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[1,5]-Brook rearrangement: an overlooked but valuable silyl migration to synthesize configurationally defined vinylsilane. The unique steric and electronic effects of geminal bis(silane)†

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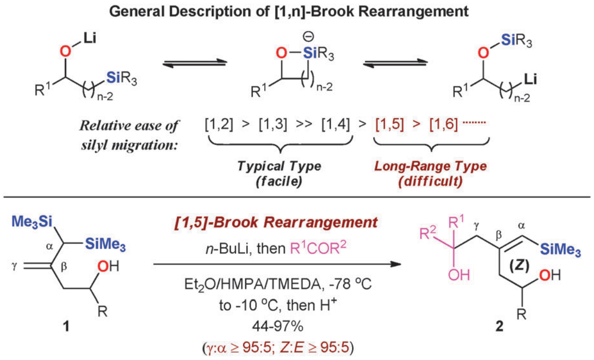
An unusual [1,5]-Brook rearrangement of the lithium alkoxide of geminal bis(silyl) homoallylic alcohol is described. The unique steric and electronic effects of geminal bis(silane) were found to be crucial for promoting this long-range silyl migration, as well as for facilitating the subsequent γ/*Z*-selective addition of silyl allyllithium with carbonyl compounds to synthesize diverse configurationally defined *Z*-vinylsilanes.

The [1,*n*]-Brook rearrangement[1] describes the intramolecular silyl group migration from a carbon to an oxygen atom *via* the penta-coordinated silicate species (Scheme 1, above). The relative ease of silyl migration has been reported to be [1,2] > [1,3] ≫ [1,4] > [1,5] > [1,6] based on the logic that shorter transfer distances are more favorable.[2] Indeed, the typical reaction types ($n = 2$–4) are usually facile and have found wide utilities in various transformations. In contrast, long-range rearrangements ($n \geq 5$) such as the [1,5]-Brook rearrangement generally proceed with much greater difficulty.[3] Inefficiency is the norm for such reactions, particularly when lithium alkoxide is used as an initiator. This inefficiency is also the main reason why the [1,5]-Brook rearrangement has been studied to such a limited extent, with very few applications in organic synthesis so far.

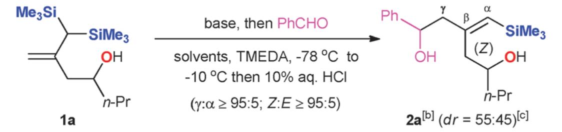


Scheme 1 General description of [1,*n*]-Brook rearrangement (above); [1,5]-Brook rearrangement–addition involving geminal bis(silyl) homoallylic alcohol and carbonyl compounds (below).

We recently launched a series of investigations on structurally novel geminal bis(silanes) and have reported their unusual behaviors and attractive bifunctionalities.[4] Here we report that the lithium alkoxide of geminal bis(silyl) homoallylic alcohol **1** can undergo an unusual [1,5]-Brook rearrangement (Scheme 1, below). The unique steric and electronic effects of geminal bis(silane) are crucial for promoting such a long-range silyl migration. These effects are also pivotal for the subsequent γ/*Z*-selective addition with carbonyl compounds to synthesize diverse configurationally defined *Z*-vinylsilanes **2** (ref. 5).

The reaction was initially examined using **1a**[6] as a model scaffold, and benzaldehyde as the electrophile. Without the polar solvent, HMPA, no C-to-O silyl migration would occur after deprotonation of **1a** with *n*-BuLi in Et_2O at −78 °C (Table 1, entry 1). Using Et_2O–HMPA (3.7 : 1) as co-solvent led to only partial silyl migration, while

Table 1 Screening of [1,5]-Brook rearrangement–addition conditions



Entry	Base	Solvents	TMEDA (equiv.)	Yield[d] (%)
1	*n*-BuLi	Et_2O/HMPA = 1.0/0	—	0
2	*n*-BuLi	Et_2O/HMPA = 3.7/1	—	23
3	*n*-BuLi	Et_2O/HMPA = 1.3/1	—	43
4	*n*-BuLi	Et_2O/HMPA = 0.6/1	—	30
5[a]	***n*-BuLi**	**Et_2O/HMPA = 1.3/1**	**2.5**	**75**
6	*n*-BuLi	THF/HMPA = 1.3/1	2.5	74
7	*n*-BuLi/*t*-BuOK	Et_2O/HMPA = 1.3/1	2.5	60

