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# Diastereoselective [3 + 2] Cycloaddition of Methyl 2-Phenylthiocyclopropyl Ketone with Enol Silyl Ethers: Synthesis of Functionalized Cyclopentanes.

Yoshiaki Horiguchi, Ichiro Suehiro, Ayumi Sasaki, and Isao Kuwajima*

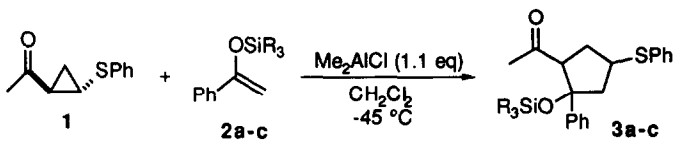
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

*Abstract:* Dimethylaluminum chloride-mediated [3 + 2] cycloaddition of methyl 2-phenylthiocyclopropyl ketone and enol TBDPS or TIPS ethers proceeds highly diastereoselectively to afford functionalized cyclopentanes in good yields.

Cycloaddition of three-carbon units is a highly efficient method for formation of odd-numbered carbocycles such as cyclopentane and cycloheptane. In particular, much efforts have been focused on [3 + 2] cycloaddition.[1] We recently reported the [3 + 2] cycloaddition of 2-alkoxycyclopropyl carbonyl compounds with enol silyl ethers *via* the 1,3-zwitterionic three-carbon intermediate.[2,3] Though the reaction provides functionalized cyclopentanes in good yields, it suffers from poor diastereoselectivity. This paper describes highly diastereoselective [3 + 2] cycloaddition of methyl 2-phenylthiocyclopropyl ketone (**1**) and enol t-butyldiphenylsilyl (TBDPS) or triisopropylsilyl (TIPS) ethers.

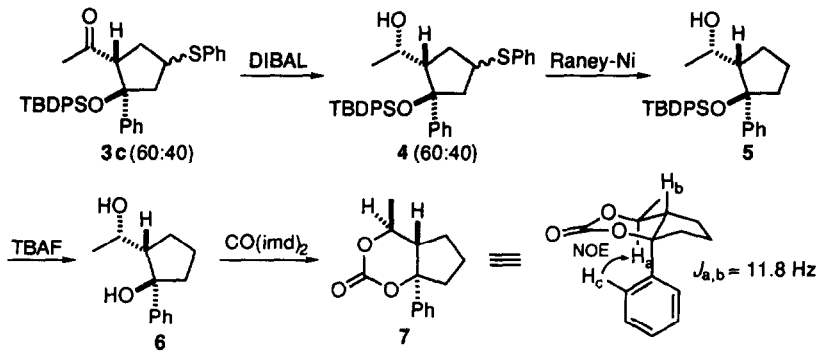
Methyl 2-phenylthiocyclopropyl ketone[4] (**1**) was found to react with enol silyl ethers[5] under the influence of dimethylaluminum chloride in dichloromethane at low temperature to afford [3 + 2] cycloadducts in good yields. The key finding for the accomplishment of the high diastereoselectivity is that steric bulk of the silyl groups in the enol silyl ethers significantly influences the stereochemical outcome of this cycloaddition. In cycloaddition of **1** and enol silyl ethers of acetophenone **2a-c** (Table 1), bulkier TBDPS and TIPS ethers predominantly afforded two of the diastereomers, while t-butyldimethylsilyl (TBS) ether gave a mixture of four diastereomers.

**Table I.** Effect of the Silyl Group on the Stereoselectivity of the [3 + 2] Cycloaddition




| entry | $R_3Si$ | enol silyl ether | product | yield (%) | diastereomeric ratio |
|---|---|---|---|---|---|
| 1 | TBS | **2a** | **3a** | 76 | 55:21:14:10 |
| 2 | TIPS | **2b** | **3b** | 66 | 68:28:2:2 |
| 3 | TBDPS | **2c** | **3c** | 95 | 60:40:0:0 |

