A Novel Transformation Involving Selective Formation and Cleavage of C-C Bonds

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Both C–C bond formation and cleavage processes are important in organic synthesis. Although reactions including both of these would constitute efficient methodologies for construction of a carbon skeleton, only intramolecular examples are well documented as carbon skeleton rearrangement reactions;[1] a scant number of papers were cited as dealing with the intermolecular version.[2]

In relation to alkenyl sulfide chemistry described previously,[3] we became intrigued by the retro-ene-type fragmentation reaction combined with regioselective C–C bond formation and thus designed an alkenyl sulfide **A** containing a β-siloxy group with a view to inducing a tandem C–C bond formation–cleavage-type reaction. We envisioned that reaction of **A** with an electrophile would afford thionium ion **B**, which in turn would lead to the more stable silyl oxonium ion **C** via C–C bond cleavage[4] (Scheme I).

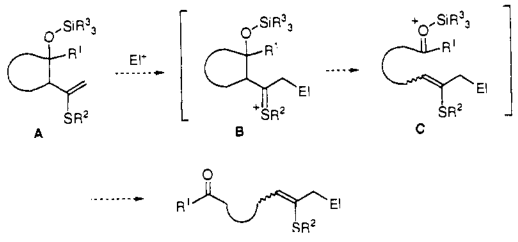
The starting materials **1a**–**1e** were prepared from corresponding oxiranes in three steps as shown in Scheme II. First, the reactions of **1a** and **1b** with aldehydes were examined in the presence of several Lewis acids. Although use of $TiCl_4$, $AlCl_3$, $SnCl_4$, or $BF_3 \cdot OEt_2$ resulted in the formation of complex mixtures or hydrolysis of the siloxy group, the choice of $TMSCl–ZnCl_2$ or $TiCl_3(O^iPr)$ cleanly induced the desired transformation. The reaction took place readily with aliphatic, aromatic, and α,β-unsaturated aldehydes, and the products were obtained as almost 1:1 mixtures of two geometrical isomers. The results are summarized in Table I.

Next, the stereochemical outcome was examined using **1c**–**1e** as substrates. Although the reaction in the presence of $TMSCl–ZnCl_2$ gave poor yield in these cases, $TiCl_4$ and $TiCl_3(O^iPr)$ effected smooth conversion. Surprisingly, the reaction was highly stereoselective to yield the corresponding products with almost complete *E* and *syn* selectivity as shown in Table II.[5,6]

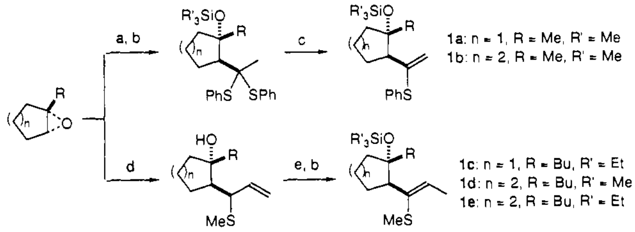
The great difference of geometrical selectivity observed in these reactions is noteworthy. To clarify the different behavior and to understand the *E* selectivity, PM3[8] calculations on **1b** and model compound of **1d** were performed (Table III). The results indicate that the energy difference between the two conformers (**C-1** and **C-2**) of **1b** was much smaller, but the conformer **C-1** of **1d** is 1.46 kcal/mol more stable than **C-2**. Even if the reaction proceeds via a stepwise mechanism, rotation of the alkenyl sulfide 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* product could be attributed to the greater stability of conformer **C-1** over **C-2**.

The diastereoselectivity of the reaction could be explained by assuming the cyclic transition state models **TS-1** and **TS-2** which

Scheme I

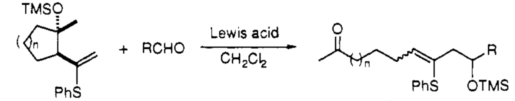


Scheme II[a]



[a] (a) $CH_3CH(SPh)_2$, BuLi, TMEDA. (b) R'_3SiCl, imidazole, DMF. (c) imidazole, DMF, reflux. (d) $CH_2{=}CHCH_2SMe$, BuLi. (e) KH, DMF.

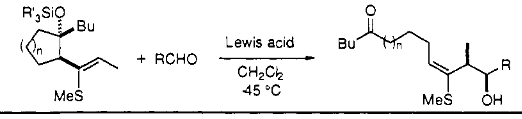
Table I. Reaction of **1a** and **1b** with Aldehydes



entry	substrate	R	Lewis acid	product (yield, %)
1	**1a**	$PhCH_2CH_2$	$TiCl_3(O^iPr)$	**2** (69)[a]
2	**1a**	Ph	$TMSCl–ZnCl_2$	**3** (83)
3	**1a**	$PhCH{=}CH$	$TMSCl–ZnCl_2$	**4** (70)
4	**1b**	$PhCH_2CH_2$	$TiCl_3(O^iPr)$	**5** (66)[a]
5	**1b**	Ph	$TMSCl–ZnCl_2$	**6** (90)
6	**1b**	$PhCH{=}CH$	$TMSCl–ZnCl_2$	**7** (67)[a]

[a] Isolated as an alcohol after hydrolysis.

