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Ring Strain-Promoted Allylic Transposition of Cyclic Silyl Ethers

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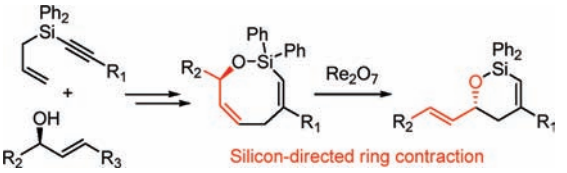
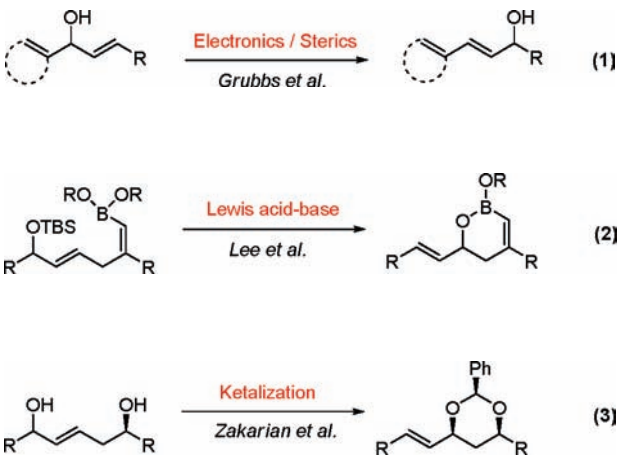
ABSTRACT



Relief of the ring strain of medium-sized rings promotes a regioselective allylic transposition of a C−O bond when catalyzed by rhenium oxide. Through the allylic transposition, eight-membered cyclic silyl ethers undergo ring contraction to the corresponding six-membered siloxacycles.

The Re(VII)-catalyzed[1] allylic [1,3]-transposition[2] of allylic alcohols and their silyl ether derivatives originally reported by Osborn is a powerful synthetic tool. The utility of this transformation, however, is significantly limited by the formation of an equilibrium mixture of regioisomeric products due to its reversibility. Recently, several approaches to control the regioselectivity have been developed. Grubbs et al. utilized electronic biasing elements such as conjugation and steric pressure around the allylic alcohol moiety (eq 1).[3] By taking advantage of the (*Z*)-vinylboronate moiety tethered to the reaction center, Lee et al. achieved excellent regiochemical control through a Lewis acid−base interaction between the boronate and the rearranged silyl ether moieties (eq 2).[4] Recently, Zakarian et al. implemented a ketalization-based trapping strategy by which the most thermodynamicallly favorable benzylidene acetals of syn-1,3-diols were efficiently generated (eq 3).[5] With our continued interest in regioselective allylic transposition, we became intrigued by the possibility of using ring strain as the regioselectivity controlling element (eq 4).



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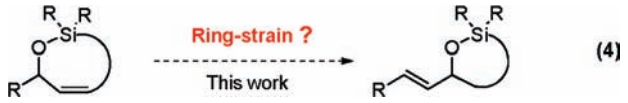
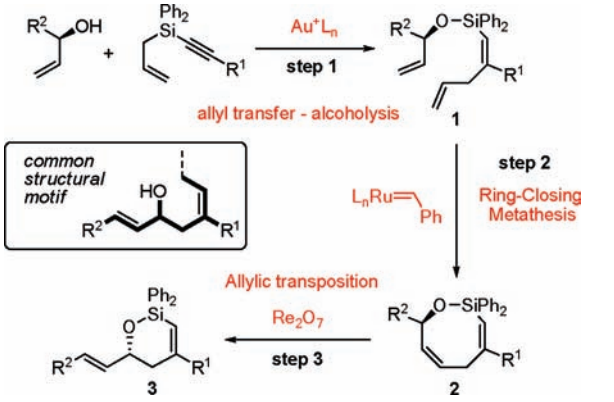


(4)

