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ARTICLE TYPE

Regioselective 1,4- over 1,2-Addition of 3,3-Bis(silyl) Allyloxy Lithium to Enals, Eones and Enoates. The Remarkable α-Effect of Silicon†

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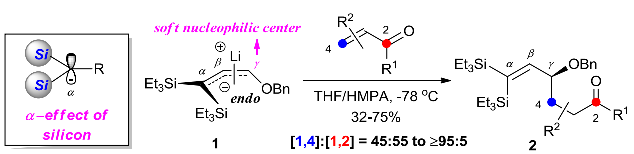
A remarkable α-effect of silicon has been discovered that results in soft nucleophilicity at the Cγ of 3,3-bis(silyl) allyloxy lithium 1. The addition of 1 to α,β-unsaturated carbonyl compounds, including enals, proceeds in a 1,4- over 1,2-manner with medium to good regioselectivity, whereas the parent allyloxy lithium 4 undergoes complete 1,2-addition. The results from DFT calculations of HMPA-complexed 1 and 4 provide the rationale to explain this different regioselectivity.

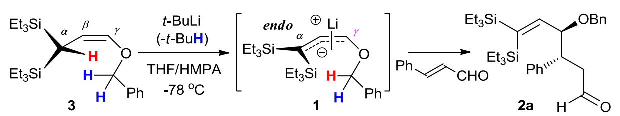
Addition of organometals to enals and enones is one of the most fundamental transformations in organic synthesis.[1] Organolithium of typical reactivity normally undergoes complete or predominant 1,2-addition over 1,4-addition. To increase the synthetic usefulness of organolithium addition, extensive efforts[2] have been made to reverse the regioselectivity in favor of 1,4-addition. Although these approach have allowed reasonably efficient addition of lithiodithianes to enones, achieving selective 1,4-addition in favor of 1,2-addition with more reactive enals remains a significant challenge.



Scheme 1. Regioselective 1,4-addition over 1,2-addition of 3,3-bis(triethylsilyl) allyloxy lithium **1** to α,β-unsaturated carbonyl compounds.

Recently, we launched a series of investigations into structurally novel geminal bis(silanes).[3] We wondered whether the presence of two silicons might provide a path to shifting the regioselectivity of organolithium addition to enals and enones. Silicon-substituted carbanions[4] usually possess different reactivity from their parent carbanions. These differences are due in part to the steric effect of the bulky silyl group, but primarily they arise from the electronic effects of silicon. Silicon is thought to stabilize the α-carbanion through a p-d π-bonding interaction or hyperconjugation, known as the *α-effect of silicon*.[5] If this effect were doubled by incorporating two silyl groups in the same molecule, such as in the case of geminal bis(silanes), would it alter the reactivity of carbanions enough to shift an organolithium addition away from a 1,2-mechanism toward a 1,4-mechanism? Here we report that the α-effect of silicon leads to soft nucleophilicity at the sterically more accessible Cγ of 3,3-bis(triethylsilyl) allyloxy lithium **1**. The addition of **1** to α,β-unsaturated carbonyl compounds, including to highly reactive enals, proceeds in a predominant 1,4-manner to give **2** with medium to good regioselectivity (Scheme 1).

Table 1 Screening of Reaction Conditions.

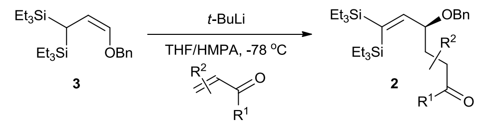


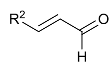
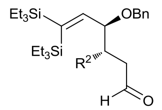
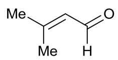
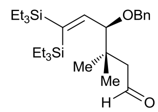
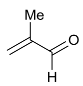
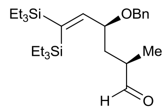
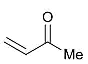
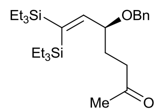
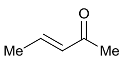
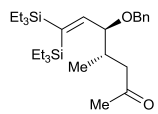
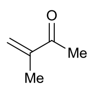
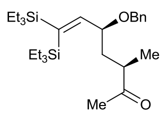
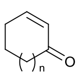
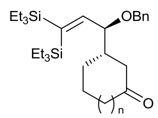
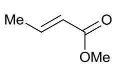
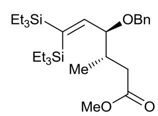
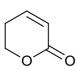
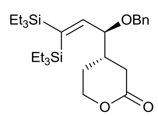
Entry	HMPA (equiv)	*T* °C	Yield[b] (**2a**)	*dr*[c]	[1,4]:[1,2][d]
1[a]	**3.0**	**-78**	**64%**	**≥95:5**	**70:30**
2	12.0	-78	56%	≥95:5	70:30
3	3.0	-98	52%	≥95:5	68:32
4	3.0	-55	87%[e]	—	—
5[f]	3.0	-78	57%	≥95:5	66:34