[a] Reaction conditions: 0.2 mmol of **1a**, 0.5 mmol of TMEDA, and 0.22 mmol of *n*-BuLi (2.5 M in pentane) in 1.3 mL of Et_2O, −78 °C to −10 °C; 0.6 mmol of PhCHO and 1.0 mL HMPA; crude products were treated with 1.0 mL of 10% aq. HCl. [b] The *Z*-configuration was assigned based on NOE experiments on **2j** (Table 2). [c] Ratios were determined by ^1H NMR spectroscopy. [d] Isolated yields after purification by silica gel column chromatography.

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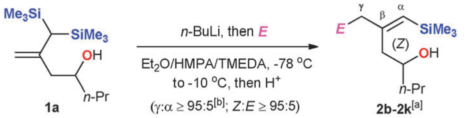
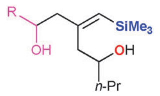
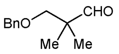
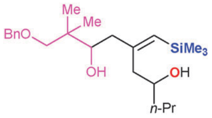
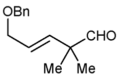
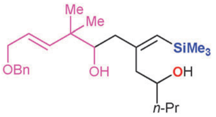
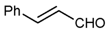
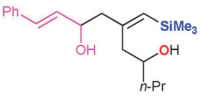
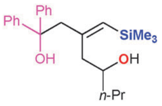
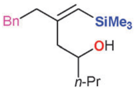
the subsequent addition at −10 °C proceeded in a highly γ-regioselective manner and with complete *Z*-configurational control to form vinylsilane. After acid-promoted selective desilylation, the desired 1,5-diol **2a** was obtained in 23% yield (entry 2). Increasing the loading of HMPA to an Et_2O–HMPA ratio of 1.3 : 1 gave **2a** in higher 43% yield (entry 3); using even more HMPA, however, appeared to lower the yield (entry 4). In our efforts to improve the addition step, we found that using 2.5 equiv. of TMEDA as an additive dramatically increased the yield to 75% without changing the high γ/*Z*-selectivity (entry 5). TMEDA probably stabilizes the silyl allyllithium, the high basicity of which makes it prone to protonation. THF–HMPA also proved to be suitable as a co-solvent, and gave **2a** in comparably good yield of 74% (entry 6). While the transmetalation of the lithium alkoxide to potassium ions still led to the smooth silyl migration, it made the addition less effective (entry 7). The reduced efficiency may be due to the fact that the carbon–potassium bond has less covalent character than a C–Li bond.

The reaction showed good applicability to a wide range of aldehydes and ketones (Table 2). The electrophiles include aryl and heterocyclic (entries 1–3), α-di- or trisubstituted alkyl (entries 4–7), and α,β-unsaturated aldehydes (entry 8), and benzophenone (entry 9). The desired 1,5-diols **2b–2j** were generally obtained in good yields and with high γ/*Z*-selectivity.

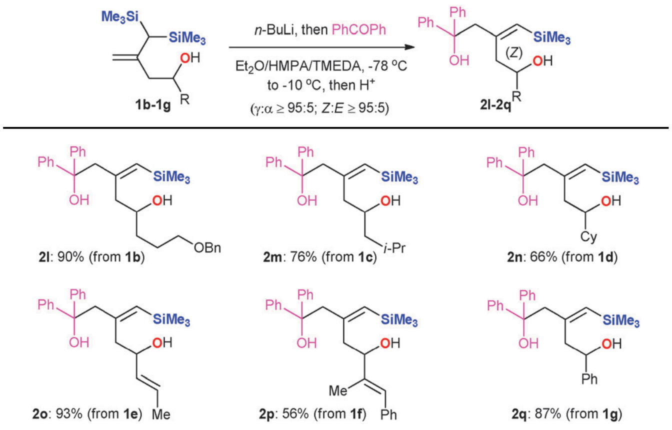
Table 2 Scope of [1,5]-Brook rearrangement–addition of **1a** with electrophiles



