New Aspects of Vinylsulfide Chemistry

Isao Kuwajima and Keiji Tanino

Department of Chemistry, Tokyo Institute of Technology, [REDACTED]

Abstract: By utilizing the characteristic features of vinylsulfides, 2-(alkylthio)allyl silyl ethers were designed as efficient ene substrates, and their use led to exploration of general carbonyl and imine ene reactions. By using 3-(alkylthio)-2-siloxyallyl acetates, a useful [3 + 2]cyclopentane annulation methodology was developed. Further, a tandem C-C bond formation/cleavage methodology was also designed.

1. Introduction

Owing to high HOMO level and the large α -cation stabilizing effect of the siloxy group, enol silyl ethers have shown great advantages in the reactions with electrophiles and have been widely used for selective carbon-carbon bond formation and introduction of functional groups. In contrast, vinylsulfides having a similarly high HOMO level have not been fully utilized for synthetic purposes. The major drawback to the use of vinylsulfides as nucleophiles seems to be mainly attributable to the much lower α -cation stabilizing effect of sulfur, which often brings on serious side reactions. However, appropriate design of successive reaction pathways of the cationic species initially formed has allowed the development of several useful transformations not realized with enol ethers. We describe herein our efforts to explore new synthetic methodologies by using the characteristic features of these compounds.

2. Ene Reactions of 2-(Alkylthio)allyl Silyl Ethers I

High HOMO level (1) of vinylsulfides as well as the lower cation stabilizing effect (2) of sulfur may provide ideal features of the ene substrate: high reactivity facilitates the initial reaction with enophiles, and the less stabilized cationic species favors the selective abstraction of hydrogen to afford an ene adduct. Under such assumptions, we attempted to design the most efficient ene substrate and examined the reactions of 2-(alkylthio)allyl silyl ethers **I**. In addition to the effects (1) and (2) of sulfur, the siloxy group is expected to enhance the acidity of hydrogen to be abstracted (3), and to lower the reactivity of the ene adduct due to much smaller HOMO coefficients on the carbon atom (4).

2.1. Reactions with Aldehydes (ref. 1)

Under the influence of several Lewis acids, **I** reacts with a variety of aldehydes at low temperature to produce the corresponding ene adducts in good to high yields. The Lewis acid appears to have considerable influence on the reaction mechanism: Me_2AlCl usually gave a (*Z*)-*anti* adduct preferentially irrespective of the geometry of the ene (ref. 2), while in TiCl_4 -mediated reactions, stereochemical outcome of the adduct is highly dependent on the geometry (ref. 3). Typical examples are shown in Eq 1 and 2.

These results indicate the Al-mediated reactions proceed through the usual ene mechanism including a 5-membered transition state, whereas the Ti-induced reactions favor the 6-membered chair-like transition state (ref. 3). Selective formation of the (Z) adduct observed in the former has attracted mechanistic interest. Such selectivity could be attributed to the electrostatically stabilized conformation, through which the reaction proceeds preferentially.

Other synthetically useful features of the ene reactions are also shown in the following equations (ref. 4).

Kinetic Resolution

Chelation-Controlled *Syn* Selective Ene Reaction

2.2. Chirality Transferred Ene Reactions

On using a chiral substrate in this reaction, it was expected a rigid transition state (Fig 2) involved in the ene reaction induces effective chirality transfer from the ene to the resulting alcohol. The following results verified such expectation. The requisite chiral ene, e.g., **Id-(R)**, was readily prepared from the corresponding thiol ester by Tebbe methylenation (Eq 5) (ref. 5).

On treating the optically pure ene with aldehydes in the presence of Me_2AlCl , most aliphatic and aromatic aldehydes gave the corresponding ene adduct with high ee. The following example shows the efficacy of the reaction with an aliphatic aldehyde (ref. 6).

