Mechanistic Insight into Allylmetal-Thioacetal Reactions Employing 2-Acetoxy-2-phenylacetaldehyde Thioacetals

Tsuneo Sato, Junzo Otera,* and Hitosi Nozaki

Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700, Japan

Received May 25, 1990

The mechanism of allylmetal-thioacetal reactions has been investigated by using 2-acetoxy-2-phenylacetaldehyde thioacetals in the presence of trimethylsilyl triflate. The results unamibguously revealed the occurrence of both S_N1- and S_N2-type reactions. Upon treatment with the monothioacetal 1, allylsilane **3a** and -germane **3b** provided allylation product **5** in a ca. 80:20 syn-anti ratio irrespective of the stereochemistry of 1. With trimethyl- and tributylallyltin (**3c** and **3d**), the syn product **5a** was obtained from the *u*-monothioacetal and the anti product **5b** from *l*-monothioacetal. These results indicate that the reactions of less nucleophilic silicon and germanium compounds proceed through an S_N1 mechanism while organotin compounds react through an S_N2-type mechanism. Reaction of the dithioacetal **2** furnished predominantly the syn product **6** with both allylsilane and -stannane, indicative of an S_N2-type mechanism. These results reflect the inferior ability of a sulfenyl group to stabilize an α-carbocation, relative to a methoxyl group.

Introduction

In connection with the extensively studied condensations of carbonyls and acetals with organometallic nucleophiles, considerable attention has been paid to the corresponding thioacetal reactions.[1,2] They provide useful means of carbon-carbon bond formation, which complement the established carbanion methodology that is effective for the incorporation of electrophiles.[3] Dithioacetals are synthetically useful since they are tolerant of various reaction conditions and, upon nucleophilic displacement, are transformed to reaction products whose sulfenyl group is readily eliminated through by manipulations or reductive cleavages to the desired hydrocarbon skeletons. We previously disclosed that monothioacetals can be converted into either ethers or thioethers selectively, by the appropriate choice of Lewis acid.[2a] Despite this synthetic potential, the mechanism of the thioacetal reaction remains uncertain. Since the mechanistic study of relevant acetal reactions has progressed to some extent recently,[4] it seems of interest to investigate whether significant differences in the reaction mode arise as a result of replacing the alkoxy groups with alkylthio groups. In a reaction of this sort, the S_N1/S_N2 problem is inevitably encountered and should be solved first of all. Yamamoto pointed out the importance of the timing of bond breaking and bond making in the allylation of cyclic acetals.[5] Noyori implicated an S_N1 mechanism involving a carboxonium ion intermediate for the trimethylsilyl triflate (TMSOTf) promoted reaction between enol silyl ethers and acetals.[6] Denmark reported that both reaction mechanisms were feasible depending on the acetal in his intramolecular version of allylation reactions.[7,8] As far as thioacetals are concerned, a study by Bartlett and Heathcock is, to the best of our knowledge, the only precedent directed toward this end; the possibility of thionium intermediacy was suggested in dithioacetal-enol silyl ether reactions.[1g] In

Scheme I

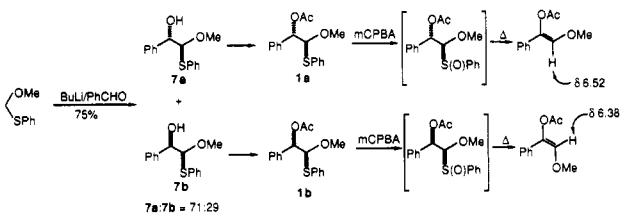
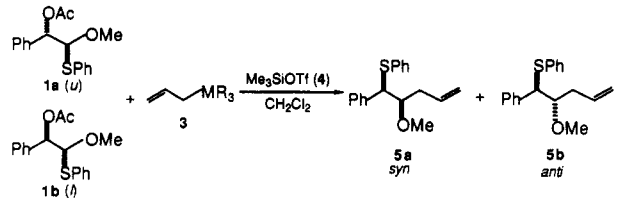


Table I. Reaction of 1 with Various Allylmetals 3 in the Presence of 4



1	3 (MR_3)	reaction temp, °C	reaction time, h	yield of 5a + 5b,[a] %	5a:5b[b]
1a	3a ($SiMe_3$)	−78 to 20	6	72	80:20
1b		−78 to 20	7	69	79:21
1a	3b ($GeMe_3$)	−50	6	43 (67)[c]	84:16
1b		−50	6	50 (75)[c]	73:27
1a	3c ($SnMe_3$)	−78	6	89	96:4
1b		−78 to 50	6	79	14:86
1a	3d ($SnBu_3$)	−78	2	89	89:11
1b		−78 to 50	4	72	12:88
1a	3e ($SnPh_3$)	−50	2	79	78:22
1b		−50	4	52 (76)[c]	76:24

[a] Isolated yields after column chromatography. [b] Determined by capillary GLC. [c] Based on the consumed reactant.

(1) Dithioacetals: (a) Reetz, M. T.; Huettenhain, S.; Walz, P.; Loewe, U. *Tetrahedron Lett.* **1979**, 4971. (b) Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315. (c) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (d) Trost, B. M.; Murayama, E. *Tetrahedron Lett.* **1982**, *23*, 1047. (e) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. (f) Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1871. (g) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199.

(2) Monothioacetals: (a) Sato, T.; Okura, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1987**, *28*, 6299. (b) Sato, T.; Inoue, M.; Kobara, S.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1989**, *30*, 91.

(3) Dithioacetals: Groebel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Synthesis* **1989**, 7643. Monothioacetals: Otera, J. *Synthesis* **1988**, 95.

(4) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. Mori, A.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668. Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765. Silverman, R.; Edington, C.; Elliot, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180. Mukaiyama, T.; Ohshima, M. Miyoshi, N. *Chem. Lett.* **1987**, 1121.

(5) Yamamoto, Y.; Nishii, S.; Yamada, J.-I. *J. Am. Chem. Soc.* **1986**, *108*, 7116. Yamamoto, Y.; Yamada, J.-I. *J. Chem. Soc., Chem. Commun.* **1987**, 1218.

(6) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259.

