Organic LETTERS

Letter

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Intramolecular [1,4]-*S*- to *O*-Silyl Migration: A Useful Strategy for Synthesizing *Z*-Silyl Enol Ethers with Diverse Thioether Linkages

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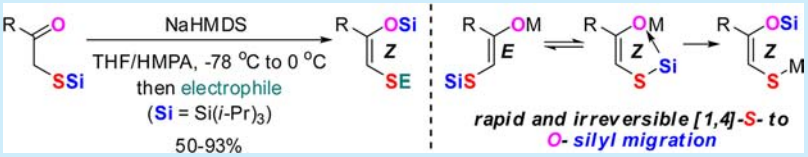
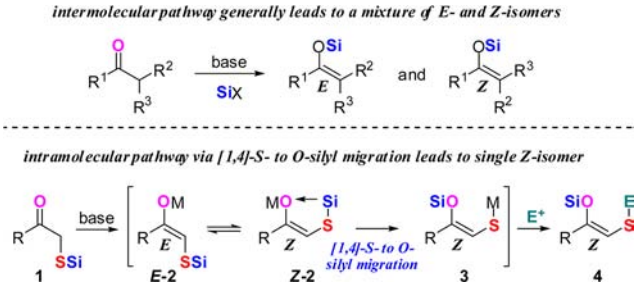
Supporting Information



ABSTRACT: An intramolecular [1,4]-S- to O-silyl migration has been used to form silyl enol ethers with *Z*-configurational control. The silyl migration also creates a new anion center at sulfur, which can subsequently react with electrophiles to generate *Z*-silyl enol ethers with diverse thioether linkages. The synthetic utility of this pathway was demonstrated by modifying the Z-silyl enol ethers with aldehydes via a Mukaiyama aldol reaction or Prins cyclization to generate functionalized organosulfur compounds.

Silyl enol ethers[1] are important synthons in a broad array of synthetic transformations. The double-bond configuration is a key determinant of the stereochemical outcomes of reactions in which they participate, making the preparation of geometrically defined silyl enol ethers a longstanding goal of organic synthesis.[2] Traditionally silyl enol ethers are synthesized by α-deprotonation of carbonyl compounds, followed by intermolecular silylation of the resulting enolate. Extensive studies have shown that deprotonating acyclic ketones under kinetic conditions favors formation of *E*-enolate, while deprotonating the ketone under thermodynamic conditions favors the *Z*-enolate (Scheme 1, top). However, this configurational control is sometimes inefficient and unreliable, highlighting the need for intermolecular reactions that provide better stereochemical control.

Scheme 1. Intermolecular Silylation of Enolate To Form *E*- and *Z*-Silyl Enol Ether (Top). Intramolecular [1,4]-*S*- to *O*-Silyl Migration Leads to *Z*-Silyl Enol Ether (Bottom)



A potentially better alternative might be via an intramolecular pathway through silyl migration.[3] Surprisingly, although intramolecular anionic silyl migration between a carbon and an oxygen atom is a well-established, valuable process in organic chemistry,[4] the corresponding migration from a sulfur to an oxygen has rarely been studied.[5,6] This transformation should be thermodynamically favorable because the Si−O bond is stronger than the Si−S bond (ca. 110 vs 70 kcal/mol).[7] Intrigued by the potential ease of this silyl migration,[8] we envisioned using it to form silyl enol ethers with configurational control. In our proposed process (Scheme 1, bottom), deprotonation of the α-silylthio ketone **1** would generate a mixture of enolates ***E*-2** and ***Z*-2**. It should be possible to shift the product equilibrium permanently toward ***Z*-2** if only the Z-enolate could undergo intramolecular [1,4]-*S*- to *O*-silyl migration rapidly and irreversibly to thiometallo *Z*-silyl enol ether **3**. The sulfur would act not only as a carrier for the silyl migration but also as an anion center in **3** for the subsequent formation of a C−S bond with electrophiles. In this way, a thioether linkage[9] could be introduced into **3** to provide *Z*-silyl enol ether **4**. Here, we report detailed studies of this reaction pathway.

