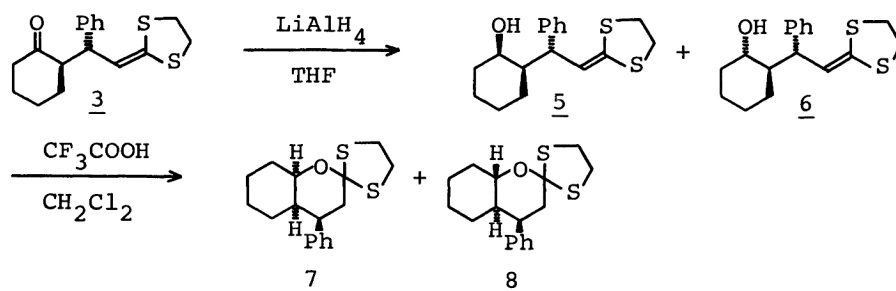
e) Silyl enol ether prepared in THF-HMPA according to Ref. 11 was used.

The Michael reaction of forming 5-oxocarboxylic acid derivatives from the ketone enolate equivalents and α,β -unsaturated ester equivalents is scarcely carried out under the basic^{2,4)} or even acidic conditions.^{3,6,12)} On the other hand, this is the first example of this type of reaction in which 5-oxocarboxylic acid derivatives are smoothly obtained diastereoselectively according to the present oxidative Michael reaction.

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- 9) Stereochemistry of the major product was assigned as follows: Lithium aluminum hydride reduction of 3 gave two diastereomeric hydroxy ketene dithioacetals 5 and 6, which were easily cyclized in the presence of a catalytic amount of trifluoroacetic acid to give lactone dithioacetals 7 and 8 (81%), and the structure of each compound is determined by 400 MHz NMR spectroscopy. We are grateful to Eizai Co., Ltd. for the measurements of 400 MHz NMR spectroscopy.



- 10) 2-Styryl-1,3-dithiolan-2-ylum trifluoromethanesulfonate (1b) is prepared as follows: Trityl chloride (3.7 mmol) and silver trifluoromethanesulfonate (3.6 mmol) are mixed in dichloromethane at room temperature and the resulting precipitate is removed by filtration under argon atmosphere. To this trityl trifluoromethanesulfonate solution is added an equimolar amount of 2-styryl-1,3-dithiolane and the mixture is refluxed for 1 h. The desired salt precipitates by cooling to -78°C and dry ether is added. The mixture is warmed to 0°C and the orange crystalline material is filtered and washed with dry ether to give 1b in 82% yield.
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