CHEMISTRY LETTERS, pp. 941-944, 1990.

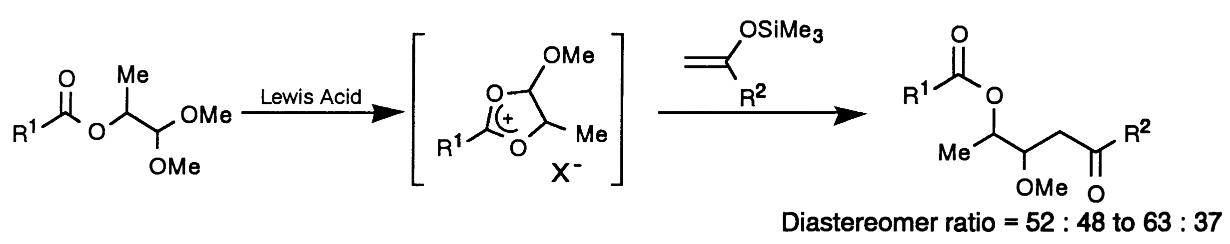
Anti-Cram Selective Reaction of α-Sulfenyl Acetals with Silylated Carbon Nucleophiles

Kazuhiko SAIGO,* Kazuaki KUDO, Yukihiko HASHIMOTO,
Hiroki KIMOTO, and Masaki HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

α-Sulfenyl acetals reacted smoothly with silylated carbon nucleophiles such as silyl enol ether, ketene silyl acetal, and allylsilane in the presence of a catalytic amount of Lewis acid mainly to give *anti*-Cram adducts with high diastereoselectivity by the asymmetric induction of the α-sulfur atom of the acetals.

Acetals are activated by Lewis acids and react with fairly weak nucleophiles such as silyl enol ether, ketene silyl acetal, and allylsilane to give the corresponding cross-coupling adducts.[1] Diastereoselective variant of such reactions has been also reported.[2] But, asymmetric induction of substituted acetals[3] are not well investigated, compared to aldehydes.[4] In this paper, we wish to report highly 1,2-*anti* selective reaction of α-sulfenyl acetals with silylated carbon nucleophiles.

Recently, 4-methoxy-1,3-dioxolan-2-ylium ion was found in our laboratory to be generated *in situ* by the reaction of 2,2-dimethoxyethyl ester and Lewis acid.[5] In the course of the study on the synthetic application of this unique cation, we found that the cation reacted with silyl enol ethers to yield aldol-type adducts. Acyclic stereocontrol in aldol reaction using neighboring group participation has not been reported and is considered to be new methodology. Then, 1-alkyl-2,2-dimethoxyethyl ester (α-acyloxy acetal) was designed as a substrate, which was expected to bring about 1,2-asymmetric induction. But, the diastereoselectivity was rather low for the reaction of 2-acyloxypropanal dimethyl acetal with silyl enol ethers. This may be due to the rapid conformational and/or configurational change of the intermediate.



The neighboring group participation of sulfenyl group, which results in the formation of episulfonium ion, is a common phenomenon,[6] and episulfonium ion is expected to be more conformationally rigid than 1,3-dioxolan-2-ylium ion. According to the considerations, α-sulfenyl acetal was chosen as a substrate. The reaction of 2-(phenylthio)propanal dimethyl acetal with trimethylsilyl enol ether of pinacolone in the presence of tin(IV) chloride was first of all attempted, and the corresponding aldol was obtained in 85% yield with