(7) Denmark, S. E.; Wilson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

(8) More recently, Heathcock et al. have disclosed the mechanistic divergence in acetal-enol silyl ether reactions: Heathcock, C. H., private communication.

0022-3263/90/1955-6116$02.50/0

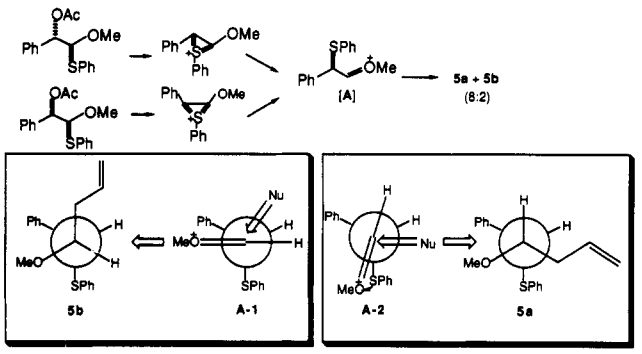


Figure 1. S_N1 mechanism.

the context of our studies on methoxy(phenylthio)-methane,[2] we have found that the reaction of 2-acetoxy-2-phenylacetaldehyde mono- and dithioacetals, **1** and **2**, with various allylmetals (**3**) in the presence of TMSOTf (**4**) is dramatically changed depending on the nucleophilicity of **3**, thus providing unequivocal evidence for the occurrence of both S_N1- and S_N2-type mechanisms.

Results and Discussion

Reaction of Monothioacetals 1. The starting materials, **1a** and **1b**, were prepared according to our previous method[9] as shown in Scheme I. The diastereomers, **7a** and **7b**, were readily separated by column chromatography and were converted to **1a** and **1b** upon acetylation. The stereochemistry of these compounds was assigned based on the stereospecific syn-elimination of the corresponding sulfoxides.[10] The *E*/*Z* structure of the resulting olefins was determined from their ^1H NMR spectra; the olefinic proton trans to the phenyl group resonates at higher field.[11]

Exposure of the *u*-monothioacetal **1a**[12] to allyltrimethylsilane (**3a**) (1.3 equiv) in the presence of **4** (1 equiv) in dichloromethane at −78 to −20 °C for 6 h furnished, stereoselectively, syn- and anti-allylation products, **5a** and **5b**, in an 80:20 ratio (Table I). The *l*-monothioacetal **1b** reacted with the same diastereoselectivity. The same selectivity occurred with a germanium analogue (**3b**). In striking contrast, allyltrimethyl- and allyltributyltin (**3c** and **3d**) provided predominantly **5a** from **1a** and **5b** from **1b**. Hence, this reaction is virtually stereospecific. The details of the stereochemical assignments of the products will be given later. Apparently, the reactions with silicon and germanium compounds proceed via an oxonium intermediate [A] (Figure 1) while an S_N2-type mechanism is most probable for the reactions with **3c** and **3d** (Figure 2). The difference is interpreted in terms of the nucleophilicity of the allylmetals as proposed in the reactions with aldehydes and acetals by Denmark[13] and Yamamoto,[5] respectively. The less nucleophilic silicon and germanium compounds are incapable of attacking the substrate until the oxonium intermediate has been generated. With respect to the stereochemical outcome, a Felkin–Anh model, A-1, cannot account for the syn preference.[14] The alternative possibility is A-2, in which electrostatic attraction between the sulfur lone pair and the oxonium ion plays a key role in the eclipsed conformation. The analogous charge attraction induced model was proposed between a sulfonium group and carbonyl oxygen in the hydride reduction of β-oxosulfonium salts by Oishi.[15]

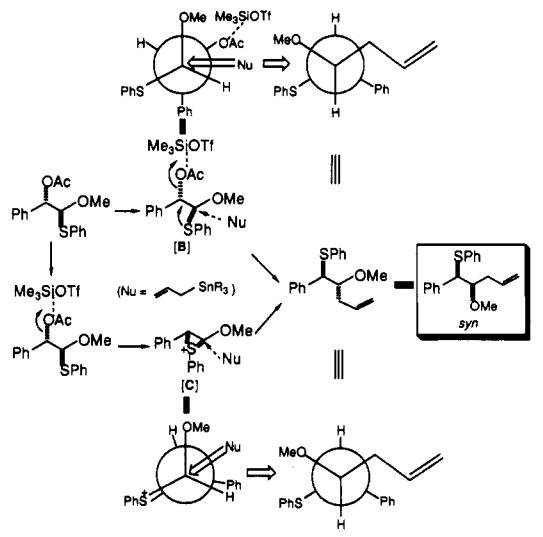


Figure 2. S_N2 mechanism.

Table II. Competition Reaction of 1a and 1b in CH_2Cl_2 at −78 °C

reactants	allyl metal	equiv of 4	reactn time, h	recovered 1, % (1a/1b)	yield of 5, (5a/5b)
1a + 1b (48:52)	3a	0.1	13	45 (32:68)	32 (80:20)
1a + 1b (52:48)	3c	1.0	1	61 (43:57)	24 (70:30)

The reaction of more nucleophilic **3c** and **3d**, on the other hand, has an earlier transition state which is responsible for the stereospecificity. Figure 2[16] shows two possible S_N2-like routes: (1) direct attack of the nucleophile on **1** in a concerted manner (transition state B) or (2) formation of an episulfonium intermediate C preceding the nucleophilic attack. In a study of the addition of phenylsulfenyl chloride to alkenyl ethers, Okuyama et al. disclosed that the episulfonium intermediate C readily equilibrated with the carboxonium ion A to give addition products with ca. 75:25 diastereoselectivity.[17] The facile equilibration to the oxonium ion is in remarkable contrast to the simple episulfonium intermediates obtained with β-nitro sulfides by Ono et al.[18] Lewis acid promoted reaction of these compounds with allyl- and cyanosilanes led to two regioisomers but the stereochemistry of the products was completely dependent on that of the β-nitro sulfides. Evidently, episulfonium intermediates were not