The model scaffold α-silylthio ketone **1a** was prepared in 92% yield by substituting α-bromo acetophenone with commercially available HSSi(*i*-Pr)$_3$. The reaction was initially performed in THF using LiHMDS as the base and 1.2 equiv of HMPA as additive (Table 1, entry 1). After deprotonation at −78 °C for 2.0 h, the reaction was warmed to 0 °C to promote *S*- to *O*-silyl migration and subsequent S-allylation with allylbromide. The *Z*-silyl enol ether **4a** was obtained in 41% yield as a single isomer. The low efficiency is probably because the relatively strong Li^+ counterion retards both silyl migration and S-allylation. Indeed, using the weaker counterions Na^+ or K^+ led to higher yields of 74% and 52%, respectively (entries 2 and 3).[10] The fact that we observed no O-allylation implies that

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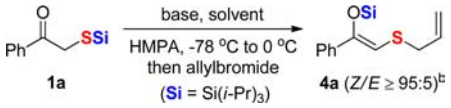
Table 1. Screening of Reaction Conditions



entry	base	solvent	HMPA (equiv)	yield[c] (%)
1	LiHMDS	THF	1.2	41
2[a]	NaHMDS	THF	1.2	74
3	KHMDS	THF	1.2	52
4	NaHMDS	THF		71
5	NaHMDS	Et_2O	1.2	65

[a]Reaction conditions: 0.15 mmol of **1a**, 0.18 mmol of HMPA, and 0.20 mmol of NaHMDS (1.0 M in THF) in 2.0 mL of THF at −78 °C, 2.0 h, warmed to 0 °C, 0.5 h; then 0.13 mmol of allylbromide at 0 °C, 2.0 h. [b]The *Z*-configuration was assigned by NOE experiments on **4a**. Ratios were determined by ^{1}H NMR spectroscopy. [c]Isolated yields after purification by silica gel column chromatography.

the *S*- to *O*-silyl migration is irreversible. The reaction proceeded readily with NaHMDS in the absence of HMPA, though a longer allylation time was required to achieve a final yield of 71% (entry 4). Et_2O was also a less effective solvent than THF, giving **4a** in 65% yield (entry 5).

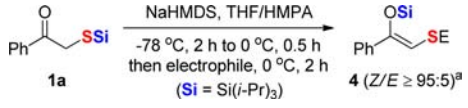
Next, the scope of electrophiles was tested using **1a** and a range of alkyl halides (Table 2, entries 1−3), benzyl bromide (entry 4), and propargyl bromide (entry 5). These reactions gave *Z*-silyl enol ethers **4a−f** tethered with diverse thioether linkages. Monosubstituted and geminal disubstituted epoxides also proved to be suitable electrophiles. The ring-opening occurred regioselectively at the less substituted carbon to afford **4g−l** in good yields (entries 6−11). Neither intra- nor intermolecular *O*- to *O*-silyl migration was observed after epoxide opening.

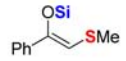
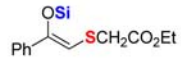
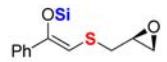
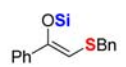
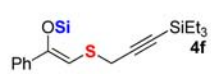
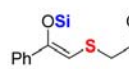
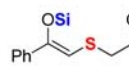
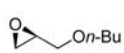
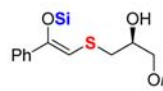
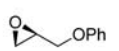
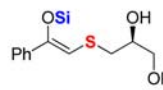
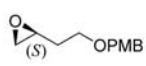
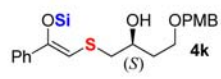
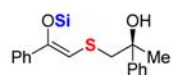
The multicomponent reaction was compatible with α-silylthio ketones **1b−f** that contained an alkyl group (Table 3, entry 1), an electron-rich or -deficient phenyl group (entries 2 and 3), or a heterocyclic moiety (entries 4 and 5). The temperature for epoxide opening had to be increased to 60 °C to ensure a good yield, except for the reaction in entry 3. Although ketone **1b** possessed two α-methylenes on each side of the carbonyl group, deprotonation occurred regioselectively at the thio-substituted methylene, even though this position is more sterically hindered. This selectivity may be because the H on the thio-substituted methylene is more acidic.

