Organic LETTERS

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# Enantioselective Synthesis of Allenylenol Silyl Ethers via Chiral Lithium Amide Mediated Reduction of Ynenoyl Silanes and Their Diels−Alder Reactions

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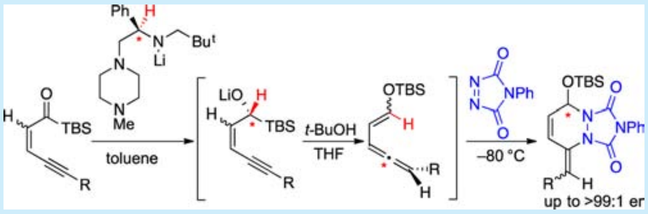
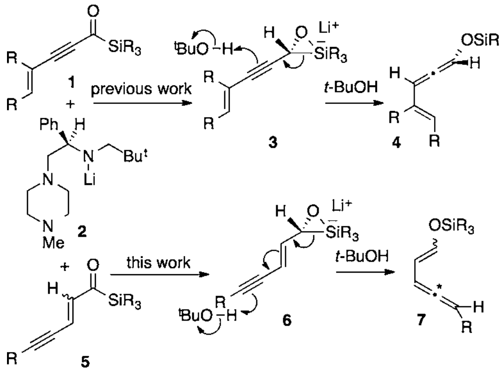
Ⓢ *Supporting Information*



**ABSTRACT:** An enantioselective Meerwein-Ponndorf-Verley-type reduction of ynenoylsilanes by a chiral lithium amide followed by a Brook rearrangement and *anti*-mode protonation across conjugated 1,3-enynes provides allene derivatives bearing a 2-siloxyvinyl moiety in high enantioselectivity. The *E*/*Z* geometry of enol silyl ethers is controlled by the geometry of the starting enyne moiety. Thus, (*E*)- and (*Z*)-enol silyl ethers are obtained from (*Z*)- and (*E*)-ynenoylsilans, respectively. The 2-siloxyvinylallene products can participate in Diels−Alder reactions with reactive dienophiles such as PTAD, which can be achieved in a one-pot operation from ynenoylsilanes.

We have recently reported the enantioselective formation of siloxyallenes **4**[1] bearing a vinyl substituent via Meerwein−Ponndorf−Verley-type reduction[2] of enynoylsilanes **1** using chiral lithium amide **2** (Scheme 1).[3,4] The enantioselectivity observed is explained by *anti*-mode $S_E2'$-type protonation via a Brook rearrangement[5] in a silicate intermediate **3** or a silicate transition state.[6] Thus, C−Si bond cleavage and protonation in **3** occurs in a concerted fashion and in an *anti*-mode while keeping a parallel alignment between the C−Si bond and the $\pi$ orbital of the triple bond. We became interested in examining whether the stereoelectronic and/or steric preferences could be extended to a vinylogous system **5**, in which a double bond is introduced between the acylsilane moiety and the triple bond, and enol silyl ethers **7** substituted by axially chiral allenes can be formed as products. Although there are some reports on *syn*-type intramolecular 1,4-addition across 1,3-enynes,[7] the stereochemical course of an anionic rearrangement across the 1,3-enyne system leading to a 1,3,4-triene system has never been explored. From a synthetic point of view,[8] **7** can serve as a versatile chiral building block in C−C bond formation reactions such as Diels−Alder reactions and aldol reactions by taking advantage of an axis of chirality of the allene moiety. Synthesis of allenylenol silyl ethers, however, is quite limited, and there are only a few reports in the literature even in their racemic form.[9,10] In this paper, we report an enantioselective synthesis of allenylenol silyl ethers using a tandem process that involves Meerwein−Ponndorf−Verley-type reduction of ynenoylsilanes by a chiral lithium amide, a Brook rearrangement in the resulting $\alpha$-silyl alkoxide, and protonation of a lithioallenyl carbanion.