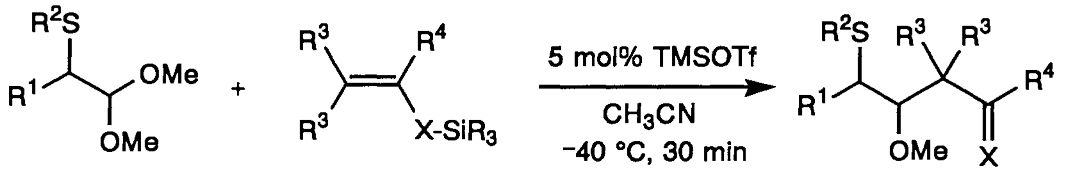
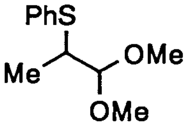
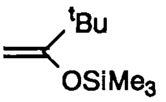
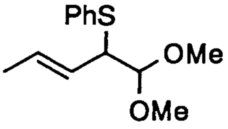
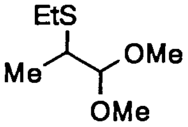
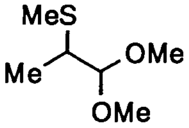
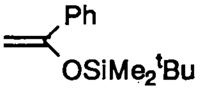
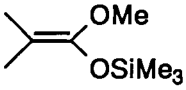
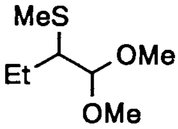
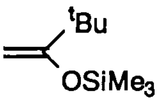
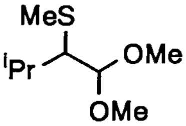
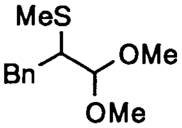
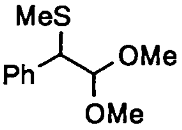


Table 1. Reactions of α-Sulfenyl Acetals with Silylated Carbon Nucleophiles

Entry	Acetal	Nucleophile	Yield/%9)	*Anti* : *Syn*8)
1			92	92 : 8
2			97	89 : 11
3			88	92 : 8
4			83	95 : 5
5			87	94 : 6
6			88	>99 : 110)
7a)			57	79 : 21
8			78	98 : 2
9			60	59 : 41
10			86	90 : 10
11			80	59 : 41

a) 10 mol% TMSOTf was used.

satisfactory diastereomer ratio of *anti* / *syn* = 87 : 13.[7,8] Then, reaction conditions were optimized for temperature (-95 to 0 °C), solvent (dichloromethane, toluene, acetonitrile, nitromethane), and Lewis acid (tin(IV) chloride, titanium(IV) chloride, boron trifluoride etherate, trimethylsilyl trifluoromethanesulfonate). The best result was realized when the reaction was carried out in acetonitrile at -40 °C using a catalytic amount of trimethylsilyl trifluoromethanesulfonate. The results for the reactions of various acetals with silylated carbon nucleophiles are summarized in Table 1.

Representative reaction procedure is as follows: To a stirred solution of 2-(methylthio)propanal dimethyl acetal (72.8 mg, 0.48 mmol) and 3,3-dimethyl-2-trimethylsilyloxy-1-butene (99.6 mg, 0.58 mmol) in acetonitrile (4 ml) was added an acetonitrile solution of trimethylsilyl trifluoromethanesulfonate (0.1 mol l^{-1}, 0.24 ml, 0.024 mmol) at -40 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at that temperature and quenched by adding saturated aqueous sodium hydrogencarbonate (3 ml). Organic materials were extracted with dichloromethane (2 × 5 ml), and the combined organic layers were dried over sodium sulfate. After evaporation of the solvents, the residue was purified by silica gel column chromatography (eluent : ether / hexane = 1 / 30) to give 5-methoxy-2,2-dimethyl-6-methylthio-3-heptanone (87.4 mg, 83%). Capillary gas chromatographic analysis showed the diastereomer ratio of 95 : 5.

For the mechanistic aspects of this reaction, the following phenomena were observed. 1) The reaction proceeded very rapidly even at -78 °C in dichloromethane. 2) Diastereoselectivity was not so much affected by the kind of Lewis acid. These phenomena are presumably due to the effect of α-sulfenyl group, that is, the lone pair of the sulfur strongly assists the release of methoxyl group and Lewis acid may be only a trigger of the reaction. Consequently, the intermediate cation, episulfonium ion, may be formed and its structure determines the stereochemical outcome. If the episulfonium ion is attacked by a nucleophile from backside of the sulfur, the intermediate cation should have the structure shown in Fig. 1, in which R^1 and the methoxyl group are oriented in *cis* configuration.

