VIP Siloxyallenes

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Enantioselective Synthesis of Siloxyallenes from Alkynoylsilanes by Reduction and a Brook Rearrangement and Their Subsequent Trapping in a [4+2] Cycloaddition**

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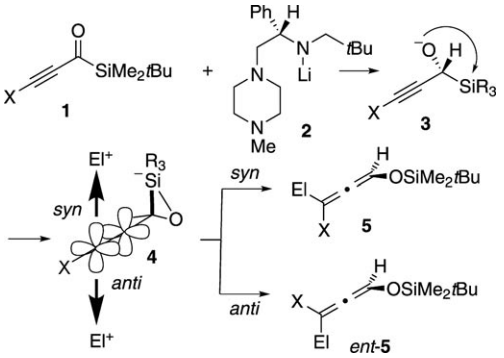
Enantioselective synthesis through the use of chiral allenes has attracted much attention because of their capability to transfer their axial chirality to one or more new stereogenic centers.[1] A well-established approach to enantiomerically enriched allenes relies on the S_N2' substitution of homochiral propargylic derivatives with organocuprates.[2]

We became interested in developing new methodologies for the synthesis of chiral, nonracemic allenes based on the enantioselective Meerwein–Ponndorf–Verley-type reduction of acylsilanes by chiral lithium amide that was developed by us.[3] We envisaged that if alkynoylsilane **1** could be enantioselectively reduced by **2**,[4] the resulting α-silyl alkoxide **3** would provide optically active siloxyallene derivatives through a Brook rearrangement;[5] subsequent S_E2' electrophilic substitutions[6] of the silicate intermediate **4**, would result in the enantioselective preparation of 1-unsubstituted siloxyallenes **5** or *ent*-**5** depending on the mode of the S_E2' process (Scheme 1). We previously reported that the Brook rearrangement mediated S_E2' protonation of allylsilanes having an oxygen substituent on the stereogenic center proceeds in an *anti* fashion.[7]

The synthesis of racemic siloxyallenes by a Brook rearrangement was originally reported independently by the Kuwajima[8] and Reich[9] groups. They generated α-hydroxypropargylsilane, a precursor for the Brook rearrangement, by reactions of acylsilanes with lithium acetylides. Scheidt et al. recently reported the synthesis of enantiomerically enriched siloxyallenes by the treatment of α-hydroxypropargylsilane, which was obtained by a catalytic asymmetric addition of acetylide to acylsilane, with a catalytic amount of *n*BuLi.[10] Consequently, their methods are limited to the synthesis of 1-alkyl-substituted siloxyallene derivatives.

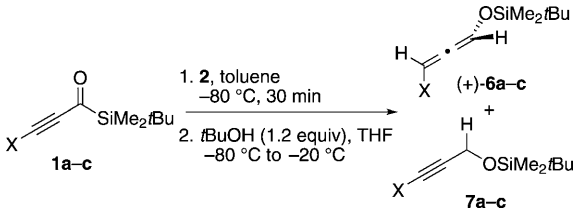


Scheme 1. Tandem process for the enantioselective formation of siloxyallenes. El = electrophile.

We report here some preliminary results for the enantioselective synthesis of 1-unsubstituted 1-siloxyallenes and their trapping by [4+2] cycloaddition.

When **1a** was treated with **2** at −80 °C in toluene for 30 min followed by addition of *t*BuOH (1.2 equiv) in THF and then warming to −20 °C, siloxyallene (+)-**6a**[11] was obtained in 52 % yield and with e.r. 95:5 together with **7a** (32 %; Table 1, entry 1).[12,13] The selectivity was markedly improved by a change in the substituent X to a 3-phenylpropyl group and the allene derivative (+)-**6b** was obtained in 86 % yield (Table 1, entry 2). Our initial choice of **1a** as a substrate was based on the assumed stabilization of the allene structure owing to the α-anion-stabilizing nature of the silyl group. The results showing that the less bulky alkyl derivative **1b**

Table 1: Enantioselective formation of siloxyallenes (+)-**6a–c** from alkynoylsilanes **1a–c** by tandem reduction/Brook rearrangement/protonation.



Entry	Starting material, X	(+)-**6** Yield [%]	e.r.	**7** Yield [%]
1	**1a**, $PhMe_2Si$	52	95:5	32
2	**1b**, $PhCH_2CH_2CH_2$	86	98:2	3
3	**1c**, $tBuPh_2Si$	37	92:8	54

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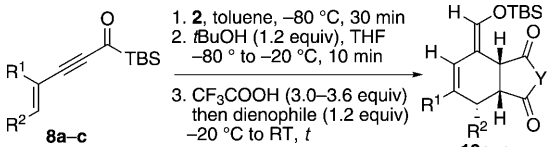
provided better allene selectivity, however, led us to consider the contribution of a steric factor to the selectivity. This was supported by the reaction using **1c**, bearing a bulkier *tert*-butyldiphenylsilyl (TBDPS) group, which afforded (+)-**6c** and **7c** in a 37:54 ratio (Table 1, entry 3).