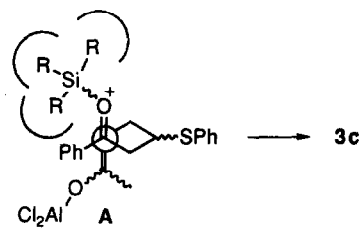
**Scheme** I. Structure Determination of **3c**




3c (60:40) 4 (60:40) 5 6 7

For the structure determination, product **3c**, without separating the diastereomers (60:40), was converted to the bicyclic carbonate **7** as shown in Scheme 1. That DIBAL reduction, which proceeded with complete facial selectivity giving a mixture of two diastereomeric alcohols **4** (60:40), and subsequent desulfurization with Raney-Ni afforded a single diastereomer **5** revealed **3c** to be an epimeric mixture at the carbon adjacent to the phenylthio group. From $^1$H NMR study of the carbonate **7**, the relative stereochemistry of the aldol portion of **3c** and, at the same time, the facial selectivity of the DIBAL reduction were determined. The large coupling constant ($J_{a,b}$ = 11.8 Hz) and the observed NOE from $H_c$ to $H_a$ mean that $H_a$, $H_b$, and the phenyl group are axially oriented as depicted. Namely, the stereochemical relationship of the aldol portion is completely controlled as *trans* during the five-membered ring cyclization.

Although the details of the reaction mechanism is unclear at present, both the steric repulsion between the enormously bulky silyl group and the enolate moiety and the likely cationic character of the transition state would cooperatively favor such an extended transition state **A** to lead to the high degree of the *trans* aldol selectivity.

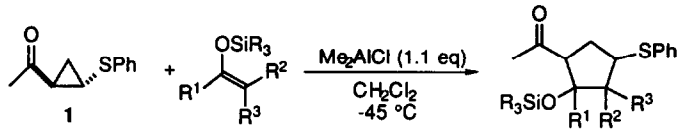


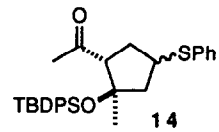
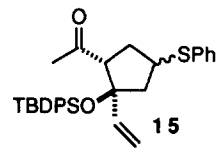
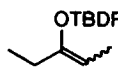
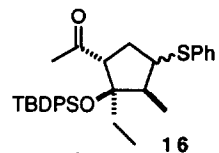
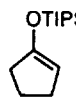
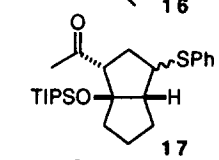
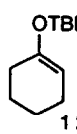
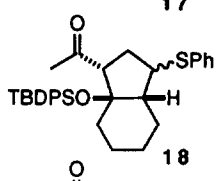
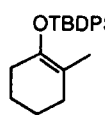
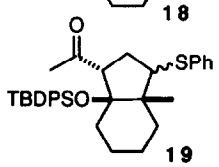

Several types of enol TBDPS or TIPS ethers were reacted with **1** and the results are summarized in Table 2.[6] The [3 + 2] cycloaddition nicely proceeds regardless of the substitution pattern, even with the tetra-substituted one, and, in general, predominantly affords the *trans* aldol. In the reaction of **9**, formation of [3 + 4] cycloadduct was not observed (entry 2). It is noteworthy that the additional stereocenter is also controlled in the case of the acyclic tri-substituted one (entry 3).[7] The cyclic enol silyl ether predominantly yields the *cis*-fused bicyclic product. Especially, exclusive formation of **19** is remarkable (entry 6).[8]

Thus, the [3 + 2] cycloaddition reaction, except the phenylthio group, stereoselectively produces highly substituted cyclopentane derivatives. Since a phenylthio group serves as a versatile clue for further synthetic

transformations for which the original stereochemistry is, in most cases, not important, the present method is of vast synthetic use. In addition, the principle of the *trans* aldol formation caused by the bulkiness of the silyl group might be efficient in other types of cycloaddition reactions.