[a] Reaction conditions: 0.13 mmol of **3**, 0.39 mmol of HMPA and 0.39 mmol of *t*-BuLi (1.3 M in pentane) in 1.0 mL of THF, –78 °C, 1.5 h; then 0.26 mmol of cinnamaldehyde, 10 min. [b] Isolated yields after purification by silica gel column chromatography. [c] The *anti*/*syn* ratios were determined using ^{1}H NMR spectroscopy. The *anti*-stereochemistry was assigned based on X-ray analysis of the di(3,5-dinitro benzoate) of **2a**. [d] [1,4]:[1,2] ratios were determined using ^{1}H NMR spectroscopy. [e] Isolated yield of product generated by [1,2]-Wittig rearrangement of **1** . [f] 3.0 equiv of CuCN was added after generation of **1**.

3,3-Bis(triethylsilyl) allyloxy lithium **1** was generated from the corresponding *Z*-benzyl enol ether **3** through sequential regio-selective deprotonation and [1,5]-anion relay.[6, 7, 8] The subsequent addition to cinnamaldehyde proceeded at -78 °C predominantly in a 1,4-manner ([1,4]:[1,2] = 70:30), giving aldehyde **2a** in 64% yield with ≥95:5 diastereoselectivity (Table 1, entry 1). Even though HMPA is believed to favor solvent-separated ion pair (SSIP) formation and thereby promote attack at the 4-position,[2e] increasing its loading from 3.0 to 12.0 equiv lowered the yield without altering the product distribution (entry 2). Similar results were obtained at -98 °C, even though low temperature has been also proposed to favor 1,4-addition (entry 3).[2h] Nevertheless, temperature did affect the stability of allyllithium **1**: conducting the reaction at -55 °C led to severe [1,2]-Wittig rearrangement before addition to the enal (entry 4). We were unsuccessful in our attempt to convert **1** into the corresponding lithium organocuprate: the reaction in the presence of 3.0 CuCN gave a [1,4]:[1,2] ratio of 66:34, comparable to the ratio in entry 1 (entry 5).

Table 2 Scope of α,β-unsaturated carbonyl compounds



Entry	Electrophile	Product		Yield[a]	dr[b]	[1,4]:[1,2][c]
1			**2a** (R^2 = Ph)	64%	≥95:5	70:30
2			**2b** (R^2 = 4-Cl-Ph)	42%	88:12	72:28
3			**2c** (R^2 = Me)	64%	90:10	70:30
4			**2d**	32%	—	45:55
5			**2e**[d]	56%	95:5	72:28
6			**2f**	71%	—	≥95:5
7			**2g**	75%	53:47	90:10
8			**2h**	69%	≥95:5	≥95:5
9			**2i** (n = 0)	50%	65:35	≥95:5
10			**2j**[e] (n = 1)	60%	82:18	83:17
11			**2k**	70%	50:50	≥95:5
12			**2l**	52%	88:12	≥95:5

[a] Isolated yields after purification by silica gel column chromatography. [b] The *dr* was determined using ^{1}H NMR spectroscopy. [c] [1,4]:[1,2] ratios were determined using ^{1}H NMR spectroscopy. [d] 1,3-*Syn* stereochemistry was assigned based on NOE experiments with the γ-lactone of **2e**. [e] 1,2-*anti* stereochemistry was assigned based on X-ray analysis of the di(3,5-dinitro benzoate) of **2j**.