We attempted to apply this methodology to the enantioselective synthesis of anthracycline precursors. Examination of the reaction using *o*-methoxybenzaldehyde gave rather discouraging results. Although the adduct was obtained in good yield, the ee of the product was only 91%. The unsatisfactory result may be attributable to the strong coordination effect of the *o*-methoxy group

Scheme 2

which produces an appreciable amount of a *cisoid* species between the aldehyde and Lewis acid to disturb the transition state. Finally, we found use of a less basic siloxy group in place of MeO circumvented such problem, to afford an almost optically pure adduct in good yield (ref. 7).

Several synthetic advantages are also involved in this synthetic Scheme 2. By using the directing effect of hydroxy group, (i) regioselective hydroxymethylation can be performed, and (ii) the enol ether moiety can be utilized for A-ring closure, which could be effected by a relatively weak Lewis acid such as Me₂AlCl and the product was obtained in good yield as the single enantiomer. (Construction of the A-ring was one of the most critical steps: use of a stronger Lewis acid is usually accompanied by aromatization.) By utilizing the methylthio group, (iii) regioselective conversion to the enol ether was performed, and the hydroxy group-directed oxidation gave the desired compounds.

2.3. Imines Ene Reactions

Since olefins employed for ene reactions are usually not so reactive as enol ethers, highly reactive enophiles are required as the reaction partner, and less reactive imines can not be utilized in usual ene reactions. In contrast, use of highly reactive **I** has made it possible to effect the imine-ene reaction with high efficacy. Aromatic imines usually gave the corresponding adduct in good yields, whereas the yields were greatly decreased with aliphatic imines. During these investigations, it has been found that, in place of imines, biscarbamates (ref. 8) can be employed as efficient imine precursors and, in the presence of BF₃·OEt₂ or TMSOTf, they reacted with **I** in good yields (Eq 7) (ref. 9).

Use of such Lewis acid appears to favor the 6-membered chair-like transition state (Fig 3) which may account for *syn/anti* selectivity depending on the geometry of the starting ene.

R	Yield(%)	<i>syn</i> : <i>anti</i>
C ₇ H ₁₅	84	96 : 4
i-C ₄ H ₉	79	94 : 6
i-C ₃ H ₇	88	>99 : <1
o-C ₆ H ₁₁	77	99 : 1

C ₇ H ₁₅	55	9 : 91
i-C ₄ H ₉	73	6 : 94
i-C ₃ H ₇	21	8 : 92
o-C ₆ H ₁₁	23	12 : 88
C ₆ H ₅	86	10 : 90

Several pyrrolidine derivatives can also be used as enophiles in the reaction with **I**. Thus, by reactions with **Ib**-(Z) or **Ib**-(E), 2-pivaloyloxy *N*-methoxycarbonylpyrrolidine gave *syn*- or *anti*-adducts, respectively, which were identified by conversion to the known natural products, heliotridane and pseudoheliotridane (Eq 8) (ref. 10).

Interestingly, the reactions with N-benzylpyrrolidones exhibited reverse selectivities: **Ib**-(Z) preferentially produced *anti* adduct as shown below (Eq 9), whereas **Ib**-(E) gave mainly *anti* adduct in lower selectivity (*syn:anti* = 29:71) (ref. 10).

These results may support the proposed mechanism involving a six-membered chair-like transition state (Fig 3).

Based on the high *anti* selectivity observed in the reaction with **Ib**-(Z), asymmetric imine ene reactions were also examined by using pyrrolidone containing a chiral benzyl moiety as the auxiliary. Results are shown below (Eq 10 and 11). In both cases, *anti* selectivity (96:4) is well consistent with the value observed in the above transformation. It should be noted that introduction of a methoxy group has a remarkable influence on the mode of asymmetric induction, and a completely different induction was attained as shown below (ref. 11).

These results may be explained by assuming two different transition states, TS-1 and TS-2. Namely, the reaction of the substrate having a phenethyl substituent is considered to proceed through a Felkin-Anh-like transition state (TS-1), which favors the approach of a nucleophile from the upper side to form mainly the (5*S*,6*S*)-product.

