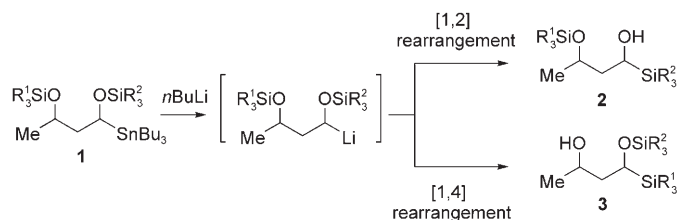


Regioselective Aliphatic Retro-[1,4]-Brook Rearrangements**

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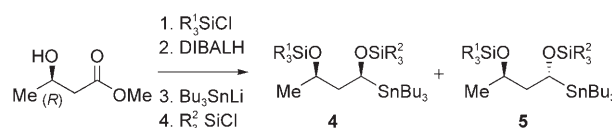
The migration of silicon is a ubiquitous process in reactions, and the Brook rearrangement is an intramolecular migration of a silicon atom from a carbon to an oxygen atom.^[1] The reverse process—migration of a silicon atom from an oxygen to a carbon atom—is referred to as the retro- or reverse-Brook rearrangement and is a common occurrence.^[2] Studies on retro-[1,2]-Brook rearrangements have revealed that the rearrangement is highly stereospecific with regard to the configuration at the carbon atom and proceeds with retention of configuration in the α -silyloxy carbanions generated from aliphatic substrates, whereas inversion is observed for benzylic and allylic carbanions.^[3] As the retro-Brook rearrangement requires excess base, the driving force for the reaction may be the formation of a lithium alkoxide that is more stable than the starting organolithium compound. Higher-order retro-[1,3]-, -[1,4]-, -[1,5]-, and -[1,6]-Brook rearrangements have also been the subject of numerous investigations, and have been utilized for the preparation of functionalized organosilane derivatives.^[4–8] The general trend of the ease of silyl migration has been reported to be [1,2] > [1,3] $\gg$ [1,4] > [1,5] based on the logic that the shorter transfer distance is more favored,^[9] and this order of migration has long been accepted without question.^[5a,6c] It has recently been reported that the regioselectivity of the retro-[1,2]- and [1,4]-Brook rearrangements in an allyllithium system depends upon the reaction conditions, and that the addition of hexamethylphosphoramide (HMPA) as a cosolvent improves the [1,4] selectivity.^[5b] However, there has been no study of competitive silyl migration occurring in aliphatic retro-Brook rearrangements. We decided to investigate the relative ease of otherwise comparable [1,2] and [1,4] migrations. We report here the first documented example of the preference of retro-[1,4]-migration over retro-[1,2] migration in an α,γ -disilyloxy organolithium system.

To evaluate the regioselectivity of the retro-Brook rearrangement, we examined 1,3-disilyloxy-1-tributylstannylbutane derivatives **1**, which can form [1,2] and [1,4] products **2** and **3**, respectively, after transmetalation and rearrangement (Scheme 1). The optically active stannanes **4** and **5** were synthesized in a pure form by the reaction of tributylstannyl-



Scheme 1. Retro-[1,2]- and [1,4]-Brook rearrangements.

lithium^[10] and an aldehyde prepared from methyl (*R*)-3-hydroxybutyrate (98% *ee*) followed by silylation and separation by flash chromatography (Scheme 2). The configurations of **4** and **5** were determined to be *syn* and *anti*, respectively, by formation of the acetonide^[11] and by ¹³C NMR analysis using the Rychnovsky method.^[12]



Scheme 2. Synthesis of 1,3-disilyloxy-1-tributylstannylbutane derivatives. DIBALH = diisobutylaluminum hydride

Initial experiments focused on the retro-Brook rearrangement of the *syn*-1,3-disilyloxystannane derivatives **4** (Table 1). Treatment of **4a** with *n*BuLi (5.0 equiv) in THF at -78°C for 30 minutes did indeed give *C*-silyl products. However, instead of the expected *C*-trimethylsilylated product **6a**, the *C*-triethylsilylated product **7a** was obtained as a major product in a stereochemically pure form (Table 1, entry 1). This result was particularly surprising, considering that the relative ease of migration of silyl groups has been reported as [1,2] $\gg$

Table 1: Rearrangement of *syn*-1,3-disilyloxystannane derivatives **4a–g**.