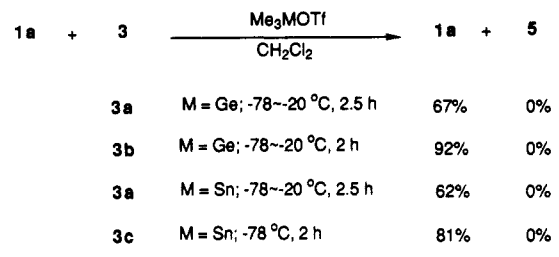
(9) Mandai, T.; Hara, K.; Nakajima, T.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1983**, *24*, 4993.
(10) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453.
(11) Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 185. Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.
(12) In this paper, the syn/anti notation is usually employed for its readiness with which readers can visualize the structures. However, it is not applicable to 1, for which the *u*/*l* notation is our choice. For the *u*/*l* notation, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
(13) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970.
(14) The phenyl group was estimated bulkier than the phenylthio group on the basis of conformational analysis of mono-substituted cyclohexanes (Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; Chaptor 8). Nevertheless, various precedent outcome on nucleophilic addition to α-heteroatom substituted carbonyls suits well to the Felkin–Anh model in which the heteroatom functional group is located anti to an incoming nucleophile: (a) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775. (b) Reich, H. J.; Hotan, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 312 and references cited therein.
(15) Shimagaki, M.; Matsuzaki, Y.; Hori, I.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4779.
(16) Only the reaction of the *u* isomer **1a** is illustrated in Figure 2 for simplicity.
(17) Toyoshima, K.; Okuyama, T.; Fueno, T. *J. Org. Chem.* **1978**, *43*, 2789.
(18) Kamimura, A.; Sasatani, H.; Hashimoto, T.; Ono, N. *J. Org. Chem.* **1989**, *54*, 4998.

Table III. Product Distribution at Low Conversions[a]

1	3	reactn temp, °C	recovered 1,[b] %	5, yield of % (5a/5b)
1a	3a	−78 to 50	1a, 75	16 (81:19)
1b	3a	−78 to 50	1b, 72	10 (82:18)
1a	3c	−78	1a, 34	64 (97:3)
1b	3c	−78	1b,44	24 (12:88)

[a] Reaction conditions: 1:3:4 = 1.0:1.3:1.0, CH_2Cl_2, 2 h. [b] No isomer was detected.

Scheme II



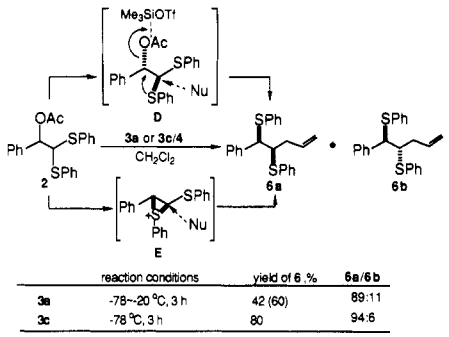
transformed to carbocations. In other words, the methoxy group tends to facilitate formation of an α-carbocationic intermediate, as is generally accepted. However, the superior selectivities in our case relative to Okuyama's outcome suggest that the path via B is more plausible. The methoxy group thus serves to increase the regioselectivity of the substitution but seldom induces an S_N1 reaction. Allyltriphenyltin (**3e**), of less nucleophilic character due to the presence of electron-withdrawing phenyl groups, exhibits no stereospecificity, consistent with the results of Yamamoto.[5]

The anti elimination premised in the above discussion was confirmed by competition reactions (Table II). A mixture of **1a** and **1b** (48:52) was treated with **3a** at −78 °C. After 13 h, the mixture (45%) was recovered in a 32:68 **1a/1b** ratio together with a 32% yield of a **5a/5b** mixture (80:20). The analogous reaction of a 52:48 **1a/1b** mixture with **3c** left the starting materials (61%) in a 43:57 **1a/1b** ratio accompanied by a 70:30 **5a/5b** mixture (24%). Obviously, **1a**, which places the phenylthio and acetoxy groups trans to one another in the most energetically favored conformer, reacts faster than **1b**. The diastereoselectivities attained in these reactions are reasonable on the basis of the results in Table I, indicative of no isomerization of the reaction products under the present reaction conditions. This was further confirmed by treating **5a** or **5b** with **4** at 78 °C for 1 h. Stereochemically pure **5a** and **5b** were recovered quantitatively.

The possible isomerization of the starting material was checked by quenching the reactions at low conversions (Table III). In every case, **1a** or **1b** was recovered without contamination by the isomer. Analyses of the allylation products in these experiments again support the independence of the **5a/5b** ratio on the reaction period.

Treatment of **1a** with **3a** or **3b** (1.3 equiv) in the presence of trimethylgermyl triflate (1.0 equiv) failed to provide **5** at all (Scheme II). That is, the germyl triflate was unable to promote the allylation even though it was produced in situ through transmetalation between **3b** and **4** in the reaction of **1** and **3b**. The same holds for trimethyltin triflate. NMR spectroscopy supported that no transmetalation occurred. ^1H and ^{13}C NMR spectra of an equimolar mixture of **3b** (δ 0.16 for CH_3 and −2.74 for CH_3) and **4** (δ 0.52 for CH_3 and 0.38 for CH_3) in CD_2Cl_2 at 20 °C exhibited no signals assignable to **3a** (δ 0.03 for CH_3 and −2.08 for CH_3) or trimethylgermyl triflate (δ 0.91 for CH_3 and 3.74 for CH_3). It also should be noted that no redistribution of **3b** to tetramethylgermane and diallyldimethylgermane occurred. With a mixture of **3c** (δ 0.12 for CH_3 and −10.3 for CH_3) and **4**, the transmetalation between these two components along with the redistribution of **3c** was observed to some extent at 27 °C.[19] However, no sign of transmetalation was detected at −50 °C although a signal attributable to the redistribution product, tetramethyltin (δ −9.68 for CH_3), appeared (ca. 2%) after the mixture had been kept standing for 30 min at this temperature. All of the above results leads us to conclude that **4** works in its intrinsic form as a promoter.

Scheme III[a]



[a] The yield in the parentheses is based on the consumed reactant.