The allylic transposition with medium-sized ring systems involving ring contraction is expected to be regioselective due to two main factors. First, the endocyclic double bonds in most medium rings are *cis*-, which would have a significant driving force to become a *trans*-double bond after the ring contraction. Second, due to their transannular interactions, the medium-sized rings are generally more strained than their smaller counterparts. Among medium-sized rings, the ring contraction of eight-membered rings to the corresponding six-membered rings would be most favorable because this transformation would induce more relief of ring strain compared to the process involving other rings. As a platform for the development of an allylic transposition strategy, we became interested in a 1,5-dien-4-ol motif containing a (*Z*)-trisubstituted double bond for it is a common structural feature found in many biologically active natural products including zampanolide,[4b,6] bryostatin 1,[7] rubifolide,[8] and various amphidinolides.[9] Herein we describe a successful implementation of the ring strain-driven allylic transposition employing eight-membered siloxadienes as an efficient method for the synthesis of (*Z*)-trisubstituted vinylsilanes containing a 1,5-dien-4-ol moiety.

To examine the new allylic transposition concept, we required an economic[10] access to eight-membered siloxacycles. This need was easily addressed by an intramolecular allyl transfer–alcoholysis of silylalkynes[11] (Scheme 1) followed by ring-closing metathesis (RCM)[12] of corresponding silyl ethers **1**. Considering the ring strain of siloxadienes **2**, a negative factor for its formation via RCM but a prerequisite for the subsequent allylic transposition to **3**, the presence of an extra double bond in the form of a vinylsilyl moiety in the siloxacycle platform **2** is critical for its formation and ring contraction.

Scheme 1. Ring Contraction of Eight-Membered Siloxacycles and Their Synthesis



Our strategy was first tested with benzyloxymethyl-substituted silylalkyne ($R^1 = CH_2OBn$) and allyl alcohol (Table 1). An intramolecular allyl transfer reaction driven by an alcoholysis afforded silyl ether **1a** in high yield with (*Z*)-stereochemistry (entry 1). The silyl ether **1a** was treated with Grubbs second-generation catalyst (G-II) for 4 h at 25 °C in CH_2Cl_2, affording eight-membered siloxacycle **2a** in 96% yield.

The proposed ring contraction was demonstrated by treatment of **2a** with a catalytic amount of Re_2O_7 (5 mol %, ether, 25 °C, 3 h), providing siloxene **3a** in 49% yield. Although the yield was marginal, this clearly illustrated the feasibility of the proposed reaction sequence. The low yield of the ring contraction is most likely to be the consequence

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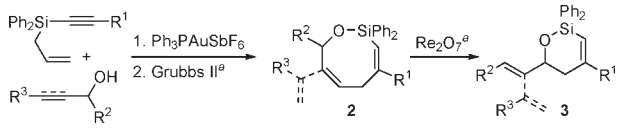
Table 1. Synthesis of Functionalized (*Z*)-Trisubstituted Vinylsilanes



Entry	1st	Yield[b] (%)	2nd	Yield[b] (%)	3rd	Yield[b] (%)
1	**1a**, R = H	74	**2a**	96	**3a**	49
2	**1b**, R = ^{i}Pr		**2b**	58[c]	**3b**	83
3	**1c**		**2c**	51[c]	**3c**	65
4	**1d**, R = Me		**2d**	69[c]	**3d**	82
5	**1e**, R = C_5H_{11}		**2e**	62[c]	**3e**	87
6	**1f**	70	**2f**	85	**3f**	85
7	**1g**		**2g**	47[c]	**3g**	53[e]
8	**1h**, R = Me	73	**2h**	60 (62:38)[d]	**3h**	76
9	**1i**, R = C_5H_{11}	78	**2i**	61(63:37)[d]	**3i**	75
10	**1j**	67	**2j**	63 (67:33)[d]	**3j**	61
11	**1k**	60	**2k**	57 (71:29)[d]	**3k**	74

[a] 5 mol % of catalyst was used. [b] Isolated yield. [c] Isolated yield overall for 2 steps. [d] NMR ratio of eight- and five-membered siloxacycles. [e] Combined yield of **3g** and aromatized product.

of generating the thermodynamically less favorable terminal alkene from the internal one in the starting material.