Entry	*E*	Product		Yield[c] (%)
1	*p*-MeO-PhChO		**2b**	88
2	*p*-Cl-PhCHO		**2c**	60
3	2-Thienyl-CHO		**2d**	78
4	i-PrCHO		**2e**	45
5	*t*-BuCHO		**2f**	44
6			**2g**	58
7			**2h**	83
8			**2i**	60
9	PhCOPh		**2j**	97
10	BnBr		**2k**	31

[a] Entries 1–8 gave dr = 50 : 50 to 63 : 37. Ratios were determined by ^1H NMR spectroscopy. [b] The ratio of γ : α = 50 : 50 in entry 10 was determined by ^1H NMR spectroscopy. [c] Isolated yields after purification by silica gel column chromatography.

Table 3 Scope of [1,5]-Brook rearrangement–addition of geminal bis(silyl) homoallylic alcohol **1** with benzophenone

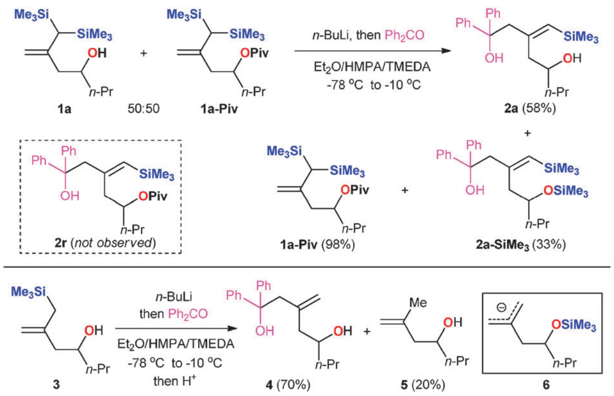


2l: 90% (from **1b**)
2m: 76% (from **1c**)
2n: 66% (from **1d**)
2o: 93% (from **1e**)
2p: 56% (from **1f**)
2q: 87% (from **1g**)

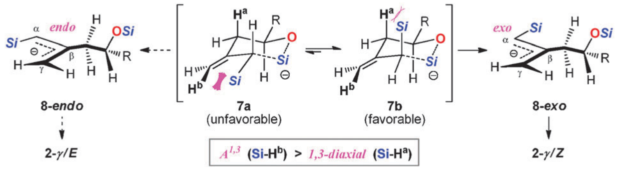
The reaction in entry 4 gave a comparably lower yield of 45%. This may be due to deprotonation of the α-position of isobutyraldehyde by the basic silylallyl lithium. Reaction with the less reactive benzyl bromide proved to be a challenge. The addition proceeded slowly and with poor regioselectivity, giving **2k** in only 31% yield (entry 10).

The process was also compatible with diverse geminal bis(silyl) homoallylic alcohols, in which the R groups featured unbranched or branched chains, a cyclohexyl ring, and vinyl or phenyl substituents. Varying the R group sterically and electronically did not affect the high γ/*Z*-selectivity, giving 1,5-diols **2l–2q** in good to excellent yields (Table 3).

A control experiment to determine whether the reaction indeed proceeds *via* intramolecular [1,5]-silyl migration was performed (Scheme 2, above). An equimolar mixture of **1a** and **1a-Piv** reacted with benzophenone to give **2a** and **2a-SiMe$_3$** in overall 91% yield. The original **1a-Piv** was recovered in 98% yield, and no cross-product **2r** was observed. These results indicate that [1,5]-C-to-O silyl migration proceeds intramolecularly *via* a pentacoordinated silicate species.[3b] The reaction of mono-$SiMe_3$-substituted homoallylic alcohol **3** was repeated (Scheme 2, below) and appeared to be more complex than that of **1a** (Table 2, entry 9). The 1,5-diol **4** was produced in 70% yield,



Scheme 2 Control experiment to confirm the intramolecular [1,5]-silyl migration (above); [1,5]-Brook rearrangement–addition of mono-$SiMe_3$-substituted homoallylic alcohol **3** with benzophenone (below).