Reaction of Dithioacetals 2. The dithioacetal **2** was prepared by treating a lithium salt of bis(phenylthio)methane with benzaldehyde followed by acetylation. The reaction of **2** with **3a** and **3c** is noteworthy in that the syn product **6a** was produced predominantly, in a highly selective manner, irrespective of the nucleophilicity of the allylmetals (Scheme III). This bias, in contrast to the monothioacetal reactions, suggests an S_N2-type mechanism due to the inferior ability of the phenylthio group to generate an α-carbocation, relative to the methoxy group.[17,20] The S_N1 reaction involving a thionium intermediate, if it occurred, would not give rise to such high selectivities, judging from the results obtained by using **1**, although the intermediary cationic species are somewhat different in these two sets of reactions. There are again two possibilities for the reaction course: direct attack of the nucleophiles on **2**, D, or initial formation of the episulfonium ion, E. In the present case, the latter path cannot be ruled out since the episulfonium ion is not highly susceptible to equilibration to the carbothionium ion. Our results are inconsistent with the S_N1 mechanism proposed for Bartlett–Heathcock's α-chiral dithioacetal reactions.[1g] The discrepancy, however, can be ascribed to the presence of a good leaving group which either assists the C–S bond cleavage through the 1,2-phenylthio migration upon nucleophilic attack or facilitates the formation of the episulfonium intermediate.

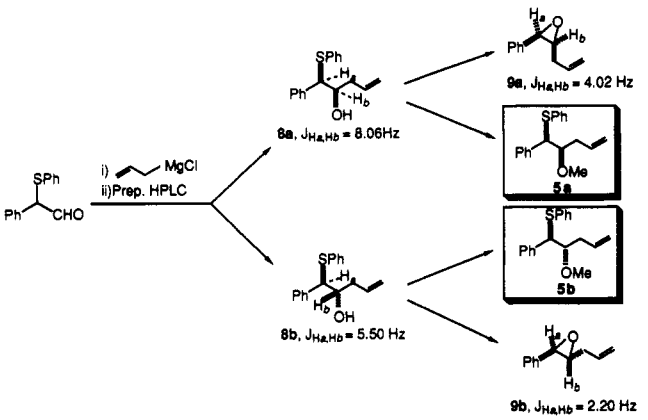
Stereochemistry of the Products. All of the products were confirmed by comparison with authentic samples. Scheme IV demonstrates the routes to **5a** and **5b**. To arrive at **8**, 2-phenyl-2-(phenylthio)acetaldehyde[21] was exposed to allyl Grignard reagent in THF at −78 °C for 3 h. The desired compound was obtained in 67% yield

(19) Denmark discussed the transmetalation as well as the redistribution of **3c** upon exposure to Lewis acids: Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984 and references cited therein.

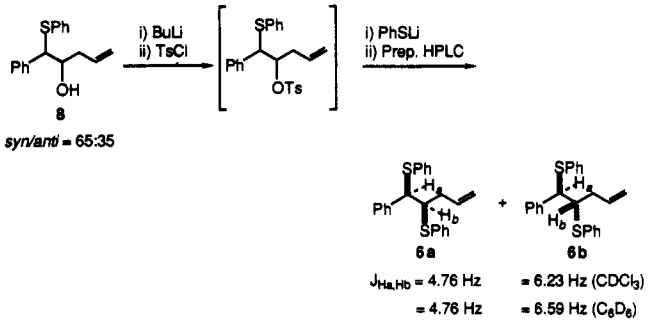
(20) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978; p 128. Kozikowski, A. P.; Greco, M. N. *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, p 263.

(21) Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209.

Scheme IV



Scheme V



with a 65:35 **8a**/**8b** ratio. The pure diastereomers were obtained by HPLC separation. The vicinal coupling constants ($J_{Ha,Hb}$) of β-hydroxy sulfides have proven to be smaller for anti isomers than for the syn counterparts.[14a] Hence, **8a** and **8b** are attributable to syn and anti isomers, respectively. Furthermore, these compounds were converted to oxiranes, **9a** and **9b**, with TIOEt.[22] Their NMR data are consistent with the established knowledge that *cis*-oxiranes possess greater vicinal coupling constants ($J_{Ha,Hb}$) than the trans isomers.[23] Finally, **5a** and **5b** were obtained by treating **8a** and **8b** with KH and MeI.

The independent synthesis of *syn*- and *anti*-**6** is depicted in Scheme V. A mixture of **8a** and **8b** (65:35) was treated successively with BuLi, tosyl chloride, and PhSLi in THF to afford a mixture of **6a** and **6b** (60:40) in 28% yield. The diastereomers were separated by preparative HPLC. Few stereochemical assignments for compounds substituted vicinally by phenylthio groups have been made. Shevlin, however, unambiguously showed that the vicinal coupling constant of 1,2-bis(phenylthio)butane is greater for the meso compound in which the two substituents are located anti to one another than for the racemic mixture with the substituents in the gauche positions.[24] It is therefore reasonably assumed that **6a** and **6b** are syn and anti isomers, respectively.

In summary, we conclude that in the Lewis acid promoted reactions of mono- and dithioacetals with nucleophiles, the S_N2-type mechanism operates when the acetals have access to a transition state that is of lower energy than that leading to an oxonium ion intermediate, and the nucleophilicity of the allylmetals is sufficiently great. Otherwise, an oxonium ion intermediate exists when the less nucleophilic reagents are involved. The comparison of the mono- and dithioacetals clearly reveals the difference between methoxy and phenylthio groups in their ability to generate a carbocation at the α-position and their resulting determination of the reaction mode. It is important that the reactive species as well as the promoter which are actually responsible for the reaction have been elucidated. On the above grounds, the present reaction systems promise to provide us with explicit data to assess the nucleophilicity of other allylmetals and with profound mechanistic insights into thioacetal–nucleophile reactions. Particularly intriguing would be the employment of more complicated allylic derivatives, such as crotyl and cinnamyl, whose reaction mechanism is still unknown. Studies along this line will be published in due course.