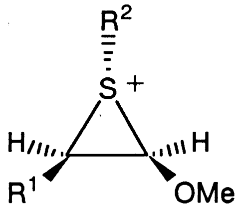


Fig. 1.

Such episulfonium ion must be labile because the nucleophilicity of the reagent is correlative with both yield and diastereoselectivity (Table 1, entries 4 - 7). When R^1 is isopropyl or phenyl group, only low diastereoselectivity was observed. This fact is also rationalized by assuming the intermediate depicted in Fig. 1, i. e., steric repulsion of R^1 and the methoxyl group leads to instability of the intermediate.[11] But effect of substituent on sulfenyl group remained uncertain (Table 1, entries 1,3,4).

Detailed mechanism of this reaction and asymmetric induction of other acetals are now under investigation in this laboratory.

References

1) T. Mukaiyama and M. Murakami, *Synthesis*, **1987**, 1043.

2) S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron*, **44**, 4259 (1988); T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, **1984**, 1759; H. Sakurai, K. Sasaki, and A. Hosomi, *Bull. Chem. Soc. Jpn.*, **56**, 3195 (1983); A. Hosomi, M. Ando, and H. Sakurai, *Chem. Lett.*, **1986**, 365; K. Ishihara, H. Yamamoto, and C. H. Heathcock, *Tetrahedron Lett.*, **30**, 1825 (1989).

3) Recently, diastereoselective reaction of β-silyloxyalkanal diselenoacetal was reported: R. W. Hoffmann and M. Bewersdorf, *Tetrahedron Lett.*, **31**, 67 (1990).

4) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); M. Shimagaki, H. Takubo, and T. Oishi, *Tetrahedron Lett.*, **26**, 6235 (1983).

5) Y. Hashimoto, S. Machida, K. Saigo, J. Inoue, and M. Hasegawa, *Chem. Lett.*, **1989**, 943.

6) Neighboring group participation of sulfenyl group is so strong that even nitro group acts as a leaving group; A. Kamimura, H. Sasatani, T. Hashimoto, and N. Ono, *J. Org. Chem.*, **54**, 4998 (1989).

7) A report including the preparation of β-methoxy-γ-(phenylthio)ketones has been appeared, but the stereochemistry of the products was not reported; T. Sato, M. Inoue, S. Kobara, J. Otera, and H. Nozaki, *Tetrahedron Lett.*, **30**, 91 (1989).

8) The diastereomer ratio was determined by 400 MHz ^{1}H-NMR and/or capillary gas chromatography. In order to elucidate the stereochemistry of the product, single crystal X-ray analysis was carried out for the purified main isomer of 5-methoxy-2,2-dimethyl-6-phenylthio-7-nonen-3-one (Table 1, entry 2), and it was proved to be *anti* isomer (the crystal data: $C_{18}H_{26}O_2S$, MW = 306.5, space group $P2_1/c$, a = 9.156 Å, b = 15.782 Å, c = 12.458 Å, β = 98.5°, V = 1780.4 Å^3, Z = 4, D_{calc} = 1.147 g cm^{-1}, R = 0.07). All of *anti* and *syn* isomers showed precisely different chemical shift each other for the methyl in methoxyl group (400 MHz ^{1}H-NMR). Then, the stereochemistry of the products was determined on the basis of the correlation of the chemical shift.

9) All products gave satisfactory ^{1}H-NMR and IR spectra.

10) Relative configuration is uncertain because only one isomer was observed.

11) The reaction of 2-benzyloxypropanal dimethyl acetal with trimethylsilyl enol ether of pinacolone gave rather low diastereoselectivity (diastereomer ratio = 75 / 25). This fact and the correlation between the bulkiness of R^1 and the diasereoselectivity can not be interpreted by assuming an acyclic intermediate, but a cyclic one. However, the reason for the preferencial formation of the *cis* intermediate is not clear.

(Received March 15, 1990)