Entry	4	nBuLi, THF, -78°C , 30 min		Yield [%] ^[b]	6:7 ^[c]
		R ¹ Si ^[a]	R ² Si ^[a]		
1	4a	TES	TMS	91	11:89
2	4b	TES	TES	90	15:85
3	4c	TBS	TMS	95	3:97
4	4d	TBS	TES	98	3:97
5	4e	TBDPS	TMS	98	0.3:99.7
6	4f	TBDPS	TES	98	8:92
7	4g	TBDPS	TBS	NR	–

[a] TMS = trimethylsilyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl. [b] Yield of isolated product. NR = no reaction. [c] Determined from the yields of **6** and **7**.

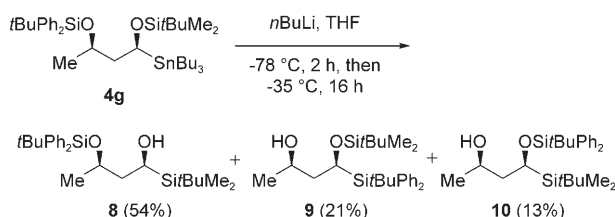
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[1,4],^[5a,6c,9] and that α -silyloxyalkylstannane derivatives undergo rapid retro-[1,2]-Brook rearrangement (< 15 min) under the same conditions.^[3e] Silyl groups of various size migrate in high yields and the predominance of [1,4] migration over [1,2] migration is general (Table 1). Notably, a larger silyl group at the γ position enhances the preferential [1,4] selectivity for the rearrangement (Table 1, entries 3–6).

Under the standard transmetalation/rearrangement conditions, the retro-Brook rearrangement of stannane **4g** containing bulky TBDPS and TBS groups did not occur because of the steric bulk around the Sn atom. This limitation of the transmetalation was addressed by increasing the reaction temperatures from -78 to -35 °C, which yielded three products, **8**, **9**, and **10** (Scheme 3). Compound **10** was



Scheme 3. Retro-Brook rearrangement of **4g**.

evidently the result of the retro-[1,2]-Brook rearrangement of the TBS group, followed by the [1,5] oxygen to oxygen migration of the TBDPS group.^[13] The net ratio of the retro-[1,2] versus the -[1,4] rearrangement was 76:24, thus showing opposite selectivity to the reactions of **4a–f**.

We next explored the generality of the trend of the retro-Brook rearrangement using the *anti*-1,3-disilyloxystannane derivatives **5**. In all of the cases examined, transmetalation and rearrangement proceeded in good to excellent yields (Table 2). The product ratios revealed again the relative ease of migration to be $[1,2] \ll [1,4]$. As in the case of a *syn* series, increasing the size of the silyl group at the γ position relative to that at the α position caused complete [1,4] rearrangement (Table 2, entries 5 and 6). Considering that the rate of retro-[1,4]-Brook rearrangements decreases with increasing bulkiness of the silyl group,^[5b,d] it is noteworthy that the reaction of stannane **5g** with bulky TBDPS and TBS groups also

Table 2: Rearrangement of *anti*-1,3-disilyloxystannane derivatives **5a–g**.

Table 2. Rearrangement of *anti*-1,5-*di*-*n*-alkoxyalkane derivatives **5a–g** to *syn*-1,5-*di*-*n*-alkoxyalkane derivatives **11a–g** and **12a–g**.

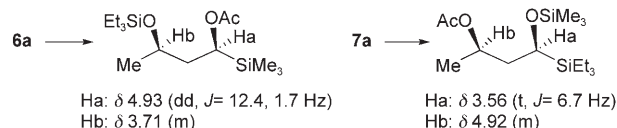
Reaction scheme showing the rearrangement of *anti*-1,5-*di*-*n*-alkoxyalkane derivatives **5a–g** to *syn*-1,5-*di*-*n*-alkoxyalkane derivatives **11a–g** and **12a–g** using *n*BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 30 min.