Experimental Section

NMR spectra were recorded on JEOL JNM-FX 100 and GSX-400 spectrometers. Mass spectra were obtained with a JEOL JMS-DX 303-HF mass spectrometer using electron impact ionization. IR spectra were measured with a Hitachi 260-10 infrared spectrometer. GLC analysis was performed on a Shimadzu GC-14A capillary gas chromatograph with ULBON HR-20M (0.2 × 25000 mm). HPLC analysis was made with a Shimadzu LC-8A machine equipped with column A (Develosil Si 30, 3 μm, 4.6 × 250 mm), column B (Develosil Si 30, 10-20 μm, 50 × 300 mm), column C (Chemcosorb ODS-UH, 5 μm, 4.6 × 250 mm), and column D (Chemcosorb ODS-H, 10 μm, 20 × 250 mm). Column chromatography was performed on Kieselgel 60 (70–230 mesh) (E. Merck). Thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254}. All the solvents were purified by standard methods before use. Allylmagnesium chloride in THF, BuLi in hexanes, mCPBA, 4-(dimethylamino)pyridine, thiophenol, **3a**, and **4** were purchased from Aldrich. Potassium hydride (25% dispersion in mineral oil) and thallium ethoxide were obtained from Janssen and other reagents were from Wako Chemicals. These commercially available reagents were used as received. The following compounds were prepared according to the methods described in literatures: **3b**,[25] **3c**,[26] **3d**,[25] **3e**,[27] methoxy(phenylthio)methane,[28] bis(phenylthio)methane,[29] 2-phenyl-2-(phenylthio)acetaldehyde,[21] and trimethylgermyl and stannyl triflate.[30]

Preparation of *u*- and *l*-Monothioacetals 1a and 1b. To a THF solution (200 mL) of methoxy(phenylthio)methane (46.2 g, 0.3 mol) were added BuLi (2.5 N in hexanes, 120 mL, 0.3 mol) at −50 °C and benzaldehyde (41.3 g, 0.39 mol) at −78 °C. After being stirred for 3 h at this temperature, the reaction mixture was combined with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. HPLC analysis (column A, 80:20 hexane–ethyl acetate) showed that the crude product consisted of **7a** and **7b** in a 71:29 ratio. Column chromatography (97:3 hexane–ethyl acetate) provided **7a** (40.5 g, 52%) and **7b** (18.0 g, 23%). **7a**: ^1H NMR ($CDCl_3$) δ 2.98 (br, 1 H), 3.56 (s, 3 H), 4.60 (d, 1 H, J = 7.70 Hz), 4.72 (d, 1 H, J = 7.70 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 56.1, 75.7, 95.6, 127.4, 127.5, 127.8, 127.9, 128.6, 133.0, 133.2, 139.2; IR (CCl_4) 3580 cm^{-1}; MS m/z 260 (M^+). **7b**: ^1H NMR ($CDCl_3$) δ 3.01 (br, 1 H), 3.40 (s, 3 H), 4.56 (d, 1 H, J = 7.32 Hz), 4.62 (d, 1 H, J = 7.32 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 57.0, 73.9, 97.7, 127.0, 127.8, 128.0, 128.9, 131.9, 133.9, 139.7; IR (CCl_4) 3550 cm^{-1}; MS m/z 260 (M^+); HRMS m/z calcd for $C_{15}H_{16}O_2S$ (M^+) 260.0871, found 260.0811.

Acetylation of **7a** and **7b** with Ac_2O/4-(dimethylamino)-pyridine/pyridine afforded the desired monothioacetals **1a** and **1b** in 88 and 91% yields, respectively. **1a**: ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.51 (s, 3 H), 4.83 (d, 1 H, J = 6.96 Hz), 5.98 (d, 1 H, J = 6.96 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 57.2, 76.9, 93.8, 128.0, 128.1, 128,4, 128.7, 129.2, 133.4, 133.8, 137.1, 170.0; IR (CCl_4) 1740 cm^{-1}; MS m/z 302 (M^+); HRMS m/z calcd

(22) Laboureur, J. L.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1984**, *25*, 4569.
(23) Lyle, G. G.; Keefer, L. K. *J. Org. Chem.* **1966**, *31*, 3921 and ref 14a.
(24) Shevlin, P. B.; Green, J. L., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 8447.
(25) Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1959**, *24*, 1395.
(26) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515.
(27) Gilman, H.; Eisch, J. J. *J. Org. Chem.* **1955**, *20*, 763.
(28) Vatel, J. *Tetrahedron Lett.* **1984**, *25*, 5997.
(29) Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R. *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. VI, p 737.
(30) Schmeisser, M.; Sartori, P.; Lippsmeier, B. *Chem. Ber.* **1970**, *103*, 868.

for $C_{15}H_{14}OS$ ($M^+ - CH_3COOH$) 242.0766, found 242.0687. **1b**: ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 3.39 (s, 3 H), 4.84 (d, 1 H, J = 5.86 Hz), 5.90 (d, 1 H, J = 5.86 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 56.9, 76.1, 94.4, 127.7, 128.1, 128.3, 128.9, 133.3, 133.6, 136.9, 169.5; IR (CCl_4) 1742 cm^{-1}; MS m/z 302 (M^+); HRMS m/z calcd for $C_{15}H_{14}OS$ ($M^+ - CH_3COOH$) 242.0766, found 242.0762.

A mixture of **1a** (288 mg, 0.96 mmol) and mCPBA (80% pure, 237 mg, 1.1 mmol) in dichloromethane (4 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with dichloromethane and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated. The resulting sulfoxide was heated in toluene (5 mL) in the presence of $NaHCO_3$ (126 mg, 1.5 mmol) at 100 °C for 30 min. The reaction mixture was combined with brine and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography of the residue (90:10 hexane–benzene) provided (*Z*)-1-acetoxy-2-methoxy-1-phenylethene (92 mg, 50%): ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 3.75 (s, 3 H), 6.52 (s, 1 H), 7.20–7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.4, 60.6, 122.9, 127.1, 128.4, 130.5, 133.2, 137.2, 168.3; IR (CCl_4) 1768, 1680 cm^{-1}; MS m/z 192 (M^+); HRMS m/z calcd for $C_{11}H_{12}O_3$ (M^+) 192.0786, found 192.0826.

Subjection of **1b** to the same procedure provided (*E*)-1-acetoxy-2-methoxy-1-phenylethene in 60% yield: ^1H NMR ($CDCl_3$) δ 2.25 (s, 3 H), 3.78 (s, 3 H), 6.38 (s, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 61.1, 125.1, 127.1, 128.1, 131.2, 132.7, 142.7, 170.4; IR (CCl_4) 1770, 1671 cm^{-1}; MS m/z 192 (M^+); HRMS m/z calcd for $C_{11}H_{12}O_3$ (M^+) 192.0786, found 192.0728.