**Table II.** Diastereoselective [3 + 2] Cycloaddition of 1 and Enol Silyl Ethers




| entry | enol silyl ether | yield (%) | major isomer | major : the other isomers |
|---|---|---|---|---|
| 1 |  **8** | 76 |  **14** | 96:4 |
| 2 |  **9** | 61 |  **15** | 81:19 |
| 3 |  **10** | 87 |  **16** | 84:16 |
| 4 |  **11** | 89 |  **17** | 93:7 |
| 5 |  **12** | 62 |  **18** | 56:44 |
| 6 |  **13** | 93 |  **19** | >99:<1 |

## References and Notes

(1) Reviews on [3 + 2] cycloadditions for five-membered carbocycle formation: (a) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Little, R. D. *Comprehensive Organic Synthesis*; Trost, B. M.;

Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 239-270. (c) Chan, D. M. T. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 271-314.

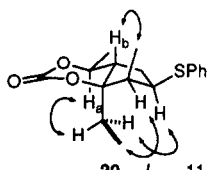
(2) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771.

(3) Related studies on the synthetic use of vicinally donor-acceptor substituted cyclopropanes *via* Lewis acid mediated retro-aldol type ring opening: (a) A review: Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. (b) Reissig, H.-U.; Bohm, I. *Tetrahedron Lett.* **1983**, *24*, 715. Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139. (c)Shimada, S.; Saigo, K.; Hashimoto, Y.; Maekawa, Y.; Yamashita, T.; Yamamoto, T.; Hasegawa, M. *Chem. Lett.* **1991**, 1475. Saigo, K.; Shimada, S.; Hasegawa, M. *Chem. Lett.* **1990**, 905. Saigo, K.; Shimada, S.; Hashimoto, Y.; Nagashima, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1101. Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093. Saigo, K.; Shimada, S.; Hashimoto, Y.; Hasegawa, M. *Chem. Lett.* **1989**, 1293.

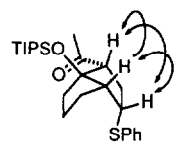
(4) Preparation of **1**; Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1982**, *47*, 748. The stereochemistry of **1** seems not to be essential for this reaction; see ref 2.

(5) Enol trimethylsilyl ethers fail to react with **1** under the similar reaction conditions presumably due to rapid silicon-aluminum exchange. The aluminum enolate seems not to participate in the cycloaddition.

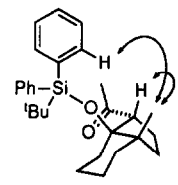
(6) The stereochemistry of the major products in entries 3, 4, and, 6, was determined by $^1$H NMR studies on **20**, derived from **16** (1. DIBAL reduction, 2. separation of one of the epimers by silica gel column chromatography, 3. desilylation with TBAF, 4. cyclic carbonate formation with $CO(imd)_2$), **17** (one of the epimers separated by silica gel column chromatography), and **21** derived from **19** (desulfurization with Raney-Ni). The diagnostic NOEs and coupling constant for the structure determination are shown below. For **17**, *cis* relationship of the ring system was presumed on the basis of the general *cis* preference for such a five-membered ring annulation on a five-membered ring. The stereochemistry of the other major products was assigned on the analogy of these cases.




**20** $J_{a,b}$ = 11.4 Hz




**17**




**21**

(7) The *cis* relationship between the siloxy group and the vicinal methyl group in the major isomer suggests that the silyl oxonium ion is *transoid* to the forming five-membered ring in the transition state (cf. **A**) because the alternative *cisoid* silyl oxonium ion would strongly disfavor the vicinal *cis* methyl group. The β-orientation of the methyl group should be favored to prevent a 1,3-diaxial type repulsion with the enolate moiety.

(8) The sharp contrast between entries 5 and 6 is striking. Though the stereochemistry of the products obtained in entry 5 has not been determined, the aldol moiety should be highly controlled as *trans* by analogy of other cases. Therefore, it is likely that *trans* fused isomers formed to some extent. The methyl group in **13** is supposed to play the following two roles for the high *cis* selectivity during the five-membered ring cyclization; 1) it sterically disfavors the *trans* cyclization, 2) it cancels the equatorial preference of the enolate side chain on the six-membered ring in the transition state in entry 5 (the enolate side chain must be necessarily equatorial for *trans* cyclization).

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