ORGANIC LETTERS

2003
Vol. 5, No. 1
51−54

Lewis Acid-Catalyzed Nucleophilic Substitutions of Propargylic and Allylic Silyl Ethers with Enol Silyl Ethers

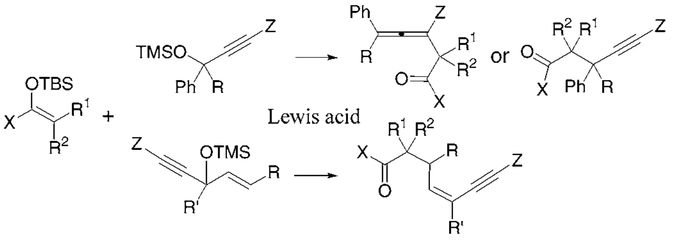
Teruhiko Ishikawa,* Toshiaki Aikawa, Yumiko Mori, and Seiki Saito*

Department of Bioscience and Biotechnology, School of Engineering,
Okayama University, Tsushima, Okayama, Japan 700-8530

seisaito@biotech.okayama-u.ac.jp

Received October 23, 2002

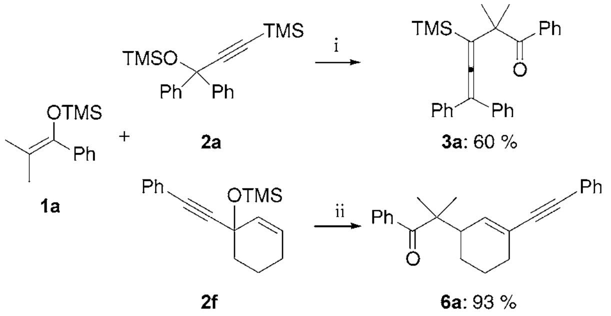
ABSTRACT



Nucleophilic reactions of various enol silyl ethers with carbocation species generated from propargyl silyl ethers by the action of a Lewis acid have been developed. The present method is highly useful for the introduction of allenic or enyne functionalities into the α-position of substituted ketones.

Enol silyl ethers have been widely used in carbon−carbon bond-forming processes such as nucleophilic additions or cycloaddition reactions[1] because of their high reactivity and ready availability with reasonable thermal stability. Although in most of the nucleophilic additions the enol silyl ethers attack activated carbonyl compounds, the nucleophilic reaction of the enol silyl ethers with propargylic or allylic cations has been limited to a few examples.[2] In the course of our research concerned with carbon−carbon bond-forming reactions using carbocations produced from substituted propargyl silyl ethers by the action of trimethylsilyl triflate (TMSOTf), we found that enol silyl ether (**1a**) can play a role as a nucleophile to smoothly react with propargyl silyl ethers (**2a** or **2f**) leading to a substituted allene (**3a**) or alkyne derivative (**6a**), respectively (Scheme 1).[3] Since then, we have been making extensive efforts to develop the reaction of this class into a general organic reaction for carbon−carbon bond formation. Thus, various enol silyl ethers (**1a−k**)[4] and

Scheme 1[a]



[a] Reaction conditions: (i) TMSOTf (0.1 equiv), **1a** (1.6 equiv)/CH_2Cl_2/from −78 °C to rt, 8 h; (ii) TMSOTf (0.1 equiv), **1a** (1.2 equiv)/CH_2Cl_2/−30 °C, 15 min.

---

(1) (a) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1−103. (b) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 2.5.

(2) (a) Itoh, A.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2050−2054. (b) Mayr, H.; Heilmann, W.; Lammers, R. *Tetrahedron* **1986**, *42*, 6663−6668. See also: Hibino, M.; Koike, T.; Yoshimatsu, M. *J. Org. Chem.* **2002**, *67*, 1078−1083.

(3) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635−4642. Only three examples, including those shown in Scheme 1, were reported therein.