Preparation of Dithioacetal 2. To a THF solution (150 mL) of bis(phenylthio)methane (23.2 g, 0.1 mol) were added BuLi (2.5 N in hexanes, 40 mL, 0.1 mol) at −30 °C and benzaldehyde at −78 °C. Workup and acetylation of the product as described above provided **2** in 73% yield: ^1H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 4.65 (d, 1 H, J = 4.39 Hz), 6.12 (d, 1 H, J = 4.39 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 64.6, 76.2, 127.2, 127.7, 128.0, 128.3, 128.8, 128.9, 132.3, 133.1, 133.9, 134.2, 136.9; IR (CCl_4) 1742 cm^{-1}; MS m/z 380 (M^+); HRMS m/z calcd for $C_{22}H_{20}O_2S_2$ (M^+) 380.0905, found 380.0880.

Reaction of 1 with Allylmetals 3 in the Presence of 4 (Typical Procedure). To a dichloromethane solution (5 mL) of **1a** (151 mg, 0.5 mmol) and **3a** (74.2 mg, 0.65 mmol) was added **4** (1.0 M dichloromethane solution, 0.5 mL, 0.5 mmol) at −78 °C. The reaction mixture was stirred for 6 h, during which time the temperature was gradually raised up to −20 °C. Aqueous $NaHCO_3$ was added to this solution, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The crude product proved to consist of **5a** and **5b** in an 80:20 ratio based on GLC and was purified through column chromatography (97:3 hexane–ethyl acetate) to give **5** (102 mg, 72%). Other reactions were carried out analogously under the conditions shown in Table I.

Competition Reaction of 1a and 1b. A mixture of **1a** and **1b** (48:52) (288 mg, 0.96 mmol) was treated with **3a** (148 mg, 1.3 mmol) in the presence of **4** (1.0 M dichloromethane solution, 0.1 mL, 0.1 mmol) for 13 h under the similar conditions described above. After workup, GLC analysis of the crude product indicated that the ratio of **1a**/**1b** was 32:68 and that of **5a**/**5b** was 80:20. Column chromatography provided **1** (90:10 hexane–benzene, 130 mg, 45%) and **5** (50:50 hexane–benzene, 91 mg, 32%). Exposure of the **1a**/**1b** mixture (52:48) to **3c** (1.3 equiv) in the presence of **4** (1.0 equiv) resulted in 61% recovery of **1** (**1a**/**1b** = 43:57) and 24% yield of **5** (**5a**/**5b** = 70:30) after 1 h.

Treatment of 5 with 4. A dichloromethane solution (1 mL) of **5a** (10 mg, 0.037 mmol) and **4** (1.0 M dichloromethane solution, 0.037 mL, 0.037 mmol) was stirred at −78 °C for 1 h. Workup and column chromatography (98:2 hexane–ethyl acetate) left **5a** (9 mg, 90%). Under the same conditions, 80% of **5b** was recovered.

Reaction in the Presence of Trimethylgermyl and -stannyl Triflates. To a dichloromethane solution (1.5 mL) of trimethylgermyl triflate (58 mg, 0.22 mmol) were added **1a** (63 mg, 0.22 mL) and **3a** (33 mg, 0.29 mmol) at −78 °C. The mixture was stirred for 2.5 h, during which time the temperature was raised gradually up to −20 °C. Workup and column chromatography (80:20 hexane–benzene) left **1a** (42 mg, 67%). Even a trace amount of **5** was not detected by means of GLC. Other relevant reactions were carried out analogously under the conditions shown in Scheme II.

Reaction of 2 with 3a and 3c. To dichloromethane solution (4.0 mL) of **2** (380 mg, 1 mmol) and **3a** (171 mg, 1.5 mmol) was added **4** (1.0 M dichloromethane solution, 1.2 mL, 1.2 mmol) at −78 °C. The reaction mixture was stirred for 3 h, during which time the temperature was raised up to −20 °C. Aqueous $NaHCO_3$ was added to this solution, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. The residue proved to consist of **6a** and **6b** in an 89:11 ratio based on HPLC (column C, 80:20 CH_3CN–H_2O). The crude oil was subjected to column chromatography to give **6** (99:1 hexane–ethyl acetate, 153 mg, 42%) and **2** (95:5 hexane–ethyl acetate, 114 mg, 30%). Reaction with **3c** provided **6** (**6a**/**6b** = 94:6) in 80% yield.

Synthesis of Authentic 5a and 5b. To a THF solution (20 mL) of 2-phenyl-2-(phenylthio)acetaldehyde (2.6 g, 11 mmol) was added allylmagnesium chloride (2.0 N THF solution, 11 mL, 22 mmol) at −78 °C. The reaction mixture was stirred for 3 h and quenched with aqueous NH_4Cl. Extraction with ethyl acetate, drying the organic layer (Na_2SO_4), and evaporation left an oil. Column chromatography (98:2 hexane–ethyl acetate) of this oil gave **8** (2.0 g, 67%): **8a**/**8b** = 65:35 based on HPLC, column A, 90:10 hexane–ethyl acetate. Preparative HPLC (column B, 90:10 hexane–ethyl acetate) provided pure **8a** and **8b**. **8a**: ^1H NMR ($CDCl_3$) δ 2.10 (m, 1 H), 2.32 (m, 1 H), 4.00 (m, 1 H), 4.11 (d, 1 H, J = 8.06 Hz), 4.90–5.10 (m, 2 H), 6.85 (m, 1 H), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 38.7, 61.6, 73.1, 118.2, 127.7, 128.5, 128.7, 129.0, 132.9, 134.1, 134.4, 140.0; IR (CCl_4) 3520 cm^{-1}; MS m/z 270 (M^+); HRMS m/z calcd for $C_{17}H_{18}OS$ (M^+) 270.1078, found 270.1054. **8b**: ^1H NMR ($CDCl_3$) δ 2.12–2.45 (m, 2 H), 4.00 (m, 1 H), 4.24 (d, 1 H, J = 5.50 Hz), 5.05–5.15 (m, 2 H), 5.75–5.80 (m, 1 H), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 38.5, 59.2, 72.2, 117.9, 127.3, 127.6, 128.3, 128.8, 129.0, 132.1, 132.7, 134.2, 138.0; IR (CCl_4) 3600 cm^{-1}; MS m/z 270 (M^+); HRMS m/z calcd for $C_{17}H_{18}OS$ (M^+) 270.1078, found 270.1057.