Encouraged by this observation, eight-membered siloxadienes **2b** and **2c** were synthesized via the same but one-pot reaction without isolating intermediates (entries 2 and 3). Gratifyingly, after purification, treatment of **2b** and **2c** with Re_2O_7 (5 mol %, ether, 25 °C, 10 min) provided six-membered siloxenes **3b** and **3c** in good yields with *trans*-stereochemistry of the newly generated double bond. Under these reaction conditions, the TBS-group of the primary alcohol was cleaved (entry 3); yet, diphenylsilyl group migration from the secondary alcohol moiety to the primary one was not observed. Compounds **3d** and **3e** were obtained similarly from metoxymethyl-substituted silylalkyne (R^1 = CH_2OMe) and secondary allylic alcohols (entries 4 and 5).

The generality of the sequence was further examined with a variety of substrates including allylic alcohols bearing aromatic substituents, tertiary allylic alcohols, and propargylic alcohols. Influence of the substituent on the silylalkyne moiety was also examined. Allyl transfer−alcoholysis with propargylic alcohols afforded vinylsilanes **1f** and **1g**, which were subsequently ring closed to give compounds **2f** and **2g** (entries 6 and 7). Although the ring-closing enyne metathesis of silyl ethers **1f** and **1g** required longer reaction times and an ethylene environment,[13] eight-membered siloxacycles containing a 1,4-diene moiety were formed without difficulty albeit the yield of **2g** is marginal. The rhenium oxide catalyzed allylic transposition of **2f** afforded siloxene **3f** with high efficiency. However, the allylic transposition of **2g** provided a mixture of **3g** and an aromatized byproduct, which should be the result of methanol elimination. Not surprisingly, tertiary allylic and secondary benzylic alcohols were not compatible with the allyl transfer conditions as opposed to nonallylic tertiary and secondary allylic alcohols.[11] Probably, this is due to the formation of relatively stable allylic and benzylic cations from the starting alcohols or the products thereof.

Changing the nature of the substituent on the silylalkyne significantly affected the efficiency of both the gold-catalyzed allyl transfer reaction and RCM (entries 8−11). As opposed to the substrates with alkoxymethyl substituents, those with a simple methyl group showed slower allyl transfer and diminished RCM yields. Yet, under reoptimized reaction conditions,[13] (*Z*)-vinylsilanes **1h**−**k** were obtained in good yields and stereoselectivity. RCM of these silyl ethers required a high reaction temperature (85 °C, toluene) and provided mixtures of the desired eight-membered cyclic siloxadiene together with a varying amount of the five-membered siloxene.[14,15] The ring contraction of siloxadienes **2h**−**k** under standard conditions afforded siloxenes **3h**−**k** in good yields.

The chirality transfer during allylic transposition was examined with substrates **2l** and **2m** obtained from (*S*)-1-octen-3-ol (*ee* > 95%) and (*S*)-3-pentyne-2-ol (*ee* > 99%[16]), respectively (Scheme 2). The chiral HPLC analysis of the desilylated alcohol derived from

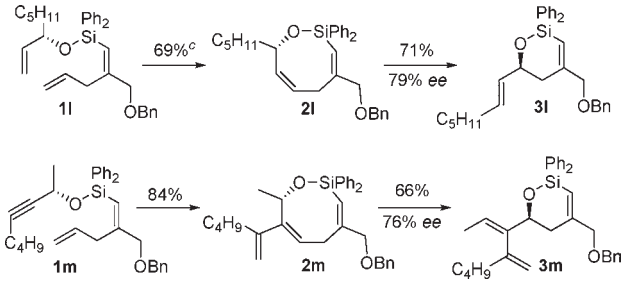
(13) See Supporting Information for details.

