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Bissilyl Enal: A Useful Linchpin for Synthesis of Functionalized Vinylsilane Species by Anion Relay Chemistry

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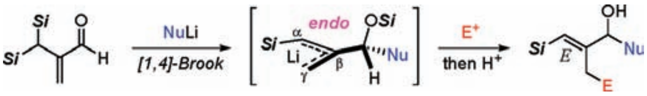
ABSTRACT



Bissilyl enal, prepared by a Mannich reaction of 3,3-bissilyl aldehyde with formaldehyde, has proven to be a useful linchpin in an efficient three-component coupling process. The reaction features a [1,4]-Brook rearrangement to generate the silylallyl anion, which adopts a predominant *endo*-orientation and can undergo addition to electrophiles in a regio- and stereoselective manner, giving various *E*-vinylsilane species in good yields.

The multicomponent reaction[1] is a powerful synthetic strategy for the rapid and efficient construction of complex molecules in a single operation. In the past decade, Smith III et al. have developed a series of fascinating multicomponent coupling protocols by anion relay chemistry (ARC) involving negative charge migration in a “through-space” fashion.[2] In these reactions, the key step is a Brook rearrangement[3] of organosilane species as a bifunctional linchpin to generate a new carbanion, which allows subsequent addition to a wide range of electrophiles. Generally, the newly formed carbanions either involve aryl,[4,2d,2g,2h]

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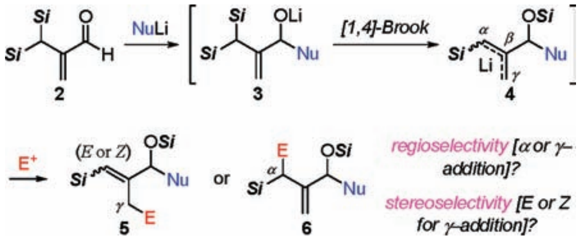
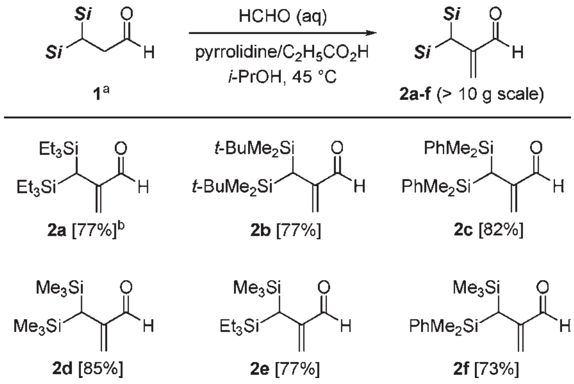
Scheme 1. Anion Relay Chemistry of Bissilyl Enals



vinyl,[5,2e] and allyl anions[6] or are stabilized by dithiane,[7] nitrile,[6,8]phenyl,[2f] and dihalide[9] groups. Although the stabilization of α-carbanions by silicon through the $p-d$ π-bonding interaction is well-known,[10] little attention has been paid to the silyl group as a stabilizing element in such ARC reactions.[11]

Scheme 2. Preparation of Bissilyl Enals

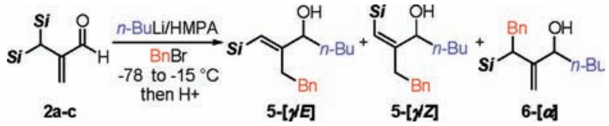


[a] Reaction conditions: 3,3-bissilyl aldehyde (1.0 equiv), aqueous HCHO (1.0 equiv), pyrrolidine (0.1 equiv), $C_2H_5CO_2H$ (0.1 equiv) in *i*-PrOH at 45 °C. [b] Isolated yields after purification by silica gel column chromatography.

Recently, we reported a facile retro-[1,4]-Brook rearrangement of 3-silyl allyloxysilanes to generate a variety of 3,3-bissilyl carbonyl compounds efficiently.[12] These new synthons afford the opportunity to test the feasibility of ARC using the corresponding bissilyl enal **2** as a linchpin. In the proposed process (Scheme 1), [1,4]-Brook rearrangement of lithium alkoxide **3** provides a new route to the silylallyl anion **4**.[13] Subsequent capture by electrophiles could then lead to potentially interesting regio- and stereoselective issues. First, the reaction could undergo either α-addition to give allylsilane **6** or γ-addition to give vinylsilane **5**. Second, in the case of γ-addition, the double bond could assume either the *Z*- or *E*-configuration. Here we report detailed studies of this reaction.

The necessary enals were quickly prepared by a Mannich reaction of 3,3-bissilyl aldehydes **1** with formaldehyde.[14] A combination of pyrrolidine and $C_2H_5CO_2H$ appeared to be the most effective catalyst to give a range of bissilyl enals **2** in good yields (Scheme 2). It is noteworthy that these reactions can be reproducibly performed on a scale greater than 10 g. Moreover, all of the bissilyl enals produced could be purified simply by silica gel chromatography and stored in the refrigerator for several weeks while maintaining good quality.