10.1021/ol0271537 CCC: $25.00

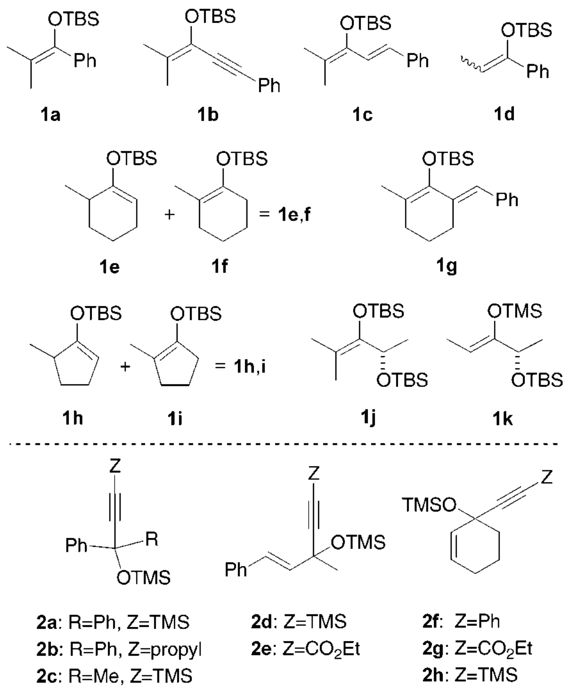
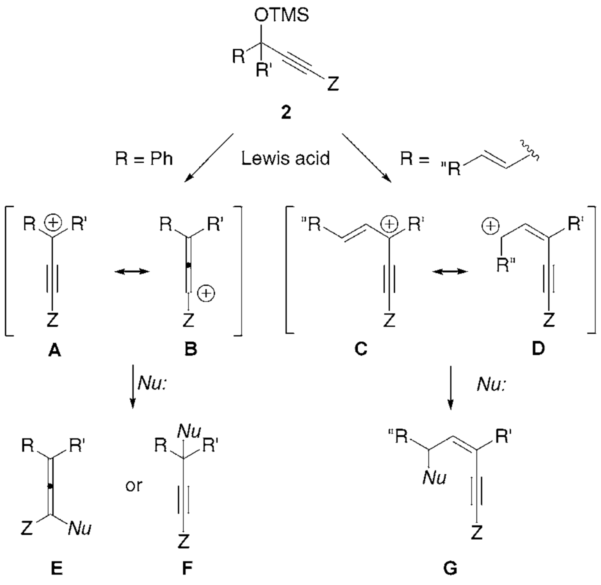


Figure 1. Enol silyl ethers (**1a**−**k**) and propargylic and allylic silyl ethers (**2a**−**h**).

propargyl silyl ethers (**2a**−**h**)[5] listed in Figure 1 were subjected to systematic experiments, and we have succeeded in establishing the generality of the reaction. In addition, the recent report by Matsuda and Ito concerned with the same kind of reaction promoted by an iridium complex[6] has prompted us to quickly report our own efforts in this field. This paper will disclose our recent findings in nucleophilic reactions of carbocation species generated from **2a**−**h** with **1a**−**k** by the action of a Lewis acid as a catalyst.

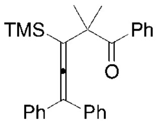
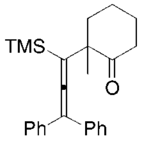
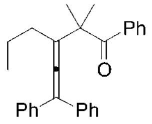
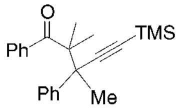
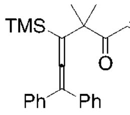
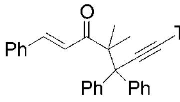
Scheme 2



It was clearly observed in our previous work that the regioselectivity of nucleophilic trapping of cationic species produced from substituted propargyl silyl ethers by the action of TMSOTf could be specified depending on the structure of **2**. This is summarized in Scheme 2. When **2** bears a phenyl group on the oxygen-centered carbon (R = Ph), a **B**-type cation was usually trapped by nucleophiles such as arenes or allylsilanes to give allenyl frameworks (**E**) whereas the formation of propargyl product (**F**) was highly sensitive to the nature (the type of remaining substituent R′) or situation (inter- or intramolecular attack) of the nucleophiles. When **2** bears a vinyl group such as a styryl group, a **D**-type conjugated enyne cation was trapped by the nucleophiles to exclusively afford conjugated enyne products (**G**) without fail.