**Scheme 1. Tandem Processes for the Enantioselective Formation of Allenes**

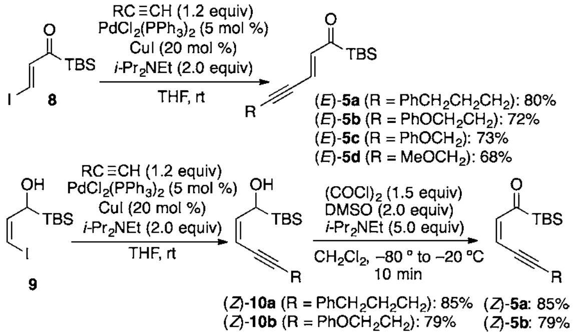


In the case using ynenoylsilanes **5** as substrates, in contrast to the case of **1**, the *E*/*Z* geometries in **5** potentially affect the *E*/*Z* geometry in the enol silyl ether moiety in the products **7**,[11] and we therefore decided to conduct the reaction on both (*E*)- and (*Z*)-derivatives. While (*E*)-**5** was successfully prepared by Sonogashira cross-coupling[12] of $\beta$-iodoacryloyl silanes **8** with the corresponding alkynes, some modifications in the case of (*Z*)-**5** were needed; thus, the coupling of 3-iodo-1-silyl-2-propen-1-ol followed by oxidation was carried out, as shown in Scheme 2.

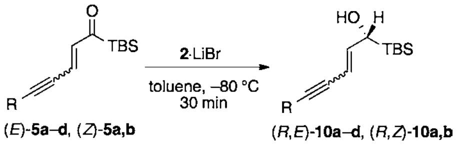
**Received:** January 27, 2015
**Published:** February 17, 2015

DOI: 10.1021/acs.orglett.5b00261
*Org. Lett.* 2015, 17, 1280−1283

### Scheme 2. Syntheses of Ynenoylsilanes



### Table 1. Reduction of Ynenoylsilanes 5 Using Chiral Lithium Amide 2



| entry | 5 | R | yield (%) | er |
|---|---|---|---|---|
| 1 | (*E*)-**5a** | PhCH$_2$CH$_2$CH$_2$ | 85 | >99:1 |
| 2 | (*E*)-**5b** | PhOCH$_2$CH$_2$ | 88 | >99:1 |
| 3 | (*E*)-**5c** | PhOCH$_2$ | 87 | >99:1 |
| 4 | (*E*)-**5d** | MeOCH$_2$ | 92 | >99:1 |
| 5 | (*Z*)-**5a** | PhCH$_2$CH$_2$CH$_2$ | 79 | 99:1 |
| 6 | (*Z*)-**5b** | PhOCH$_2$CH$_2$ | 81 | >99:1 |

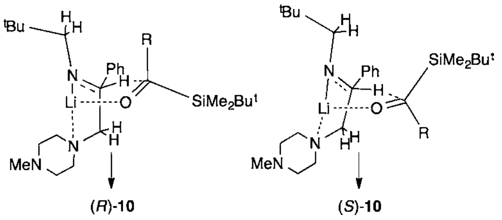
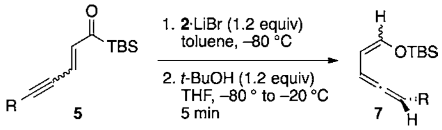


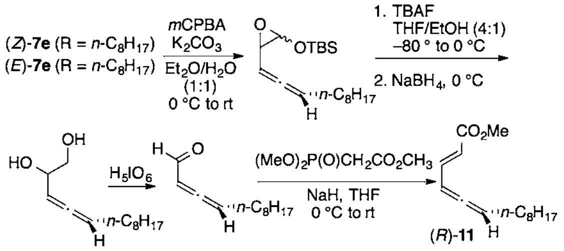
**Figure 1.** Transition state structures of the reduction.

### Table 2. Enantioselective Formation of Allenylenol Silyl Ethers 7 from Ynenoylsilanes 5



| entry | 5 | R | 7 | yield (%) | er |
|---|---|---|---|---|---|
| 1 | (*E*)-**5a** | PhCH$_2$CH$_2$CH$_2$ | (*Z*)-**7a** | 71 | 93:7 |
| 2 | (*E*)-**5b** | PhOCH$_2$CH$_2$ | (*Z*)-**7b** | 78 | 99:1 |
| 3 | (*E*)-**5c** | PhOCH$_2$ | (*Z*)-**7c** | 79 | 90:10 |
| 4 | (*E*)-**5d** | MeOCH$_2$ | (*Z*)-**7d** | 81 | 94:6 |
| 5 | (*Z*)-**5a** | PhCH$_2$CH$_2$CH$_2$ | (*E*)-**7a** | 64 | 97:3 |
| 6 | (*Z*)-**5b** | PhOCH$_2$CH$_2$ | (*E*)-**7b** | 59 | >99:1 |