Table 1. Screening of Reaction Conditions



entry	enal[a]	TMEDA	solvent	product	yield (%)[c]	γ(*E*:*Z*) : α[b]
1	**2a**	–	THF	**5a**	67	81(73:8):19
2	**2a**	1.1 equiv	THF	**5a**	86	87(81:6):13
3	**2a**	3.0 equiv	THF	**5a**	62	87(81:6):13
4	**2a**	1.1 equiv/CuI (1.1 equiv)	THF	**5a**	46	77(57:20):23
5	**2a**	1.1 equiv/*t*-BuOK (1.1 equiv)	THF	**5a**	61	78(71:6):23
6	**2a**	1.1 equiv	Et_2O	**5a**	57	82(77:5):18
7	**2a**	1.1 equiv	toluene	**5a**	30	54(26:28):46
8	**2b**	1.1 equiv	THF	**5b**	77	78(77:1):22
9	**2c**	1.1 equiv	THF	**5c**	75	65(63:2):35

[a] Reaction conditions: bissilyl enal (1.0 equiv), *n*-BuLi (1.1 equiv) in THF at −78 °C; then TMEDA (1.1 equiv), warm to −15 °C; then benzyl bromide (3.0 equiv) and HMPA (4.0 equiv); crude products were treated with *p*-TsOH (0.2 equiv) in MeOH. [b] Selectivity was determined by ^1H NMR spectroscopy and configuration by NOE experiments on **5a**. [c] Isolated yields after purification by silica gel column chromatography.

Using bistriethylsilyl enal **2a** as the model linchpin, we then examined ARC involving *n*-BuLi as the nucleophile and BnBr as the electrophile. The reaction was initially performed in THF and promoted by 4.0 equiv of HMPA. After selective desilylation of the silyl ether moiety with *p*-TsOH in MeOH, the three products **5a-[γ/*E*]**, **5a-[γ/*Z*]**,

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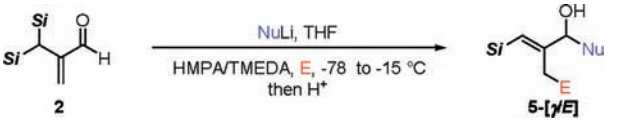
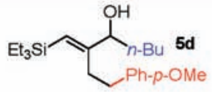
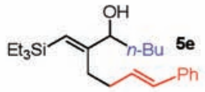
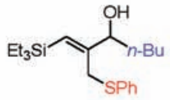
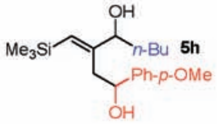
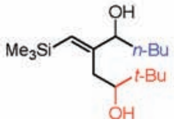
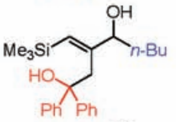
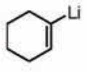
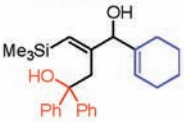
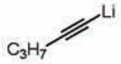
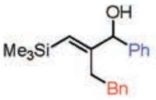
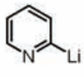
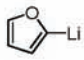
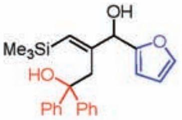
Table 2. Scope of Nucleophiles and Electrophiles



entry[a]	NuLi	E	product	yield (%)[c]	γ(E:Z) : α[b]
1	n-BuLi	MeO-p-PhCH$_2$Br	 **5d**	76	72(69:3):28
2	n-BuLi		 **5e**	71	78(78:0):22
3	n-BuLi	PhSSPh	 **5f**	81	100(65:35):0
4	n-BuLi	PhCHO	 **5g**	82	100(100:0):0 [dr = 59:41]
5	n-BuLi	MeO-p-PhCHO	 **5h**	80	100(100:0):0 [dr = 66:34]
6	n-BuLi	i-PrCHO	 **5i**	60	100(100:0):0 [dr = 67:33]
7	n-BuLi	t-BuCHO	 **5j**	75	100(100:0):0 [dr = 85:15]
8	n-BuLi	PhCOCH$_3$	 **5k**	53	100(100:0):0 [dr = 58:42]
9	n-BuLi	PhCOPh	 **5l**	70	100(96:4):0
10		PhCOPh	 **5m**	58	100(91:9):0
11		BnBr	 **5n**	70	70(65:5):30
12	PhLi	BnBr	 **5o**	71	72(68:4):28
13		BnBr	 **5p**	62	100(100:0):0
14		PhCOPh	 **5q**	75	100(100:0):0

[a] Reaction conditions: bissilyl enal (1.0 equiv), nucleophile (1.1 equiv) in THF at −78 °C; then TMEDA (1.1 equiv), warm to −15 °C; then electrophile (3.0 equiv) and HMPA (4.0 equiv); crude products were treated with p-TsOH (0.2 equiv) in MeOH. [b] Stereoselectivity was determined by ^{1}H NMR spectroscopy. [c] Isolated yields after purification by silica gel column chromatography.

and **6a-[α]** were obtained in an overall yield of 67% in the ratio 73:8:19 (Table 1, entry 1). While addition of 1.1 equiv of TMEDA apparently improved the yield and regio- and stereoselectivity (entry 2), using more TMEDA reduced the yield without changing the product ratio (entry 3). Replacing the lithium ion with other counterions such as Cu(I)[15] or K$^+$,[16] or changing the solvent to the more bulky Et$_2$O[17] or nonpolar toluene, decreased both the yield and selectivity (entries 4−7). Interestingly, enal **2b** with a (t-BuMe$_2$Si)$_2$CH- group and enal **2c** with a (PhMe$_2$Si)$_2$CH- group showed higher E/Z selectivity for γ-addition, but significantly lower regioselectivity (entries 8 and 9).

