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Regioselective Prins Cyclization of Allenylsilanes. Stereoselective Formation of Multisubstituted Heterocyclic Compounds

Takuya Okada, Airi Shimoda, Tetsuro Shinada, Kazuhiko Sakaguchi,* and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558-8585, Japan

sakaguch@sci.osaka-cu.ac.jp; ohfune@sci.osaka-cu.ac.jp

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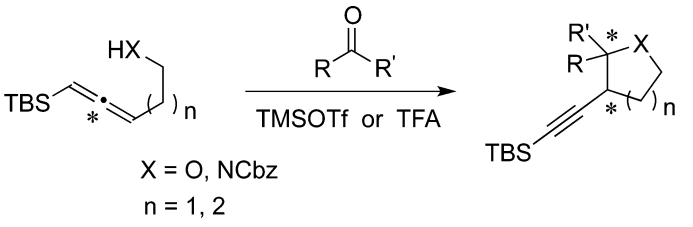
ABSTRACT



The Prins cyclization of hydroxy or amino group-containing allenylsilanes with carbonyl compounds occurred at the allenic terminus in a regio- and stereoselective manner to give the di- or trisubstituted tetrahydrofurans, tetrahydropyrans, and pyrrolidines. During the reaction, the allenic axial chirality of the starting material was efficiently transferred to the newly formed carbon chiral centers of the product.

Substituted furans, pyrans, and pyrrolidines are common structural motifs found in many natural products. The development of efficient methods for the synthesis of these heterocyclic compounds has received considerable attention in organic synthesis. The Prins cyclization, which is performed by the acidic treatment of a homoallylic alcohol with a carbonyl compound, is one of the representative methods for the synthesis of tetrahydropyrans, although it often leads to a complex mixture of products due to the use of a strong acid or high reaction temperature.[1] On the other hand, the vinylsilane-[2] and allylsilane[3]-induced cyclizations (silyl-Prins reactions)

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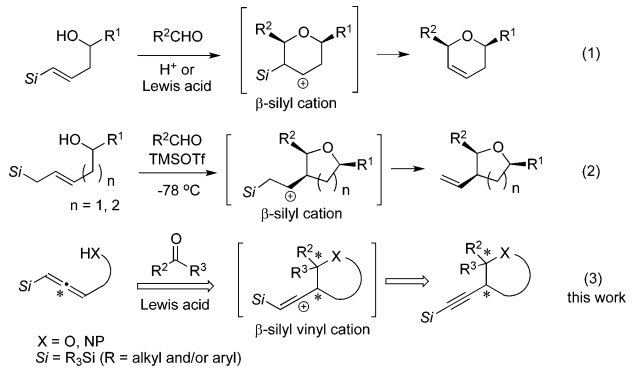
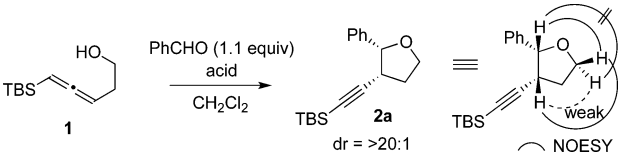
proceeded under mild conditions with complete diastereocontrol due to the intermediary formation of a stabilized β-silyl cation species to afford various heterocyclic products (eqs 1 and 2). During the course of our studies regarding the Au-catalyzed reactions of α-alkynylsilanes and allenylsilanes,[4] we hypothesized that the Prins cyclization of allenylsilanes possessing an internal hydroxy or amino group would occur at its allenic terminus to afford heterocyclic compounds via the β-silylvinyl cation intermediate (eq 3).[5] The product would possess a synthetically useful alkynyl side chain. It is of interest whether the allenic axial chirality is transferred to the product.[6] Herein, we describe the stereoselective synthesis of substituted tetrahydrofurans, tetrahydropyrans, and pyrrolidines using the Prins cyclization of allenylsilanes.