To a THF suspension (1.0 mL) of KH (25% mineral oil suspension, 35 mg, 0.22 mmol) was added **8a** (30 mg, 0.11 mmol) at 0 °C. After the mixture had been stirred for 10 min, methyl iodide (31 mg, 0.22 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C and combined with aqueous NH_4Cl. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography (97:3 hexane–ethyl acetate) provided **5a** (25 mg, 81%): ^1H NMR ($CDCl_3$) δ 2.15 (m, 1 H), 2.47 (m, 1 H), 3.42 (s, 3 H), 3.62 (q like, 1 H, J = 5.86 Hz), 4.33 (d, 1 H, J = 5.86 Hz), 5.05 (m, 2 H), 5.81 (m, 1 H), 7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 35.8, 57.1, 58.1, 84.1, 117.6, 126.7, 127.1, 128.1, 128.5, 128.6, 131.9, 134.1, 135.3, 140.0; MS m/z 284 (M^+); HRMS m/z calcd for $C_{18}H_{20}OS$ (M^+) 284.1235, found 284.1177. Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09. Found: C, 76.11; H, 7.01.

Reaction of **8b** provided **5b** in 87% yield: ^1H NMR ($CDCl_3$) δ 2.25 (m, 1 H), 2.40 (m, 1 H), 3.37 (s, 3 H), 3.65 (q like, 1 H, J = 5.13 Hz), 4.27 (d, 1 H, J = 5.12 Hz), 5.10 (m, 2 H), 5.80 (m, 1 H), 7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 36.2, 57.1, 58.7, 83.5, 117.6, 126.7, 127.1, 128.0, 128.6, 129.2, 131.6, 134.3, 135.5, 139.1; MS m/z 284 (M^+); HRMS m/z calcd for $C_{18}H_{20}OS$ (M^+) 284.1235, found 284.1142. Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09. Found: C, 76.32; H, 6.98.

Conversion of 8 into 9. A chloroform solution (3 mL) of **8a** (150 mg, 0.55 mmol) and TlOEt (180 mg, 0.72 mmol) was stirred at room temperature for 12 h. The reaction mixture was diluted with ether. Insoluble materials were removed by filtration through a Celite pad. The filtrate was washed with aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (90:10 hexane–benzene) of the residue provided the *cis*-oxirane **9a** (45 mg, 51%): ^1H NMR ($CDCl_3$) δ 1.98 (dt like, 1 H, J = 6.2 and 15.0 Hz), 2.17 (dt like, 1 H, J = 6.2 and 15.0 Hz), 3.28 (ddd, 1 H, J = 4.02, 6.22, and 6.23 Hz), 4.11 (d, 1 H, J = 4.02 Hz), 4.98–5.05 (m, 2 H), 5.73 (m, 1 H), 7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 31.3, 57.1, 58.1, 117.2, 126.4, 127.5, 128.0, 133.1, 135.2; MS m/z 160 (M^+); HRMS m/z calcd for $C_{11}H_{12}O$ (M^+) 160.0888, found 160.0895.

Reaction of **8b** provided the *trans*-oxirane **9b** in 69% yield: ^1H NMR ($CDCl_3$) δ 2.46 (m, 2 H), 3.05 (dt, 1 H, J = 2.20 and 5.49 Hz), 3.65 (d, 1 H, J = 2.20 Hz), 5.13 (dd, 1 H, J = 1.10 and 10.2

Hz), 5.19 (dd, 1 H, J = 1.10 and 17.2 Hz), 5.90 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.3, 58.0, 61.7, 117.7, 125.5, 128.0, 128.4, 132.7, 137.4; MS m/z 160 (M^+); HRMS m/z calcd for $C_{11}H_{12}O$ (M^+) 160.0888, found 160.0890.

Synthesis of Authentic 6a and 6b. To a THF solution (3.0 mL) of a mixture of **8a** and **8b** (65:35) (271 mg, 1.0 mmol) was added BuLi (2.5 N in hexanes, 0.44 mL, 1.1 mmol) at 0 °C. The solution was stirred for 10 min, and tosyl chloride (247 mg, 1.3 mmol) was added at this temperature. The reaction mixture was stirred for 30 min at room temperature. PhSLi was prepared by mixing PhSH (551 mg, 5 mmol) and BuLi (2.5 N in hexanes, 2 mL, 5 mmol) in THF (3 mL). This solution was added to the above reaction mixture, and the resulting solution was stirred for 3 h at room temperature. The reaction mixture was diluted with benzene and washed with water, 1 N NaOH, and brine. The organic layer was dried (Na_2SO_4) and evaporated. Column chromatography of the residue (90:10 hexane–benzene) provided **6** (101 mg, 28%, **6a**/**6b** = 60:40 based on HPLC, column C, 70:30 CH_3CN–H_2O). HPLC separation (column D, 80:20 CH_3CN–H_2O) of the product gave pure **6a** and **6b**. **6a**: ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 1 H), 2.88 (m, 1 H), 3.51 (ddd, 1 H, J = 4.39, 4.76, and 9.16 Hz), 4.41 (d, 1 H, J = 4.76 Hz), 5.06 (m, 2 H), 5.87 (m, 1 H), 7.20–7.40 (m, 15 H); (C_6D_6) δ 2.20 (m, 1 H), 3.00 (m, 1 H), 3.65 (ddd, J = 4.40, 4.76, and 8.79 Hz), 4.61 (d, 1 H, J = 4.76 Hz), 5.05 (m, 2 H), 5.95 (m, 1 H), 6.90–7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 35.0, 53.4, 56.6, 117.5, 126.8, 127.3, 127.5, 127.9, 128.8, 128.9, 129.1, 131.4, 132.7, 134.6, 135.0, 135.3, 138.2; MS m/z 362 (M^+); HRMS m/z calcd for $C_{23}H_{22}S_2$ (M^+) 362.1163, found 362.1184. Anal. Calcd for $C_{23}H_{22}S_2$: C, 76.20; H, 6.12. Found: C, 76.44; H, 6.02. **6b**: ^{1}H NMR ($CDCl_3$) δ 2.54 (m, 2 H), 3.61 (q like, 1 H, J = 6.23 Hz), 4.40 (d, 1 H, J = 6.23 Hz), 5.15 (m, 2 H), 5.90 (m, 1 H), 7.10–7.40 (m, 15 H); (C_6D_6) δ 2.66 (m, 2 H), 3.72 (q like, 1 H, J = 6.59 Hz), 4.52 (d, 1 H, 6.59 Hz), 5.12 (m, 2 H), 5.91 (m, 1 H), 6.90–7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 36.8, 55.4, 57.5, 117.9, 126.9, 127.1, 127.4, 128.0, 128.6, 128.8, 131.9, 132.6, 134.9, 135.0, 135.3, 139.5; MS m/z 362 (M^+); HRMS m/z calcd for $C_{17}H_{17}S$ ($M^+ - C_6H_5S$) 253.1051, found 253.0963. Anal. Calcd for $C_{23}H_{22}S_2$: C, 76.20; H, 6.12. Found: C, 76.54; H, 6.10.