### Scheme 3. Determination of Absolute Configuration of (*Z*)-7 and (*E*)-7



from (*Z*)-**7e**: $[\alpha]_D^{26}$ −111.0 (*c* 0.16, hexane), 72% ee
from (*E*)-**7e**: $[\alpha]_D^{26}$ −97.4 (*c* 0.21, hexane), 65% ee
lit. $[\alpha]_D^{24}$ −130.3 (*c* 2.23, hexane), 74.7% ee

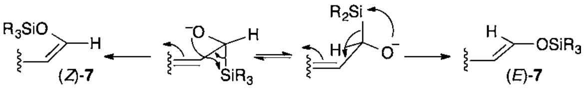


**Figure 2.** Rotamers of *α*-silyl alkoxide leading to (*E*)- and (*Z*)-7.

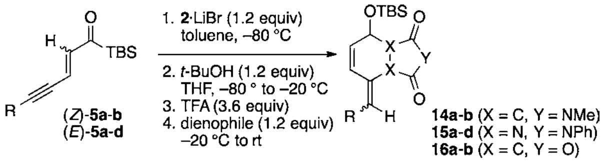
In initial experiments, we examined the MPV-type reduction of ynenoylsilanes (*E*)-**5a** with **2** in toluene at −80 °C. Although the corresponding silyl alcohol (*E*)-**10a** was obtained in an excellent enantioselectivity (er >99:1) with the absolute configuration being assigned as *R* on the basis of the modified Mosher method,[13] recovery of the starting material (7−37%) was inevitable under various conditions. The use of **2**, however, generated from MeLi·LiBr and not from *n*-BuLi, solved this problem to provide (*R,E*)-**10a** in 85% yield (Table 1, entry 1).[14,15] The enantioselectivity observed can be explained by invoking a deformed six-membered transition state in which a steric interaction between the 1′-methylene group and the carbonyl-carbon substituents due to the increased double-bond character of the C-1 nitrogen bond controls the selectivity (Figure 1). That has been previously proposed for the reduction of corresponding silylimines on the basis of the results of density functional theory (DFT) calculations.[16] Similar results were obtained with (*Z*)-**5a**,**b** as well as other (*E*)-substrates (Table 1).

Having established the applicability of enantioselective MPV-type reduction to ynenoylsilanes, we proceeded to examine the viability of the tandem process that involves MPV-type reduction, a Brook rearrangement in the resulting *α*-silyl alkoxide, and the formation of an allenylenol silyl ether by protonation across the enyne moiety. When (*E*)-**5a** was treated with **2** in toluene followed by addition of a THF solution of *t*-BuOH,[17] (*Z*)-**7a** was obtained exclusively, in sharp contrast to the result that (*Z*)-**5a** afforded only (*E*)-**7a** (Table 2). The same stereoselectivity was also observed in reactions of the other ynenoylsilanes (*E*)-**5b−d** and (*Z*)-**5b**. The absolute configurations of the allene derivatives (*E*)- and (*Z*)-**7** were determined to be both *R* by the fact that the known allene derivative (*R*)-**11**[18,19] was obtained from both of the isomers as shown in Scheme 3.

The *E*/*Z*-geometry in the products is controlled by rotamers of an *α*-silyl alkoxide, from which a Brook rearrangement occurs via a pentacoordinate-silicate transition state or intermediate to give enol silyl ethers as shown in Figure 2. This is based on the stereoelectronic requirement that the C−Si bond cleaved should be in a parallel arrangement to the *π*-bond of the double bond.

To obtain information about the origin of the strict *E*/*Z*-selectivity observed, we performed DFT calculations on ground-state conformations of *α*-silyl lithium alkoxides (*E*)-**12a**,**b** and (*Z*)-**12a**,**b** leading to (*Z*)- and (*E*)-**13**, respectively (B3LYP/6-311++G** level; see Supporting Information).[20] These calculations account for the stereoselectivity observed by showing that (*E*)-**12a** and (*Z*)-**12b** leading to (*Z*)-**13** and (*E*)-**13** are more stable than the corresponding intermediates leading to (*E*)-**13** and (*Z*)-**13**, respectively (Figure 3), although the origin of the different stabilities of the rotamers is not clear at present.