To demonstrate the synthetic utility of the method, we examined the possibility of a tandem process using enynylsilanes that would involve trapping of the generated homochiral siloxyallene by a [4+2]-type cycloaddition (**10** + **11** → **12**). The high reactivity and facial selectivity of the vinylallene system in cycloadditions has been well documented.[14,9b]

Alkynoylsilane **8a** was treated with **2** in toluene at −80 °C for 30 min followed by addition of *t*BuOH (1.2 equiv) in THF as an electrophile; subsequent reaction with maleic anhydride in the presence of CF_3COOH (3.6 equiv) at room temperature provided the tandem reaction product **13a** in 66 % yield and with e.r. 97:3 as a single isomer (Table 2, entry 1).[15] The

Table 2: [4+2] Cycloaddition of vinylallenes generated from the tandem sequence.



8a R^1, R^2 = $-CH_2CH_2CH_2-$
8b R^1, R^2 = $-CH_2CH_2CH_2CH_2-$
8c R^1 = H, R^2 = $CH_2(CH_2)_2CH_2OMe$

13 Y = O
14 Y = NMe
15 Y = *o*-C_6H_4

Entry	8	Dienophile[a]	*t* [h]	Product	Yield [%]	e.r.
1	**8a**	MA	5	**13a**	66	97:3
2	**8a**	NMM	3	**14a**	73	98:2
3	**8a**	NQ	5.5	**15a**	51[b]	95:5
4	**8b**	MA	5	**13b**	54	99:1
5	**8b**	NMM	3.5	**14b**	60	98:2
6	**8b**	NQ	4.5	**15b**	54[c]	98:2
7	**8c**	MA	5	**13c**	56	97:3
8	**8c**	NMM	5	**14c**	62[d]	95:5
9	**8c**	NQ	7.5	**15c**	57	88:12

[a] MA = maleic anhydride, NMM = *N*-methylmaleimide, NQ = naphthoquinone. [b] *E*/*Z* mixture (1:3.7); both 95:5 e.r. [c] *E*/*Z* mixture (1:4.4); (*E*)-**15b** 99:1 e.r. and (*Z*)-**15b** 98:2 e.r. [d] Since hydrolysis of the enol silyl ether occurred during purification on silica gel, **14c** was isolated as a mixture with the corresponding aldehyde (20%).

same tandem reaction was also achieved with *N*-methylmaleimide and naphthoquinone, affording **14a** and **15a**, respectively. Their relative and absolute configurations were determined on the basis of single-crystal X-ray analysis of **14a** (Figure 1). It is formed by an *endo* addition and an attack from the more hindered face of the vinylallenes, the same face as the siloxy group (Scheme 2). The unprecedented facial selectivity and *endo* selectivity were also observed in reactions of **8b** and **8c**, which afforded **13b**–**15b** and **13c**–**15c** respectively.

When (*E*)-**15a** (Table 2, entry 3), a minor product in the reaction, was exposed to conditions similar to those employed in the reaction of **8a**, an *E*-to-*Z* isomerization was not detected. Also, there was no crossover between **13a** and

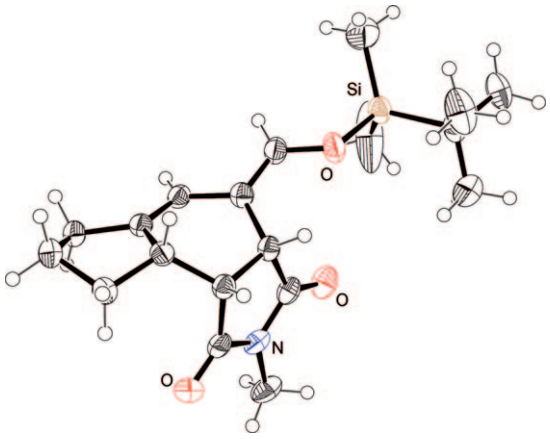
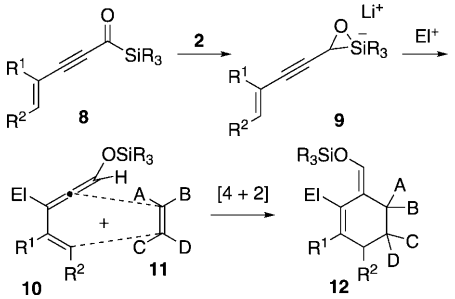


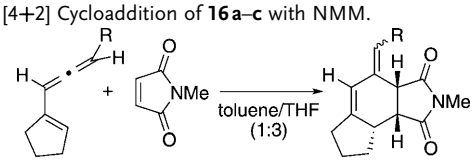
Figure 1. ORTEP drawing of **14a**; ellipsoids are drawn at the 50% probability.



Scheme 2. Trapping of vinylallenes by [4+2] cycloaddition.

NMM or between **14a** and maleic anhydride. To gain further insight into the unusual facial selectivity, we decided to conduct a [4+2] cycloaddition with NMM using siloxy, methoxy, and alkyl derivatives **16a**–**c** (Table 3). While the reaction of **16a** gave only the *Z* derivative **14a**, reaction of the methoxy derivative **16b**[16] afforded both (*Z*)- and (*E*)-**17** in 31 % and 41 % yield, respectively. In contrast, the reaction of alkyl derivative **16c** gave (*E*)-**18** exclusively. The unexpected facial selectivity[14f] depending on the substituents at the terminal position of the vinylallenes seems to be consistent as a whole with the trend in the energies of the transition states leading to the model systems **19a**–**c** and **20a**–**c**, calculated at

Table 3: [4+2] Cycloaddition of **16a**–**c** with NMM.