Table II. Stereoselective Reaction of **1c**, **1d**, and **1e** with Aldehydes



entry	substrate	R	Lewis acid	product (yield, %)	*E-syn*:*E-anti*
1	**1c**	C_6H_{13}	$TiCl_3(O^iPr)$	**8** (87)	>99:<1
2	**1c**	$PhCH_2CH_2$	$TiCl_3(O^iPr)$	**9** (84)	>99:<1
3	**1c**	Ph	$TiCl_4$	**10** (86)	>99:<1
4	**1d**	Ph	$TiCl_4$	**11** (82)	>99:<1
5	**1d**	$PhCH{=}CH$	$TiCl_4$	**12** (77)	96:4
6	**1e**	C_6H_{13}	$TiCl_4$[a]	**13** (79)	>99:<1[b]
7	**1e**	$PhCH_2CH_2$	$TiCl_4$[a]	**14** (80)	>99:<1

[a] A 9:1 mixture of $TiCl_4$ and $Ti(O^iPr)_4$ was used. [b] A small amount (5%) of the *Z-syn* isomer was also formed.

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[1] (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 705–1014. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 785–1035.

[2] Intermolecular reaction including C–C bond formation and ring cleavege: Karim, M. R.; Sampson, P. *Tetrahedron Lett.* **1988,** *29,* 6897.

[3] (a) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990,** *31,* 2165. (b) Tanino, K.; Shoda, H.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1992,** *33,* 1337. (c) Nakamura, T.; Tanino, K.; Kuwajima, I. *Chem. Lett.* **1992,** 1425. (d) Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993,** *34,* 477.

[4] Fragmentation reaction of 1-hydroxy-2-[bis(phenylthio)methyl]cyclohexane and cyclopentane: Semmelhack, M. F.; Tomesch, J. C. *J. Org. Chem.* **1977,** *42,* 2657.

[5] The $TiCl_4$-mediated reaction of enolizable aldehydes afforded a mixture of *E* and *Z* products. However, such isomerization of the alkenyl sulfide moiety can be avoided by addition of $Ti(O^iPr)_4$ as a proton accepter.

[6] The *E* configuration of the products was determined by observation of NOE between the methylthio group and the olefinic proton. The methyl ether derived from the product was treated with ozone followed by periodic acid to give a β-methoxy acid, which was methylated by diazomethane. The stereochemistry of the ester was confirmed by comparing the ^1H NMR spectra with those of authentic materials prepared from β-hydroxy acids.[7]

[7] Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980,** *45,* 1066.

[8] (a) Stewart, J. J. P. *J. Comput. Chem.* **1989,** *10,* 209. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989,** *10,* 211.

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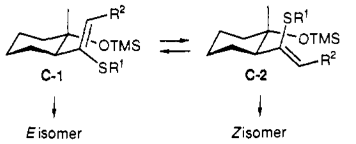
Table III. Calculated Energies for Conformers of Starting Materials[a]



	C-1	C-2	ΔE^b
$R^1 = R^2 = Me$	−120.68	−119.22	1.46
$R^1 = Ph, R^2 = H$	−75.75	−75.41	0.34

[a] Optimized using MOPAC 6.10. Energy in kcal/mol. [b] Energy difference between **C-1** and **C-2**.

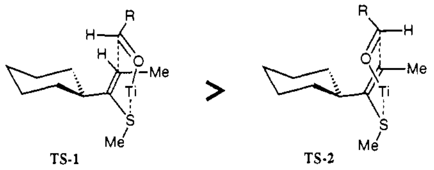


Figure 1. Cyclic transition state models **TS-1** and **TS-2**.

imposes coordination of both carbonyl oxygen and sulfur to the titanium atom (Figure 1). The reaction may proceed through an energetically favored chairlike transition state **TS-1** to afford the *syn* product predominantly.

The use of monocoordinate Lewis acid was anticipated to result in different diastereoselection. Indeed, the reaction of **1d** and benzaldehyde in the presence of $EtAlCl_2$ afforded a 83:17 mixture of *E-anti* and *E-syn* product in 61% yield.

In conclusion, a novel transformation involving both formation and cleavage of C–C bonds with high selectivity was developed, making use of the tendency of the alkenyl sulfide moiety to undergo rearrangement. Considering that the cross coupling reaction of alkenyl sulfides with Grignard reagents[9] proceeds stereospecifically, the high *E* selectivity as well as *syn* selectivity of the reaction provides wide applicability in organic synthesis. We are currently investigating the reaction of **1c**, **1d**, **1e**, and several alkenyl sulfides with various electrophiles.

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Supplementary Material Available: Experimental procedures and spectral data for **1–14** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[9] (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637. (c) Okamura, H.; Miura, M.; Kosugi, K.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 87. (d) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075. (e) Trost, B. M.; Ornstein, P. L. *Tetrahedron Lett.* **1983**, *24*, 2833. (e) Fiandanese, V.; Marchese, G.; Mascolo, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1988**, *29*, 3705.