According to the report by Denmark et al.,[3a] TMSOTf was proven to be an excellent Lewis acid for the Prins cyclization of an allylsilane. Thus, our attempt toward the Prins cyclization of an allenylsilane was investigated using TMSOTf as the Lewis acid. To our delight, the treatment of the β-hydroxy allenylsilane **1** containing the *tert*-butyldimethylsilyl (TBS) group[7] with benzaldehyde in the presence of TMSOTf at −78 °C in CH_2Cl_2 underwent the smooth uncommon 5-*endo*-*trig* cyclization to give the *cis*-2,3-disubstituted tetrahydrofuran **2a** containing a silylacetylene moiety as a single diastereomer (97%, dr = >20:1, Table 1, entry 1).[8,9] The quantity of TMSOTf could be reduced to 0.1 equiv at 0 °C for 30 min to give the tetrahydrofuran **2a** in 97% yield (entry 2). A Brønsted acid, such as *p*-TsOH, was also effective for this cyclization. However, the reaction required a higher temperature and a prolonged reaction period, and the yield was moderate (entry 3).

Table 1. Synthesis of 2,3-Disubstituted Tetrahydrofuran



entry	acid (equiv)	temp (°C)	time (h)	yield (%)
1	TMSOTf (1.1)	−78	0.5	97
2	TMSOTf (0.1)	0	0.5	97
3	*p*-TsOH-H_2O (1.0)	rt	20	77

Next, we investigated the substrate scope employing various aldehydes and ketones in the presence of a catalytic amount of TMSOTf (Figure 1). The reactions of **1** with phenylpropionaldehyde, isobutylaldehyde, methacrolein or *m*-anisaldehyde furnished the corresponding tetrahydrofurans **2b**−**d**,**f** in good yields with excellent diastereoselectivities, respectively. On the other hand, a decrease in the drs of **2e**,**g** was observed when the sterically bulky pivalaldehyde or electron-donating 3,4-dimethoxybenzaldehyde was employed.[10] This method was applicable to ketones in the presence of TMSOTf (1 equiv) at −78 °C to give the 2,2,3-trisubstituted tetrahydrofuran **2h**,**i** in good yield.

To examine whether the axis chirality of the allene was transferred to the product, the enantioenriched (a*S*)-**1** (92% ee)[7] was employed for the present cyclization (eq 4). Treatment of (a*S*)-**1** with TMSOTf (0.1 equiv) at 0 °C gave **2a** with 78% ee.[11] The ee was increased to 85% when 1 equiv of TMSOTf was employed at −78 °C (vide infra). The absolute configuration of **2a** was assigned to 2*R*,3*R* by converting it to the MTPA ester **3**.[12] These

(4) (a) Sakaguchi, K.; Okada, T.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett*. **2008**, *49*, 25–28. (b) Okada, T.; Oda, N.; Suzuki, H.; Sakaguchi, K.; Ohfune, Y. *Tetrahedron Lett*. **2010**, *51*, 3765–3768. (c) Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett*. **2011**, *52*, 5740–5743. (d) Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett*. **2011**, *52*, 5744–5746.

(5) Allenylsilanes have proven to be useful carbon nucleophiles for the intermolecular addition to carbonyl compounds in which the reaction occurred at the allenic terminus to produce homopropargylic alcohols and heterocyclic compounds. (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem*. **1980**, *45*, 3927–3929. (b) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc*. **1981**, *103*, 1604–1606. (c) Panek, J. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 2.5. (d) Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem*. **1995**, *60*, 5366–5367. (e) Brawn, R. A.; Panek, J. S. *Org. Lett*. **2009**, *11*, 473–476. (f) Brawn, R. A.; Panek, J. S. *Org. Lett*. **2009**, *11*, 4362–4365. (g) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sörgel, S.; Takahashi, T. *Org. Lett*. **2010**, *12*, 5736–5739.

(6) For selected references for the transfer of the chirality of an allene to an sp3 chirality, see: (a) Krause, N.; Hoffmann-Roeder, A. *Tetrahedron* **2004**, *60*, 11671–11694. (b) Ma, S. M. *Pure Appl. Chem*. **2006**, *78*, 197–208. (c) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259–271. (d) Brawn, R. A.; Panek, J. S. *Org. Lett*. **2009**, *11*, 4362–4365. (e) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc*. **2012**, *134*, 10807–10810.

(7) The allenylsilane **1** was prepared by the Myers protocol; see the Supporting Information. (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc*. **1996**, *118*, 4492–4493. (b) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem*. **1997**, *62*, 7507. The allenylsilane **1** was stable for several weeks as a solution of dichloromethane in a refrigerator (−30 °C) under an argon atmosphere; however, the concentrated **1** decomposed under the same conditions.