In the latter case, an electronegative methoxy group may alter the transition state to a dipolar state, where the cationic carbon is closely situated to the methoxy group (TS-2). Apparently, a nucleophile preferentially approaches from the lower side to yield the (5*R*,6*R*)-product as the major product.

Diastereo- or enantioselective carbon chain introduction is very important for construction of nitrogen-containing natural products, e.g., pyrrolizidine alkaloids. The present methodologies may satisfy several criteria for such purpose, and their synthetic utility will be clarified in the near future.

3. Formal [3 + 2] Cyclopentane Annulation

During investigation of the ene reaction using **Ie**, we noticed the extreme lability of 3-(alkylthio)-2-siloxyallyl alcohol derivatives under acidic conditions and these observations led us to explore a new type of three-carbon unit for cyclopentanone or methylenecyclopentane annulation (Fig 4). On treating electron-rich olefins with **IV** in the presence of an appropriate Lewis acid, the corresponding cyclopentanones were obtained (ref. 12). Enol silyl ethers sometimes accompanied formation of acyclic products, but enol ethers as well as vinylsulfides gave the cyclopentanones in good yield. The reaction proceeds through an initial trapping of the allylcationic species with olefins followed by cyclization, namely, formal [3 + 2] cycloaddition.

To clarify the scope and limitations of this annulation methodology, the reactions with trisubstituted olefin were also examined. In the presence of AlCl₃, the reaction occurred to give the cyclopentanone, but was accompanied by the formation of a large amount of a hydrochlorinated product. However, in the presence of proton sponge (1,8-bis(dimethylamino)naphthalene), such side reaction could be averted, affording the cycloaddition products in good yields. Other examples including [4 + 3] cycloaddition are shown in Eq 13.

Combined use of the ene reaction and the annulation provided an opportunity to examine an intramolecular reaction (Eq 14).

In a synthetic application of the annulation methodology, we attempted to synthesize a triquinane natural product, coriolin. Considering ready accessibility of an optically pure substrate, we chose **V** as the starting material, and two consecutive cyclopentanone annulation procedures were examined.

Preliminary results are shown in Eq 15 (ref. 13). An initial annulation took place selectively from the opposite side of the benzyloxy group, and the second one was introduced from the opposite face of the C ring, affording the tricyclic with correct stereochemistry. The final functional group manipulation is well established by Danishefsky, and a formal total synthesis of coriolin was completed via the shortest pathways.

By replacing the siloxy with a silylmethyl group, a similar reagent could be used for methylenecyclopentane annulation (ref. 14). Results are shown in Table 2.

A similar methylenecyclopentane annulation has been performed by a palladium-catalyzed reaction, where the olefins used were restricted to electron-deficient ones. Thus, these two methods can be used to compensate each other.

Table 2

Olefin	Lewis Acid	Product	Yield(%)	Olefin	Lewis Acid	Product	Yield(%)
	$\text{BF}_3 \cdot \text{OEt}_2$		75 (<i>trans</i> : <i>cis</i> = 94 : 6)		$\text{BF}_3 \cdot \text{OEt}_2$		50
	EtAlCl_2		81		EtAlCl_2		24
	EtAlCl_2		71				18
	MeAl(OTf)_2		78				

(R = C₅H₁₁)

4. Tandem Carbon-Carbon Bond Formation/Cleavage Reactions

As an extension of the characteristic features of vinylsulfide chemistry, we became intrigued by the retro-ene type fragmentation combined with regioselective C-C bond formation and thus designed the following transformation involving a tandem C-C bond formation/cleavage type reaction. An initial reaction with an electrophile would afford a thionium ion, which in turn would lead to the more stable oxonium cation via C-C bond cleavage (Fig 5). An intramolecular version of such transformation would be extremely useful for macrocyclic compound synthesis.