Having established the optimal reaction conditions, we further examined the scope of this approach. The results are summarized in Table 2. Reactions of benzyl and allyl bromide derivatives with n-BuLi as the nucleophile provided quite good E/Z-selectivity and moderate γ/α-selectivity (entries 1 and 2). Phenyl disulfide also proved to be a suitable electrophile, which led to complete γ-addition but only moderate E/Z-selectivity (entry 3). When aldehydes and ketones were used as electrophiles, the reactions showed excellent regio- and E/Z-selectivity (entries 4−9).[18] However, only moderate yields of **5i** and **5k** were obtained (entries 6 and 8). This may be due to deprotonation of the α-position of carbonyl compounds by the silylallyl anion. The reaction is also suitable for various organolithium species such as vinyllithium, lithium acetylide, and aryllithiums (entries 10−14). It is noteworthy

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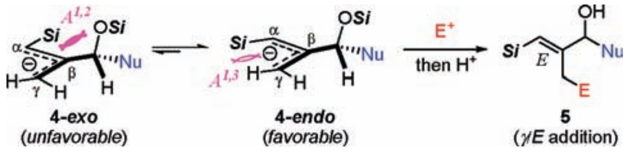
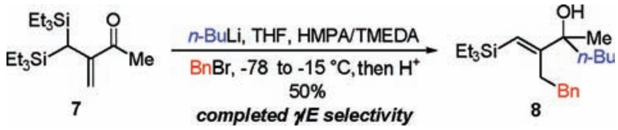
that complete γ-addition was obtained in entry 13. This result is in sharp contrast to the moderate regioselectivity observed in other alkylation reactions shown in Table 2. Probably, the nitrogen atom in the pyridine might coordinate favorably with the lithium ion attached to the γ-position of the silylallyl anion. Detailed studies of this interesting regioselectivity are ongoing. Additionally, only organolithium is applied for this reaction, as a Grignard reagent cannot trigger the silyl migration.

Scheme 3. Model Analysis for the γ/E-Selectivity



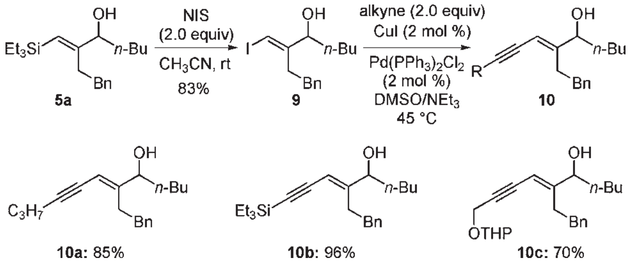
A rationalization of the observed regio- and stereoselectivity is described in Scheme 3. Although simple silylallyl lithium is widely recognized as having an *exo*-orientation,[19] the configuration of the acyclic species substituted at the 2-position is poorly understood. Only one example containing a 2-methyl group has been investigated, and it seems to retain the *exo*-orientation.[20] The observed high *E*/*Z* selectivity in our studies suggests that the formed silylallyl anion adopts the ***4-endo*** structure predominantly, which has an $A^{1,3}$ strain[21] between the silyl group and γ-H. However, this is still more favorable than the ***4-exo*** arrangement, which encounters severe $A^{1,2}$ strain between the silyl group and the 2-substituent. The γ-regioselectivity can be explained by the difference in accessibility between the α- and γ-positions: the γ-position appears to be more accessible, since the α-position is attached to a bulky silyl group. This explanation is further supported by the observed complete γ/E selectivity when the bissilyl enone **7** is used as a linchpin (Scheme 4). In this reaction, the formed silylallyl lithium contains a larger 2-tertiary alkoxy group, which increases the steric congestion at both the α- and γ-positions, completely blocking the former.

Scheme 4. Anion Relay Chemistry of Bissilyl Enone



The application of the *E*-vinylsilane[22] products to the synthesis of useful building blocks was investigated. As shown in Scheme 5, treatment of **5a** with NIS gave the vinyliodide **9** in 83% yield with retention of the *E*-configuration. Subsequent Sonogashira coupling[23] using terminal alkynes with different functional groups afforded various enynes **10** in high yield.

Scheme 5. Transformation of Vinylsilanes to Enynes



We have described a facile, three-component coupling process using the bissilyl enal as a linchpin. The route provides a practical method for synthesizing various *E*-vinylsilanes regio- and stereoselectively. We have demonstrated the synthetic value of this approach by efficiently preparing diverse enyne species. Further applications of this method are underway.

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Supporting Information Available. 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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