(8) The stereochemistry of the disubstituted **2** (Table 1) and the trisubstituted **9** (eq 7) were ascertained by the NOE experiments. The stereochemistry of the trisubstituted compound **8** was also determined by the NOE experiments after converting it to the corresponding desilylated compound **10** (eq 7).

(9) The formation of the desilylated terminal alkyne product was not observed.

(10) Even at low temperature (−78 °C), the drs of the products were almost the same as those at 0 °C (**2e**: 80% yield, dr = 2:1, **2g**: 78% yield, dr = 1:1).

(11) The product's ee was calculated by the chiral HPLC analysis (DAICEL, CHIRALPAK IC, 0.46 cm × 25 cm, *n*-Hexane/EtOH = 99:1, 0.7 mL/min, 254 nm).

(12) The MTPA ester **3** was prepared from **2a** in six steps; see the Supporting Information.

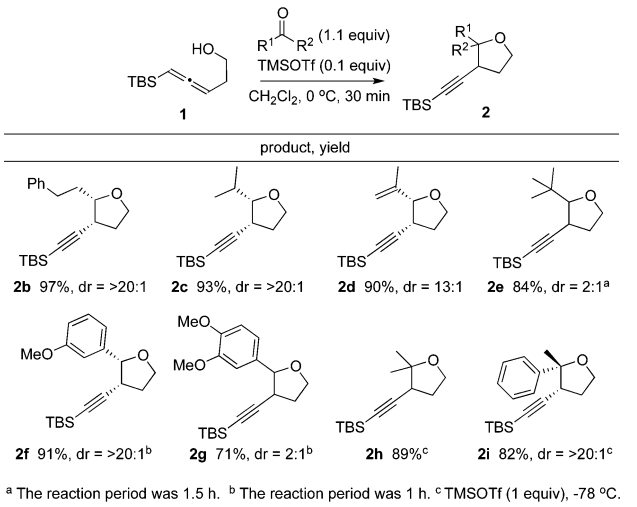
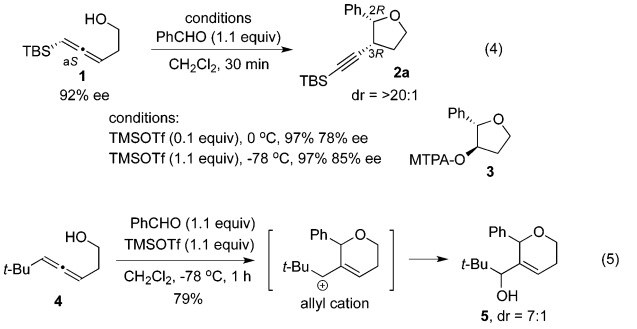


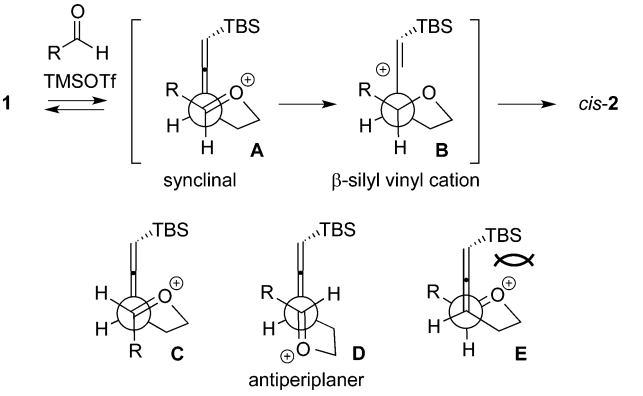
Figure 1. Synthesis of substituted tetrahydrofurans.