According to designed fashion, the reaction took place readily with aliphatic, aromatic and unsaturated aldehydes or acetals under the influence of an appropriate Lewis acid. Surprisingly, the reaction of **VIb** was highly stereoselective to yield the corresponding products with almost complete *E* and *syn* selectivity, whereas a 1:1 mixture of geometrical isomers was obtained from **VIa** (ref. 15). Similar results were also observed by using vinylsulfides containing a TMS-CH₂ group (ref. 16).

Table 3

n	R	R'	Lewis Acid	Yield (%)	syn : anti
1	C ₆ H ₁₃	Et	TiCl ₃ (O ⁱ Pr)	87	>99 : <1
1	C ₆ H ₅ CH ₂ CH ₂	Et	TiCl ₃ (O ⁱ Pr)	84	>99 : <1
1	C ₆ H ₅	Et	TiCl ₄	86	>99 : <1
2	C ₆ H ₅	Me	TiCl ₄	.82	>99 : <1
2	C ₆ H ₅ CH=CH	Me	TiCl ₄	77	96 : 4
2	C ₆ H ₁₃	Et	TiCl ₄	79	>99 : <1 ^{a)}
2	C ₆ H ₅ CH ₂ CH ₂	Et	TiCl ₄	80	>99 : <1

a) A small amount (5%) of (Z)-syn isomer.

The great difference in geometrical selectivity observed in these reactions is noteworthy. To clarify the different behavior and to understand the *E* selectivity, PM3 calculations on model C-1 and C-2 were performed. The results indicate the energy difference between the two conformers of **VIa** was much smaller, but the conformer C-1 of **VIb** is 1.46 kcal/mol more stable than C-2. Even if the reaction proceeds via a stepwise mechanism, rotation of the alkenylsulfide moiety after initial C-C bond formation may be greatly disfavored by severe repulsion between the neighboring substituents on the cyclohexane ring. Therefore, preferential formation of the *E* isomer could be attributed to the greater stability of the C-1 of **VIb** over C-2.

The diastereoselectivity could be explained by assuming the 6-membered chair-like transition state which imposes coordination of both oxygen and sulfur to Ti.

Origin of Selectivities: (*E*) Selectivity

	C-1	C-2	DE
R ¹ = R ² = Me	-120.68	-119.22	1.46
R ¹ = Ph, R ² = H	-75.75	-75.41	0.34

Optimized using MOPAC 6.10. Energy in kcal/mol.

Origin of Selectivities: *Syn* Selectivity

The use of a monocoordinate Lewis acid was anticipated to result in different diastereoselection. Indeed, the reaction of **VIb** (R, R¹, R² = Me) and benzaldehyde in the presence of EtAlCl₂ afforded a 83:17 mixture of *E-anti* and *E-syn* products in 61% yield.

In contrast, 1,4-addition took place selectively in the reactions of **VI** with α,β -unsaturated carbonyl compounds even in the reactions with enals. Although the products were obtained as a mixture of geometrical isomers of enol silyl ethers, the stereochemistry of the alkenylsulfide moiety as well as the diastereomeric center was completely controlled as *E-anti* (ref. 17).

TiCl₃(O*i*Pr) could only effect the reaction of a five-membered substrate **VI** (n = 1), but use of TMSOR with a catalytic amount of TMSOTf was found to induce such reaction on 6- and 7-membered ring compounds.

Table 4

R ¹	R ²	R ³	Yield (%)
CH ₃	H	H	88
C ₄ H ₉	H	H	73
C ₃ H ₇	CH ₃	H	61
CH ₃	H	CH ₃	76
CH ₃	H	C ₄ H ₉	84

Table 5

n	R ¹	R ²	Yield (%)
1	CH ₃	Bn	64 ^a)
1	C ₄ H ₉	Me	80
2	CH ₃	Bn	82
2	C ₄ H ₉	Me	78

a) Enol silyl ether (18%).