Entry	5	$R_1^3\text{Si}$	$R_2^3\text{Si}$	Yield [%] ^[a]	11:12 ^[b]
1	5a	TES	TMS	85	32:68
2	5b	TES	TES	96	17:83
3	5c	TBS	TMS	84	8:92
4	5d	TBS	TES	97	3:97
5	5e	TBDPS	TMS	98	0.4:99.6
6	5f	TBDPS	TES	99	0.4:99.6
7	5g	TBDPS	TBS	94	10:90

[a] Yield of isolated product. [b] Determined based on the yields of **11** and **12**.

exhibited high [1,4] selectivity, which is in sharp contrast to the reaction with **4g**.

Characterization of the *C*- and *O*-silyl groups of the rearranged products is a critical point for the discussion of the regioselectivity of the retro-Brook rearrangement and has been carried out in the following manner. The migrated *C*-silyl group was unambiguously determined by removing the *O*-silyl group of the rearranged products under acidic conditions to give the corresponding 1-trialkylsilyl-1,3-butanediols. The position of the *O*-silyl group was then established by ^1H NMR analysis of the acetylated compounds derived from the rearranged products (Scheme 4). The proton on the



Scheme 4. Diagnostic ^1H NMR data of the acetates of the [1,2]- and [1,4]-rearranged products **6a** and **7a**.

acetoxyated carbon atom of the [1,2]-rearranged products appeared at about $\delta = 4.9$ ppm as a double doublet, whereas that of the [1,4]-rearranged products was observed as a multiplet. These coupling patterns allowed us to definitively assign the position of the acetoxy group, and in turn, that of *O*-silyl group.

The stereochemistry of the rearranged products was determined by NMR analysis of the corresponding acetonides.^[12] The acetonides prepared from the [1,4]-migration products **7a** and **12a** were assigned to be *syn* and *anti*,^[14] respectively, thereby indicating that the retro-Brook rearrangements proceeded stereospecifically with retention of configuration at the carbanion center, as previously reported.^[5c]

The competitive experiments summarized in Table 1 and Table 2 clearly demonstrated that the retro-[1,4] rearrangement occurs more easily than the retro-[1,2] rearrangement. This selectivity could plausibly be explained by the relative stability of intermediates: the five-membered pentacoordinated silicate **13**^[5f] would be more favored than the three-membered silicate **14**,^[3b,h] which has higher ring strain energy (Figure 1). In general, five-membered rings are formed faster than three-membered rings, although entropic factors might favor the formation of three- over five-membered rings in some situations. Thus, we could expect the [1,4] migration to be faster than the [1,2] migration according to the ease of ring formation. The fact that the rearranged products obtained in these experiments comprised only two products, the retro-[1,2] and -[1,4] products, and no [1,5] oxygen to oxygen migration product was detected except in the case of **4g** indicates that the rearrangement proceeded under kinetically

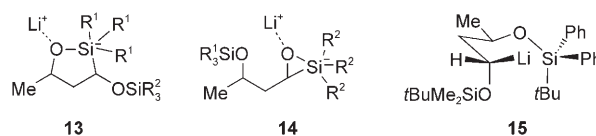


Figure 1. Intermediates of retro-Brook rearrangements.

controlled conditions. The unusual [1,2] selectivity observed in the reaction of **4g** is likely attributable to the conformational instability of α -silyloxylithium derivative **15**. The bulky *tert*-butyldimethylsilyloxy group has to adopt an unstable axial-like conformation, and the resulting steric repulsion between the TBS group and one of the substituents of the TBDPS group prevents the formation of the five-membered transition state **13**. As a result, retro-[1,2] rearrangement through the intermediate **14** became a major reaction pathway, and the elevated temperatures and prolonged reaction times induced partial [1,5] oxygen to oxygen migration.

In summary, we have demonstrated unprecedented examples of competitive aliphatic retro-[1,2]- and -[1,4]-Brook rearrangements of α,γ -disilyloxy organolithium derivatives, and clarified for the first time that the relative ease of the rearrangements is [1,2] $\ll$ [1,4], a reversal of the accepted order, and that a larger silyloxy group at the γ position relative to that at the α position induces a higher [1,4] selectivity. A mechanistic study of the regioselectivity of the rearrangements is in progress.

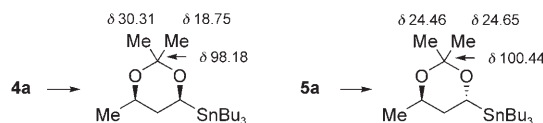
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