A control experiment was performed using an equimolar mixture of **1a** and acetophenone **5** under optimal conditions (Scheme 2). The reaction with epoxide led to *Z*-silyl enol ether **4i** in 68% yield. The original **5** was recovered in 98% yield, and no intermolecular silylation product **6** was detected. These results indicate that under our reaction conditions formation of **4i** proceeds by intramolecular [1,4]-*S*- to *O*-silyl migration of the corresponding *Z*-enolate. In contrast, β-thiosilyl propiophenone **7**, which contains an additional methylene between the carbonyl and thio groups, gave a complex reaction that did not generate the expected thiometallo *Z*-silyl enol ether **8**. The failure to form **8** probably reflects the longer transfer distance for [1,5]-*S*- to *O*-silyl migration, making it less favorable than the analogous [1,4]-migration.[8,11]

To demonstrate the synthetic utility of our approach, the resulting *Z*-silyl enol ether **4b** was used as a valuable synthon in Mukaiyama aldol reactions[12] with aldehydes (Scheme 3). The reaction using benzaldehyde gave α-thio β-silylated hydroxy ketone **9a** in 68% yield and with *syn*-stereochemical control. Performing the reaction with branched or unbranched alkyl aldehydes directly generated, respectively, α-thio β-hydroxy ketones **9b** in 50% yield or **9c** in 93% yield.

Table 2. Scope of Electrophiles



entry	electrophile	product		yield[b]
1	MeI		**4b**	93%
2	$BrCH_2CO_2Et$		**4c**	82%
3			**4d**	82%
4	BnBr		**4e**	80%
5			**4f**	86%
6			**4g**	63%
7			**4h**	70%
8			**4i**	74%
9			**4j**	67%
10			**4k**	68%
11			**4l**	62%

[a]Ratios were determined using ^{1}H NMR spectroscopy. [b]Isolated yields after purification by silica gel column chromatography.

In addition, we showed that *Z*-silyl enol ethers prepared from epoxides subsequently underwent an S-tethered Prins cyclization with an aldehyde.[13] This approach proceeded through a chairlike transition state **TS-11** to afford a wide range of functionalized 1,4-oxathianes **11** in good yields and with 2,6-*cis*/5,6-*trans* stereochemical control (Scheme 4). As some 1,4-oxathianes selectively activate the ideal M3 receptor subtype,[14] the synthetic approach we describe here may be useful for generating new potential muscarinic receptor agonists.

In summary, intramolecular [1,4]-*S*- to *O*-silyl migration has been utilized to form silyl enol ethers with *Z*-configurational control. The silyl migration also creates a new anion center at sulfur, which can subsequently react with electrophiles to generate *Z*-silyl enol ethers with diverse thioether linkages. The synthetic value of this approach was demonstrated by further

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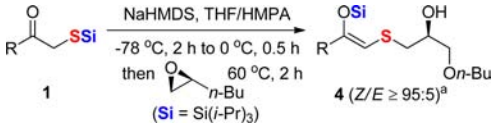
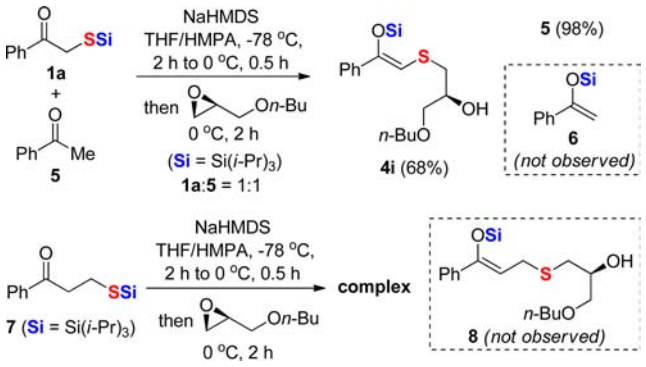
Table 3. Scope of α-Silylthio Ketone