**Table 3. Diels–Alder Reactions of Allenylenol Silyl Ethers Achieved in a One-Pot Operation from Ynenoylsilanes 5**



| entry | 5 | dienophile | product | (E)-14–16 yield (%) | (E)-14–16 er | (Z)-14–16 yield (%) | (Z)-14–16 er |
|---|---|---|---|---|---|---|---|
| 1[a,b] | (Z)-**5a** | PTAD | **15a** | 80 | 99:1 (R) | 16 | 98:2 (S) |
| 2 | (Z)-**5a** | NMM | **14a** | 61 | 99:1 (R) | – | – |
| 3 | (Z)-**5a** | MA | **16a** | 43 | >99:1 (R) | – | – |
| 4[a,b] | (Z)-**5b** | PTAD | **15a** | 62 | 99:1 (R) | 26 | 99:1 (S) |
| 5 | (Z)-**5b** | NMM | **14a** | 57 | 99:1 (R) | – | – |
| 6 | (Z)-**5b** | MA | **16a** | 43 | 99:1 (R) | – | – |
| 7[a] | (E)-**5a** | PTAD | **15a** | 51 | 96:4 (S) | 11 | 97:3 (R) |
| 8[a] | (E)-**5b** | PTAD | **15b** | 37 | 97:3 (S) | 32 | 94:6 (R) |
| 9[a] | (E)-**5c** | PTAD | **15c** | 35 | >99:1 (S) | 56 | 99:1 (R) |
| 10[a] | (E)-**5d** | PTAD | **15d** | 51 | 96:4 (S) | 30 | 96:4 (R) |

[a] PTAD (0.5 equiv), −80 °C, 1 h. [b] TFA (0.9 equiv).

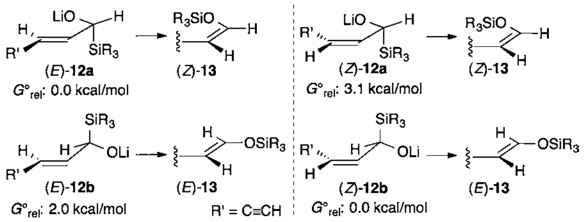
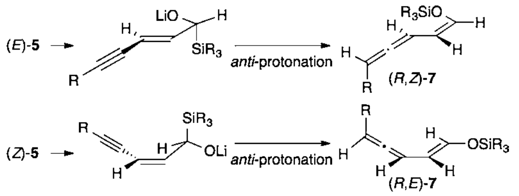
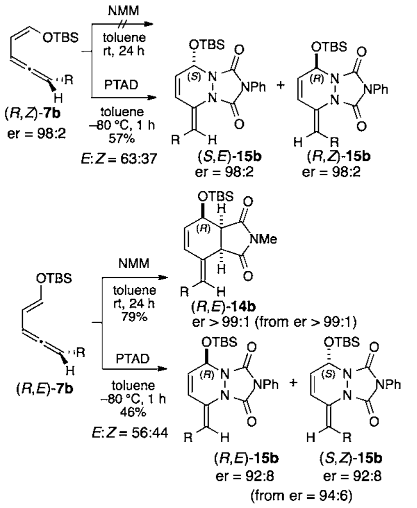


**Figure 3.** Relative energies of $\alpha$-silyl lithium alkoxides.

**Scheme 4. Stereochemical Pathway for Protonation of $\alpha$-Silyl Lihium Alkoxides**



**Scheme 5. Diels–Alder Reactions of Allenylenol Silyl Ethers 7**



The correlation between absolute configurations of the stereogenic centers of **10** and allene moieties of **7** indicates that the protonation proceeds in an *anti*-mode to the C–Si bond across the 1,3-enyne system (Scheme 4). Our previous studies on alkynoyl silanes showed that protonation on the triple bond occurs in an *anti*-mode to the C–Si bond probably because of stereoelectronic and/or steric effects.[3] If stereoelectronic effects operate also in the 1,3-enyne system, overall *syn*-protonation (*anti*, *anti*) products should be produced across the 1,3-enyne system. A possible explanation for the overall *anti* protonation observed is that the protonation is caused by *t*-BuOH(s) precomplexed with a lithium atom bound to an oxygen atom of a silicate or a silyl alkoxide,[6b] consequently from the same side as the oxygen atom and thus from the opposite side to the C–Si bond. However, a detailed understanding of the origin of the stereochemical preference for the protonation must await further mechanistic study.