Acknowledgment. This work was partially supported by Grant-in-Aid from The Ministry of Education, Science, and Culture, Japan. We also thank M. Inoue, T. Matsui, and M. Kanemoto for their technical assistance.

Registry No. **1a**, 129756-71-4; **1b**, 129732-83-8; **2**, 129732-86-1; **3a**, 762-72-1; **3b**, 762-66-3; **3c**, 762-73-2; **3d**, 24850-33-7; **3e**, 76-63-1; **4**, 27607-77-8; **5a**, 129732-84-9; **5b**, 129732-85-0; **6a**, 129732-87-2; **6b**, 129732-88-3.

Supplementary Material Available: ^{1}H or ^{13}C NMR spectra for **1a,b**, **2**, **7a,b**, **8a,b**, **9a,b**, and (*Z*)- and (*E*)-1-acetoxy-2-methoxy-1-phenylethenes (11 pages). Ordering information is given on any current masthead page.

Conformational Study of Cinchona Alkaloids. A Combined NMR and Molecular Orbital Approach

Gerard D. H. Dijkstra, Richard M. Kellogg,* and Hans Wynberg*

Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

Received June 12, 1990

1D and 2D NMR techniques have been used to elucidate the conformational behavior of cinchona alkaloids in solution. Deoxy, chloro, methoxy, and benzoyl derivatives have been studied together with the unsubstituted alkaloids. Semiempirical molecular orbital calculations (AM1) on segments as well as on the complete structures of cinchona alkaloids have given complementary quantitative information. These calculational results have been used to rationalize the experimentally obtained conformational data and to shed light on the subtilities involved that determine the conformation of cinchona alkaloids.

Introduction

Cinchona alkaloids[1] possess a rich chemical tradition. They are isolated from the bark of several species of Cinchona and Remeyia trees, native to the eastern slopes of the Andes. When, in the beginning of the 17th century, Europeans became aware of the action of powdered bark of these trees against fever, the major component, quinine, soon belonged among the most used drugs.[2] A role for cinchona alkaloids in organic chemistry was firmly established with the discovery of their potential as resolving agents.[3] Our interest in these alkaloids started in the 1970s, when we began to appreciate their great potential as chiral catalysts in asymmetric Michael additions.[4] Numerous examples have followed of reactions in which cinchona alkaloids induce asymmetry.[5] We note, however, that an example of an asymmetric synthesis using these alkaloids as catalyst was first reported in 1912.[6]

In all these examples of use of cinchona alkaloids their ability for intimate interaction, discrimination, and recognition are crucial to their success. Detailed knowledge of the conformational behavior of the cinchona alkaloids

(1) For a general review on the chemistry of cinchona alkaloids, see: Grethe, G.; Uskokovic, M. R. In *Heterocyclic Compounds, The Monoterpenoid Indole Alkaloids*; John Wiley and Sons Inc.: New York, 1983; Vol. 25, Part 4, Chapter XII, p 729 and references cited therein.

(2) For other examples of pharmaceutical usage of cinchona alkaloids see: Goodman, L. S.; Gilman, A. G. *The Pharmacological Basis of Therapeutics*, 7th ed.; McMillan Publishing Co.: New York, 1985; pp 756, 1041.

(3) The first resolution ever made was carried out with quinicine and cinchonicine, which are derivatives of quinine and cinchonine. Since then, about 25% of all resolutions have been carried out with cinchona alkaloids. Pasteur, L. *C. R. Acad. Sci.* **1853**, *37*, 110. Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87. Many examples of the use cinchona alkaloids as resolving agents are given by Wilen, S. H. In *Tables of Resolving Agents and Optical Resolutions*; University of Notre Dame Press: London, 1972. Jacques, J.; Collet, A.; Wilen, S. H. In *Enantiomers, Racemates and Resolution*; John Wiley and Sons Inc.: New York, 1981; pp 254, 257.

(4) Helder, R.; Wynberg, H. *Tetrahedron Lett.* **1975**, 4057.

(5) See for example: Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87. Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. Hummelen, J. C.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312. Pluim, H.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2498. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. Staring, A. G. J.; Wynberg, H. *J. Am. Chem. Soc.* **1982**, *104*, 166. Staring, A. G. J.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1181. Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745. Brzostowska, M.; Gawronski, J. *Monath. fur Chem.* **1984**, *115*, 1373. Soai, K.; Watanabe, M.; Koyano, M. *J. Chem. Soc., Chem. Commun.* **1989**, 534. Trost, B. M.; Shuey, C. D.; Dininno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284. Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. Jacobsen, E. J.; Marko, I.; Mungall, W. S.; Schroder, G; Sharpless, K. B *J. Am. Chem. Soc.* **1988**, *11*, 1968. Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

(6) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7.

0022-3263/90/1955-6121$02.50/0