(14) It is unusual to observe this five-membered ring product because RCM of vinylsilanes is known to be difficult with a Grubbs catalyst. (a) Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749–1752. (b) Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695–9708.

(15) We surmise that the five-membered ring formation is most likely the consequence of direct RCM of the acyclic precursors because resubjection of the eight-membered siloxacycle to the reaction conditions did not provide any five-membered ring product.

siloxene **3l** and Mosher's ester analysis of the desilylated alcohol from **3m** showed that the stereochemical integrity of the allylic alcohol was lost to some extent.

Scheme 2. Chirality Transfer in [1,3]-Transposition



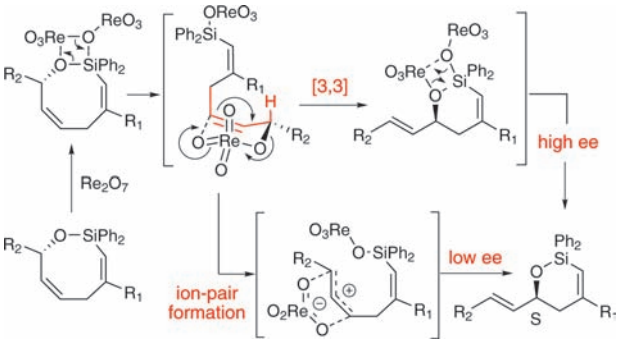
When the reaction was carried out at room temperature, **3l** and **3m** were obtained in 79% and 76% *ee*, respectively. The degree of racemization for Re_2O_7 catalyzed allylic transposition depends on the reaction time, and thus a prolonged reaction time resulted in low *ee* values.

Based on the allylic transposition of **2l** and **2m**, it is reasonable to consider that there are two distinctive mechanisms for the allylic transposition catalyzed by rhenium oxide (Scheme 3). Upon activation of the Si–O bond with rhenium oxide, σ-bond metathesis takes place, which then undergoes an allylic transposition via a [3,3]-sigmatropic rearrangement or ion-pair formation.

The product of the concerted [3,3]-sigmatropic rearrangement pathway should be enantiomerically enriched with high *ee* value. On the other hand, due to the highly Lewis acidic nature of Re_2O_7, the allylic transposition may partially occur via an allylic cation intermediate generating a product with low or no *ee* value.[3,4] The extent of the two manifolds of allylic transposition also depends on the steric and electronic nature of substituents R^1 and R^2. An electron-withdrawing R^1 should favor a concerted process

(16) This compound was obtained by kinetic resolution of its racemate with Novozym. For Novozym resolution, see: (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1990**, *112*, 7434–7436. (b) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129–6139. (c) Xu, D.; Lib, Z.; Ma, S. *Tetrahedron Lett.* **2003**, *44*, 6343–6346. (d) Xu, D.; Lib, Z.; Ma, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3657–3666.

Scheme 3. Plausible Mechanism for Silyl-Directed Allylic Transposition/Ring Contraction



while an electron-donating substituent should facilitate formation of ion pairs via an allyl cation intermediate.

In conclusion, we have developed a novel allylic transposition reaction that relies on the relief of ring strain. Through this process, eight-membered ring siloxadienes undergo a ring contraction to the corresponding six-membered siloxenes bearing an endocyclic double bond and an alkenyl substituent. The orchestrated use of three metal-catalyzed reactions, an intramolecular allyl transfer of silyl alkynes to set the (*Z*)-stereochemistry of vinylsilyl moiety, RCM to form the eight-membered ring, and a silyl-directed allylic transposition/ring contraction, constitutes an efficient entry to functionalized (*Z*)-trisubstituted vinylsilanes. Application of this synthetic method to natural product syntheses will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.