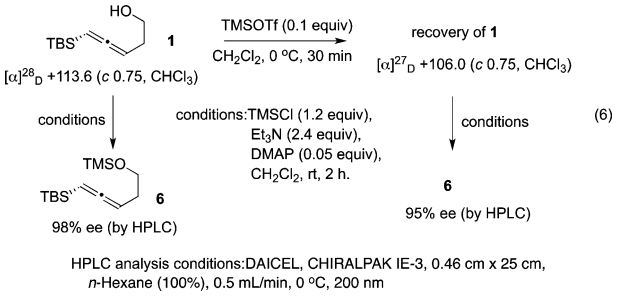
results indicated that the original axial chirality was efficiently transferred to the products. The presence of the silyl group would be essential for this regioselective transformation, since the *tert*-butyl substituted analogue **4**[13] under the same reaction conditions gave the 6-*endo*-cyclized dihydropyran **5** (79%, dr = 7:1) via a putative allyl cation intermediate (eq 5).[14]



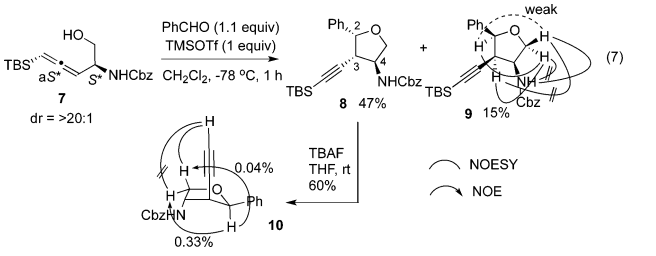
The proposed stereochemical outcome of the present Prins cyclization is shown in Scheme 1. The exclusive formation of the 2,3-*cis*-tetrahydrofuran except for **2e**,**g** would be derived from the synclinal oxonium intermediate **A**, in which the thermodynamically more favored *E*-oxonium ion than that of *Z*[15] was located on the opposite side of the sterically bulky TBS group. Subsequent formation of the silyl-group-stabilized vinyl cation **B** would be significantly attributed to the silyl-group-directed regioselective 5-*endo* cyclization. The reactions with sterically bulky or electron-donating aldehydes would involve the *Z*-oxonium ion **C** and/or antiperiplanar intermediate **D** due to steric and/or stereoelectronic reasons to give a mixture of the *cis*- and *trans*-tetrahydrofurans. The slight decrease in the ee during the conversion of the optically enriched **1** (92% ee) into **2a** (85% ee at −78 °C) suggested that the reaction would involve the sterically disfavored synclinal intermediate **E**, in which the oxonium ion was located on the same side of the TBS group. Only a slight racemization of **1** occurred under the reaction conditions. The acidic treatment of the optically active **1** [$[\alpha]^{28}_D$ +113.6 (*c* 0.75, $CHCl_3$)] without benzaldehyde [TMSOTf (0.1 equiv), CH_2Cl_2, 0 °C, 0.5 h] resulted in the complete recovery of **1** [$[\alpha]^{27}_D$ +106.0 (*c* 0.75, $CHCl_3$)]. According to the chiral HPLC analysis of the TMS ether **6** prepared from **1**, the optical purity of **6** (95% ee) derived from the recovered **1** was slightly lower than that of the starting **1** (98% ee, eq 6).

Scheme 1. Proposed Mechanism





Next, we examined the Prins cyclization using the carbobenzoxyamino (CbzNH)-substituted allenylsilane **7** (dr = >20:1), prepared by the enolate−Claisen rearrangement of an α-acyloxy-α-alkynylsilane.[4b] The treatment of **7** with PhCHO in the presence of TMSOTf (1 equiv) at −78 °C gave a mixture of 2,3,4-trisubstituted tetrahydrofurans **8** (47%) and **9** (15%, eq 7).[8] Since both diastereomers possessed the same 2,3-*cis* relationships, they would be produced via the synclinal conformation **A** (Scheme 1).

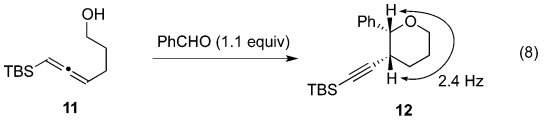


(13) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622–6630.

(14) The relative configuration of the product was not determined.

(15) (a) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435–2441. (b) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392.

The treatment of the homologous analogue **11** with PhCHO in the presence of TMSOTf (0.1 equiv) at 0 °C facilitated the 6-*endo* tetrahydropyran formation to give **12** as a mixture of the diastereomers (*cis*/*trans* = 3.5:1) in quantitative yield (eq 8).[16,17] The dr of **12** was improved to 6:1 when treated at −78 °C. An excellent diastereoselectivity (20:1) was observed when the reaction was performed using CH_3CN as the solvent.