Next the scope of α,β-unsaturated compounds was tested with **1**. Reaction of 3-methyl-2-butenal, which shows increased steric hindrance at the 4-position (Table 2, entry 4), gave a lower yield and lower [1,4]:[1,2] ratio than did 4-mono-substituted aldehydes (entries 1-3). In contrast to the high 1,2-*anti* diastereoselectivity in entries 1 and 2, a more challenging 1,3-*syn* stereochemical control using 2-methyl propenal was achieved to give aldehyde **2e** in 56% yield with 95:5 diastereoselectivity (entry 5). Switching from enals to less reactive enones (entries 6-10) and enoates (entries 11 and 12) reduced diastereoselectivity, however, increased [1,4]:[1,2] selectivity in most cases.

Whereas the reaction of **1** with crotonaldehyde gave a [1,4]:[1,2] ratio of 70:30, the reaction of the parent allyloxy lithium **4** under the same reaction conditions led to the complete 1,2-adduct **5** in 84% yield (Figure 1).[9] Apparently, the nature of the organolithium plays a key role in determining the mode of addition, in conjunction with several other factors that also influence regioselectivity, such as the metal counterion, temperature, and solvents. In an attempt to get deeper insights that how much the α-effect of silicon influences the negative charge distribution, we performed DFT calculations of HMPA-complexed allyloxy lithium **1** and **4** at the B3LYP/6-31G* level. NBO analysis indicates that the negative charge is distributed more towards Cα in **1-COM** (Cα: -1.497 and Cγ: -0.073) than in 4-**COM** (Cα: -0.853 and Cγ: -0.152). This most likely reflects the α-effect of silicon, which means that Cγ accumulates less electron density in **1-COM** than in **4-COM**, making it a softer nucleophilic center.[10] Based on the Pearson concept of hard and soft acids and bases (HSAB)[11] and the Klopman–Salem concept of charge and orbital control of organic reactions,[12] we predict that the HOMO of **1-COM** is at higher energy than that of **4-COM,** favoring attack at the C4 of crotonaldehyde, which is softer than the carbonyl C2 and has a larger LUMO coefficient.[13] This soft-soft interaction controlled by frontier orbitals contrasts with the addition of **4-COM** to C2 of crotonaldehyde, which is probably favored by a charge-controlled hard-hard interaction.

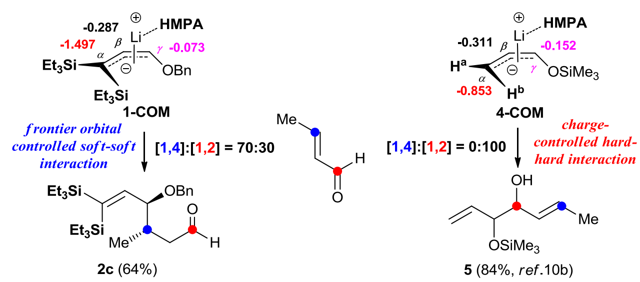
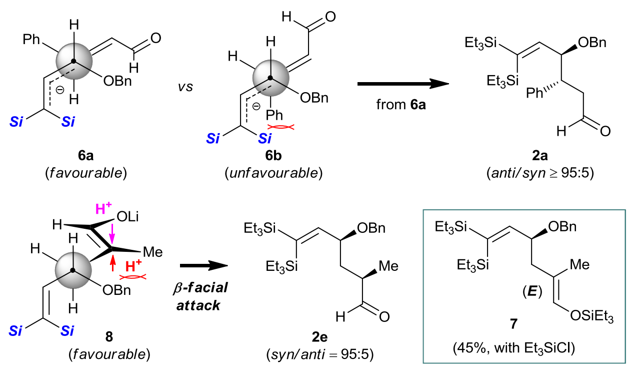


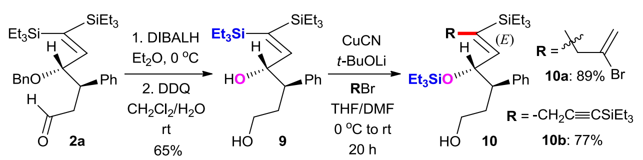
Figure 1. NBO analysis of allyloxy lithium-HMPA complexes **1-COM** and **4-COM** based on DFT calculations performed at the B3LYP/6-31G* level.