To evaluate the synthetic potential of (*Z*)- and (*E*)-enol silyl ethers having an axially chiral allene moiety, we examined Diels–Alder (D–A) reactions of (*R*,*Z*)- and (*R*,*E*)-**7b** with *N*-methylmaleimide (NMM) and *N*-phenyl-1,2,4-triazolinediones (PTAD). The latter was selected in view of its extremely high reactivity toward a diene that allows a D–A reaction with (*Z*)-dienes under mild conditions.[21] The reaction of (*R*,*E*)-**7b** with NMM proceeded smoothly to give (*R*,*E*)-**14b**, while (*R*,*Z*)-**7b** resulted in recovery of the starting materials (Scheme 5). In contrast, the reactions of both (*R*,*Z*)- and (*R*,*E*)-**7b** with PTAD proceeded even at −80 °C to give (*S*,*E*)- and (*R*,*Z*)-**15b** and (*R*,*E*) and (*S*,*Z*)-**14b**, respectively. Their stereochemical assignments were made on the basis of the results of the X-ray analysis of (*R*,*Z*)-**15c** (vide infra).

These stereochemical outcomes can be rationalized by invoking that the reaction proceeds through transition states, the geometries of which are governed by a combination of steric interactions between the dienophile and the allene substituent R, and the *E*/*Z*-geometry of the enol silyl ether, as shown in Figure 4. The low *E*/*Z* selectivity in the reactions with PTAD is attributed to the extremely high reactivity of the dienophile.

We next examined whether it is possible to bypass the isolation of 1,3,4-trienol silyl ethers **7**. As a result, we developed a one-pot procedure that enables the direct conversion of ynenoylsilanes **5** into **14**–**16** (Table 3).

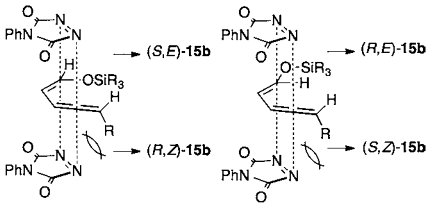


**Figure 4.** Transition-state structures of the Diels−Alder reaction.

In conclusion, the significant points arising from the study outlined here are as follows: (1) the reduction of ynenoylsilanes via an MPV-type hydride transfer from a chiral lithium amide provides $\alpha$-silyl alkoxides that undergo protonation across conjugated 1,3-enynes after a Brook rearrangement to give allene derivatives bearing a 2-siloxyvinyl moiety enantioselectively; (2) the stereoselective formation of (*E*)- and (*Z*)-enol silyl ethers depending on the geometry of the starting enyne moiety can be attributed to the difference between the stabilities of the rotamers leading to the Brook rearrangement; (3) the correlation between absolute configurations of the $\alpha$-silyl alkoxide and the allene moiety indicates that an anionic rearrangement across the 1,3-enyne system followed by protonation proceeds in an *anti*-mode to the C−Si bond; (4) the 2-siloxyvinylallene products can participate in Diels−Alder reactions with reactive dienophiles, which can be achieved in a one-pot operation from ynenoylsilanes.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedure, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was partially supported by a Grant-in-Aid for Scientific Research (C) 25460015 (M.S.) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Hoan Sha Foundation (M.S.), the Takeda Science Foundation (M.S.) and the Naito Foundation Natural Science Scholarship (M.S.). We thank the staff of Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University for the use of their facilities.

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(19) The decline in the enantiopurity of **11** was attributed to partial racemization at the stage of the aldehyde.

(20) Calculations were performed on the Spartan '14 (Ver. 1.1.4 for Mac), Wave function, Inc., Irvine, CA. Calculations of the transition structures for the formation of (*E*)- and (*Z*)-**7** were not attempted due to the difficulty associated with several mechanistic possibilities.

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*Org. Lett.* 2015, 17, 1280−1283