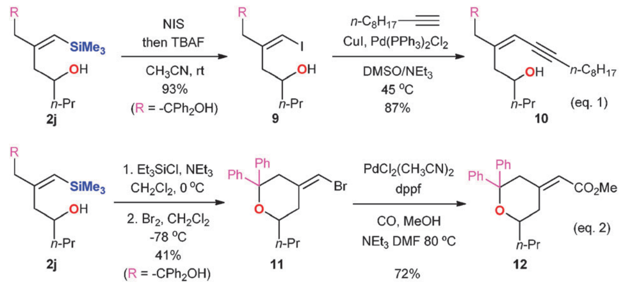


Scheme 3 Model to explain the observed high γ/Z-selectivity of [1,5]-Brook rearrangement–addition reaction.

a sharp contrast to the 97% yield of **2j**. Homoallylic alcohol **5** was also obtained in 20% yield from acidic hydrolysis of the unmigrated **3** and O-SiMe$_3$-substituted **5**, which was generated before work-up when the highly basic allyl anion **6** rapidly abstracted a proton instead of adding to benzophenone.[7] Such a large difference in efficiency suggests that the geminal bis(silyl) group plays a crucial role in both silyl migration and the subsequent addition.

In the mechanism model, two chair-like transition states **7a** and **7b** featuring pentacoordinated silicate were hypothesized (Scheme 3). Transition state **7b**, despite a 1,3-diaxial interaction between SiMe$_3$ and H^a, likely still be favored over **7a**, which suffers an even more severe A^{1,3} strain[8] between SiMe$_3$ and H^b. Thus, starting from **7b**, relieving the bulkiness of geminal bis(silane) would drive the cleavage of the C–Si bond to give anion **8-*exo***. This allyl anion would be further stabilized by the unmigrated SiMe$_3$ through the p–d π-bonding interaction (α-silicon effect).[9] It would then undergo addition with an electrophile at the more accessible γ-position to generate **2**-γ/*Z* predominantly. In other words, the steric effect of geminal bis(silane) would kinetically facilitate the [1,5]-Brook rearrangement, and its electronic effect would thermodynamically favor the subsequent addition. This mechanism could also explain why the reaction of **3**, which lacks the dual effects of geminal bis(silane), proved to be less efficient in both silyl migration and addition.

The resulting *Z*-vinylsilane was subjected to further reactions in order to demonstrate the bifunctionality of geminal bis(silane). Treating **2j** with NIS in CH$_3$CN gave *Z*-vinyl iodide **9** in 93% yield, which was transformed into the corresponding *Z*-enyne **10** in 87% yield *via* Sonogashira coupling with terminal alkyne (Scheme 4, eqn (1)). In contrast, treatment of mono-SiEt$_3$-protected **2j** with bromine at −78 °C led to an interesting bromination–cyclization process, giving *exo*-cyclic *Z*-vinyl bromide substituted tetrahydropyran **11** in an overall 41% yield. Subsequent carbonylation to *Z*-methyl enoate generated **12** in 72% yield; this compound is related to the ring B of bryostatins.[10]



Scheme 4 Iodination of **2j**, and Sonogashira coupling of the formed *Z*-vinyl iodide **9** with terminal alkyne to form *Z*-enyne **10** (eqn (1)); bromination–cyclization of **2j**, and carbonylation of the resulting *exo*-cyclic *Z*-vinyl bromide **11** to form *Z*-methyl enoate **12** (eqn (2)).

In summary, we have described a facile [1,5]-Brook rearrangement of geminal bis(silyl) homoallylic alcohols. The unique steric and electronic effects of geminal bis(silane) were found to be crucial for promoting this long-range silyl migration, as well as for facilitating the subsequent γ/*Z*-addition of silyl allyllithium with carbonyl compounds. The reaction provides a valuable protocol for synthesizing diverse *Z*-vinylsilanes. Further applications of this methodology are underway.

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5 To simplify the discussion, the resulting vinylsilane, in which the silyl group lies on the same side as the hydroxyl group in the substrate, is assigned to have a *Z*-configuration.

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