Selective conjugate addition of vinylsulfides has attracted much interest both synthetically and theoretically. We would like to propose the mechanism including two types of HOMO/LUMO interactions. The HOMO and LUMO coefficients of the nucleophile and electrophiles are shown in Table. As judged from these values, a significant interaction between the sulfur and carbonyl carbon, each having the largest HOMO and LUMO coefficients, respectively, is expected to play an important

role in the early stage of the reaction to fix the transition state as a [3 + 3] six-membered one (ref. 18). The reaction may proceed through a thermally favored chair-like transition state leading to the *E-anti* adduct selectively.

Mechanism for (*E*)-*Anti* Selective 1,4-Addition Reaction

The reaction with an acetylenic aldehyde gave the corresponding 1,2-addition product exclusively. The linear electrophile may be prevented from entering into the six-membered chair-like transition state (Fig 8), and consequently, the reaction preferentially proceeds through TS as shown in Fig 7 to afford such product.

5. Conclusion

The major purpose of this article is to show how different the reaction styles of vinylsulfides are from those of the corresponding enol ethers or enol silyl ethers. Vinylsulfides have been apt to be recognized as derivatives of the enol ethers, and were expected to behave similarly with ethers. But, as described above, they often follow completely different reaction pathways, especially in the cases involving the thionium cationic species. Keeping their characteristic features in mind, further appropriate design will lead to disclosing useful synthetic methodologies not effected with oxygen analogs.

References and Notes

- (1) For reviews on the ene reaction, see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.*, **1969**, 8, 556. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.*, **1978**, 17, 476. (c) Snider, B. B. *Acc. Chem. Res.*, **1980**, 13, 426. (d) Dubac, J.; Laporterie, A. *Chem. Rev.*, **1987**, 87, 319. (e) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 1.1, pp 1-27. (f) Mikami, K.; Shimizu, M. *Chem. Rev.*, **1992**, 92, 1021.
- (2) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.*, **1990**, 31, 2165.
- (3) Nakamura, T.; Tanino, K.; Kuwajima, I. *Chem. Lett.*, **1992**, 1425.
- (4) Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.*, **1993**, 34, 477.
- (5) Tanino, K.; Shoda, H.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.*, **1992**, 33, 1337.
- (6) Masuya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.*, **1994**, 35, 7965.
- (7) Adachi, A.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.*, **1993**, 58, 4189. Kamei, S.; Sasaki, Y.; Ohashi, Y.; Adachi, A.; Tanino, K.; Kuwajima, I. *Acta Cryst.*, **1993**, C49, 1509.
- (8) Geminal biscarbamate as a precursor of *N*-acyliminium intermediate in hetero Diels-Alder reactions: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 2, p 34 and references cited therein.
- (9) Tohyama, Y.; Tanino, K.; Kuwajima, I. *J. Org. Chem.*, **1994**, 59, 518.
- (10) Unpublished observation by K. Sato in this laboratory.
- (11) Sato, K.; Koga, T.; Masuya, K.; Tanino, K.; Kuwajima, I. *Synlett* in press.
- (12) Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *Synlett*, **1996**, 157.
- (13) Domon, K.; Tanino, K.; Kuwajima, I. to be published.
- (14) Takahashi, Y.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* in press.
- (15) Takayanagi, M.; Umamori, N.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.*, **1993**, 115, 12635.
- (16) Unpublished results by M. Sugai in this laboratory.
- (17) Takayanagi, M.; Tanino, K.; Kuwajima, I. *Synlett*, **1995**, 173.
- (18) Similar HOMO/LUMO interactions are also suggested for [2 + 2] cycloaddition reactions of alkenylselenides and enones: Yamazaki, S.; Tanaka, M.; Yamaguchi, A.; Yamabe, S. *J. Am. Chem. Soc.*, **1994**, 116, 2356.

(Received June 27, 1996)