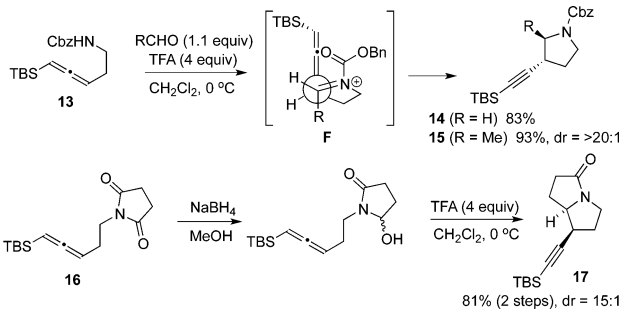


(8)

TMSOTf (0.1 equiv) in CH_2Cl_2, 0 °C, 30 min, quant (dr = 3.5:1)
TMSOTf (1.0 equiv) in CH_2Cl_2, -78 °C, 30 min, quant (dr = 6:1)
TMSOTf (1.0 equiv) in CH_3CN, -30 °C, 1 h, 81% (dr = 20:1)

Finally, we examined the synthesis of nitrogen-containing heterocyclic compounds using the allenylsilanes **13** and **16** (Scheme 2).[18] Although TMSOTf was not effective for the reaction of **13** with paraformaldehyde,[19] the use of TFA (4 equiv)[3c] underwent a smooth 5-*endo* cyclization to give the pyrrolidine **14** (83%). The reaction with acetaldehyde furnished the 2,3-disubstituted pyrrolidine **15**[20] as a single diastereomer (93%).[21] Contrary to the 1,2-*cis*-tetrahydrofuran formation from the alcohol **1**, the product **15** possessed the 1,2-*trans*-substituents, presumably because the reaction proceeded through the iminium ion intermediate **F** in which the substituent R was located *trans* to the Cbz group to avoid the severe steric repulsion. The fused bicyclic pyrrolidine **17**[20] was also synthesized from the succinimide-containing allenylsilane **16**[22] in a similar manner.

Scheme 2. Synthesis of Pyrrolidine Derivatives



In summary, The Prins cyclization of the hydroxy or amino group-containing allenylsilanes with aldehydes gave various 2,3-disubstituted tetrahydrofurans, tetrahydropyrans, and pyrrolidines having an alkynyl substituent. The formation of a stable β-silylvinyl cation intermediate would play an essential role in promoting this reaction. The axial chirality of the allenylsilane was efficiently transferred to the newly formed two contiguous carbon stereocenters of the product. Application of this silylallene−Prins cyclization for the synthesis of biologically important compounds is in progress in our laboratories.

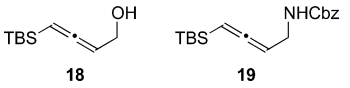
Acknowledgment. This study was financially supported by a Grant-in-Aid (16201045 and 19201045) for Scientific Research from the Japan Society of the Promotion of Science (JSPS). We thank the Daicel Corporation for the chiral HPLC analysis of the allenyl compound **6**.

Supporting Information Available. Full experimental details and characterization data of all the synthetic products are available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) The relative configuration of **12** was assigned by the *J* values between the methine protons (major isomer: 2.4 Hz, minor isomer: 9.9 Hz).

(17) The trial for the formation of the four-membered heterocyclic compounds using 4-(*tert*-butyldimethylsilyl)buta-2,3-dien-1-ol (**18**) and benzyl 4-(*tert*-butyldimethylsilyl)buta-2,3-dienylcarbamate (**19**) was unsuccessful; see the Supporting Information.

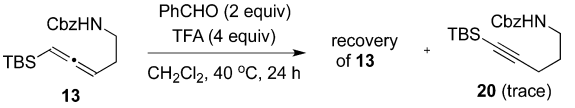


(18) The allenylsilanes **13** and **16** were prepared from **1**; see the Supporting Information.

(19) The reaction using TMSOTf as the Lewis acid afforded **14** in low yield (32%).

(20) The relative configurations of **15** and **17** were determined by the NOE experiments; see the Supporting Information.

(21) The reaction of **13** with PhCHO resulted in the almost complete recovery of **13** with a trace amount of the isomerized alkyne **20** (eq 9).



(9)

(22) Judd, W. R.; Ban, S.; Aubè, J. *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741.