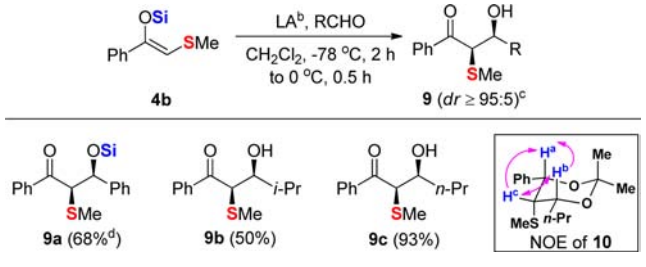
entry	R	product	yield[b]
1	Et (**1b**)	**4m**	50%
2	*p*-MeO-Ph (**1c**)	**4n**	55%
3[c]	*p*-Cl-Ph (**1d**)	**4o**	72%
4	2-furyl (**1e**)	**4p**	55%
5	2-thienyl (**1f**)	**4q**	62%

[a]Ratios were determined by ^{1}H NMR spectroscopy. [b]Isolated yields after purification by silica gel column chromatography. [c]Epoxide opening was performed at 0 °C.

Scheme 2. Control Experiment To Confirm the Intramolecular [1,4]-*S*- to *O*-Silyl Migration and Attempts To Achieve [1,5]-*S*- to *O*-Silyl Migration of 7

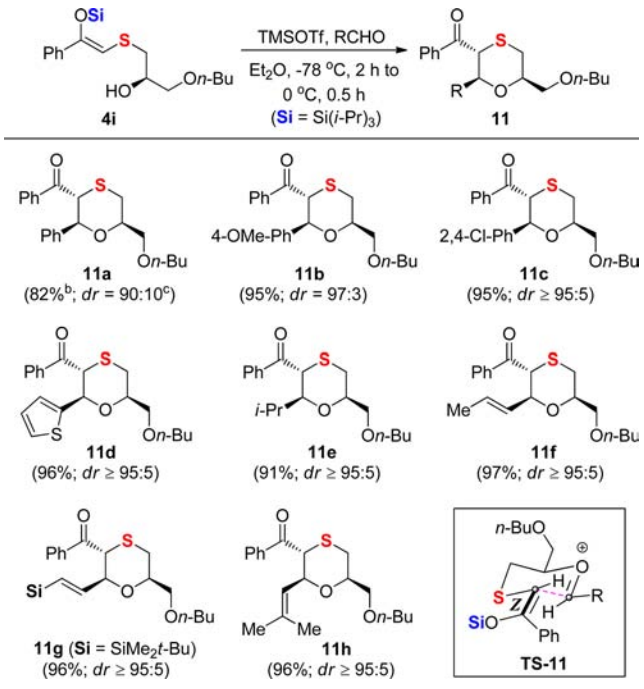


Scheme 3. Mukaiyama Aldol Reaction of 4b with Aldehydes[a]



[a]Reaction conditions: 0.10 mmol of **4b**, 0.20 mmol of aldehyde, and 0.10 mmol of Lewis acid in 1.5 mL of CH_2Cl_2 at −78 °C. [b]$BF_3{\cdot}OEt_2$ was used to generate **9a** and **9b**; $TiCl_4$, to generate **9c**. [c]The *syn*-stereochemistry was assigned based on NOE experiments on **10**. Ratios were determined by ^{1}H NMR spectroscopy. [d]Isolated yields after purification by silica gel column chromatography.

Scheme 4. S-Tethered Prins Cyclization of 4i with Aldehydes[a]



[a]Reaction conditions: 0.10 mmol of **4i**, 0.20 mmol of aldehyde, and 0.10 mmol of TMSOTf in 1.5 mL f Et_2O, −78 to 0 °C. [b]Isolated yields after purification by silica gel column chromatography. [c]The 2,6-cis/5,6-trans-stereochemistry was assigned based on NOE experiments on **11a**. Ratios were determined by ^{1}H NMR spectroscopy.

reacting the Z-silyl enol ethers with aldehydes via the Mukaiyama aldol reaction or the Prins cyclization to provide functionalized organosulfur compounds. Further applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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