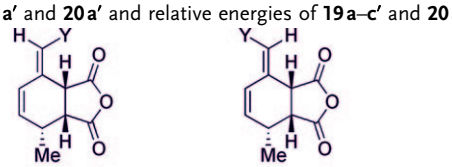


16a (R = $OSiMe_2tBu$)
16b (R = OMe)
16c (R = $CH_2(CH_2)_3CH_3$)

	T [°C]	*t* [h]	Product	*Z* [%]	*E* [%]
16a	0	14	**14a**	42	–
16b	5	48	**17**	31	41
16c	20	23	**18**	–	30

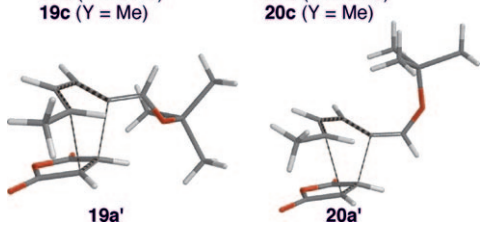
B3LYP/6-311 + G** using SPARTAN 08[17] (Table 4).[18] Thus, energies of the transition states for the siloxy and methoxy derivatives **19a′** and **19b′** leading to (*Z*)-**19a** and (*Z*)-**19b** are approximately 2,23 and 1.47 kcal mol^{-1} lower than the corresponding energies for the transition states leading to (*E*)-**20a′** and (*E*)-**20b′**. This is in sharp contrast to the results with the methyl derivatives **19c′** and **20c′**, in which the latter transition state leading to the *E* product is more stable.

Table 4: B3LYP/6-311 + G** Optimized geometries of transition-state structures **19a′** and **20a′** and relative energies of **19a–c′** and **20a–c′**.



19a (Y = $OSiMe_3$)
19b (Y = OMe)
19c (Y = Me)

20a (Y = $OSiMe_3$)
20b (Y = OMe)
20c (Y = Me)



19a′ **20a′**

Entry		**19′** G_{298}[a]	**20′** G_{298}[a]	ΔG_{298}[a]
1	**a**	−688137.15	−688133.92	3.23
2	**b**	−456334.41	−456332.94	1.47
3	**c**	−409128.42	−409130.53	−2.11

[a] Zero point energy corrected free energies are given in kcal mol^{-1}.

In conclusion, we have developed a consecutive process for the enantioselective formation of siloxyallenes from alkynoylsilanes, taking advantage of reduction by a chiral lithium amide followed by stereoselective S_E'-type process through a Brook rearrangement of an alkynyl silicate intermediate. In the case of enynoylsilanes, the resulting vinylallenes undergo in situ [4+2] cycloaddition to afford highly functionalized polycyclic compounds with excellent enantiomeric ratios. We are continuing to explore the scope, limitations, generality, and synthetic applications of these transformations.

Experimental Section

Synthesis of **14a**: To a cooled (−80 °C) solution of **2**, generated from (*S*)-2,2-dimethyl-*N*-(2-(4-methylpiperazin-1-yl)-1-phenylethyl)propan-1-amine (76.1 mg, 0.263 mmol) and *n*BuLi (1.67 M in *n*-hexane, 157 μL, 0.263 mmol) in toluene (1.0 mL) at 0 °C, was added dropwise a solution of **8a** (51.3 mg, 0.219 mmol) in toluene (0.8 mL). The reaction mixture was stirred at the same temperature for 30 min before a solution of *t*BuOH (25 μL, 0.263 mmol) in THF (5.5 mL) was added. The reaction mixture was allowed to warm to −20 °C over 10 min, and then trifluoroacetic acid (0.5 M in THF, 1.58 mL, 0.788 mmol) and *N*-methylmaleimide (29.2 mg, 0.263 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 3 h, and then diluted with hydrochloric acid (1%, 10 mL) and extracted with Et_2O (10 mL × 3). The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ solution (5 mL) and saturated brine (5 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 5 g, elution with hexane/CH_2Cl_2/Et_2O = 15:10:1) to give **14a** (49.6 mg, 76%).

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[13] When **1a** was treated with **2** in THF, which is our original protocol, a complex mixture was obtained. However, the reduction proceeds in toluene at −80 °C to give the corresponding alcohol in 79% yield and with e.r. 99:1. Addition of THF was essential to effect the Brook rearrangement.

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[15] The reaction without the addition of CF_3COOH proceeded well but required the use of an excess of the dienophile, presumably owing to the presence of nitrogen nucleophiles originating from **2**.

[16] Allene **16b** was prepared by base-catalyzed isomerization of 1-(3-methoxyprop-1-yn-1-yl)cyclopent-1-ene, which was obtained from the Sonogashira coupling of iodocyclopentene and propargyl alcohol.

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