To provide a mechanistic basis for probing the stereochemistry of this reaction, two "open" transition states **6a** and **6b** were proposed for the addition of **1** to cinnamaldehyde (Scheme 2). We predict that **6a** is favored over **6b**, which suffers a severe gauche interaction between geminal bis(triethylsilyl) and phenyl groups, and that this preference for **6a** leads to the observed 1,2-*anti* diastereoselectivity. On the other hand, to interpret the 1,3-*syn* diastereoselectivity in the addition with 2-methyl propenal, we initiated the reaction and quenched it with Et_3SiCl. *E*-silyl enol ether **7** was obtained in 45% yield, suggesting that the lithium enolate that forms after addition is in an *E*-configuration and probably adopts a gauche conformation as in **8**, such that the bulky geminal bis(triethylsilyl) group is antiperiplanar to the enolate in order to minimize the nonbonded interaction. Protonation of **8** from the sterically more accessible β-face would then give **2e** with high 1,3-*syn* diastereoselectivity.



Scheme 2 Model to explain 1,2-*anti* and 1,3-*syn* diastereoselectivity.

In order to extend the synthetic usefulness of our addition approach, anionic silyl migration was utilized to functionalize the geminal bis(silyl) group in **2a** (Scheme 3). Reduction and deprotection of **2a** gave rise to 1,4-diol **9** with an overall yield of 65%. In the presence of CuCN and *t*-BuOLi, a [1,4]-Csp^2 to O silyl migration of **9** occurred regioselectively on the secondary hydroxyl group to generate vinyl anion.[14] Subsequent alkylation with allyl and propargyl bromide provided trisubstituted *E*-vinylsilanes **10a** and **10b**, respectively, in yields of 89% and 77%. In this way, the second electrophile was added to the α-position of benzyl enol ether **3**.



Scheme 3 Anionic [1,4]-silyl migration of **9** to synthesize *E*-vinylsilanes **10a** and **10b**.

In summary, we have described the 1,4- over 1,2-addition of 3,3-bis(triethylsilyl) allyloxy lithium **1** to α,β-unsaturated carbonyl compounds, including highly reactive enals. Experimental and computational results suggest that the unusual regioselectivity is because the α-effect of silicon makes **1** soft nucleophilic at the Cγ. Further studies into the mechanism of this unique α-effect and its synthetic applications are underway.

Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data for new compounds, CCDC (974929, 974934). See DOI: 10.1039/b000000x/

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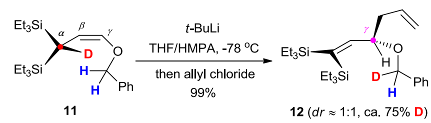
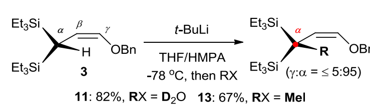
7 X. W. Sun, J. Lei, C. Z. Sun, Z. L. Song, L. J. Yan, *Org. Lett*. 2012, **14**, 1094. Reaction of **11** with allyl bromide under the optimal conditions provided **12** in 99% yield with ca.75% of deuterium labeled at the benzylic position. This result unambiguously confirmed that formation of **1** proceeds predominantly by [1,5]-anion relay based on an intramolecular proton transfer.



8 Deprotonation of **3** and the subsequent addition to D_2O and MeI, respectively, occurred exclusively at the α-position to afford **11** and **13** in 82% and 67% yield with the exclusive *Z*-configuration. These results combined with those in Table 2 show a sterically-dependent shift in regioselectivity, suggesting that the α-position of **1** has greater electron density than the γ-position, but that the γ-position is sterically more accessible than the α-position, which bears a bulky geminal bis(triethylsilyl) group. Formation of *Z*-enol ethers also suggests that allyllithium **1** adopts an *endo*-orientation, probably promoted by coordination of an internal lithium ion with the OBn group. For references, see: ref. 4d and 9.



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10 The role of geminal bis(silane) is reminiscent of 1,3-dithiane group, which has been recognized to stabilize the adjacent allyllithium,

therefore creating a soft nucleophilicity at Cγ to undergo 1,4-addition to enone. For references, see: (*a*) F. E. Ziegler, J.-M. Fang, *J. Org. Chem*. 1981, **46**, 825; (*b*) T. Cohen, M. Myers, *J. Org. Chem*. 1988, **53**, 457.

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