Again these previous trends were observed in the case of **1** as a nucleophile. When **2a** or **2b** was employed as a partner, the reaction proceeded to result in trapping allenyl cations by **1a** or **1e**,**f** to give allenic products (**3a**−**c**) exclusively (entries 1−3 in Table 1), whereas the reaction of **2c** with **1a** exclusively afforded alkyne **4a** (entry 4). On the other hand, the combination of **1c** with **2a** led to a mixture of type **E** (**3d**) and **F** (**4b**) products in preference to **4b** (entry 5).[7] It should be mentioned with regard to entry 2 that only **1f** led to the expected product **3b**.[8] The operational simplicity

Table 1. Synthesis of Allenic Frameworks[a]

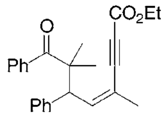
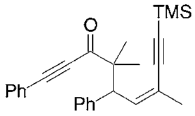
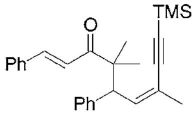
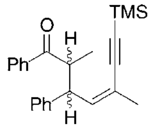
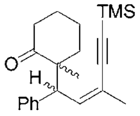
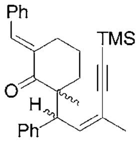
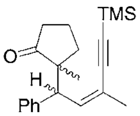
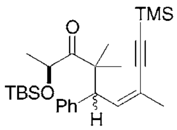
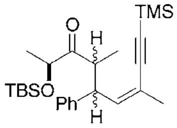
entry	substrate	product		yield/%[b]
1	**1a** + **2a**		**3a**	80
2	**1e**, **f**[c]+ **2a** (1 : 2)		**3b**	20 [43]
3	**1a** + **2b**		**3c**	67
4	**1a** + **2c**		**4a**	65
5	**1c** + **2a**	 **3d** +  **4b**		75 (**3d** : **4b** = 1 : 5) 70 (**3d** : **4b** = 1 : 3.5)[d]

[a] Conducted with alkynes **1** (1.2 equiv) and 10 mol % $BF_3{\cdot}OEt_2$ based on **2** unless otherwise indicated. [b] Yields for isolated products; yield in square bracket (entry 2) was based on consumed **2**. [c] Conducted with 1.4 equiv of **1e**,**f**. [d] Result for TMSOTf.

of this synthesis should be also mentioned: the addition of Lewis acid (TMSOTf or $BF_3{\cdot}OEt_2$) in a catalytic amount to a mixture of **1** and **2** in dichloromethane is sufficient to effect the reaction, and $BF_3{\cdot}OEt_2$ usually afforded better results in terms of product yields than TMSOTf.[9]

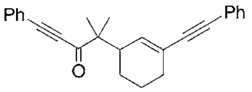
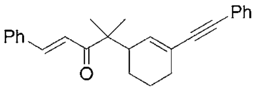
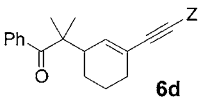
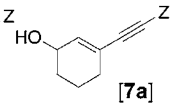
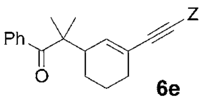
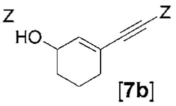
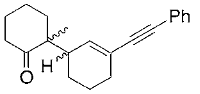
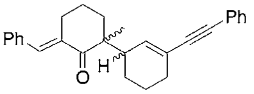
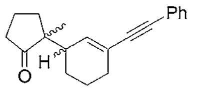
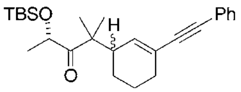
Thus, the synthesis of conjugated acyclic and cyclic enynes could be realized by the combination of **2d**−**g** with **1**. Results pertinent to this synthesis are summarized in Tables 2 and 3, respectively. In all cases, the substitution reactions regioselectively proceeded to afford conjugated enynes (**5a**−**j** or **6a**−**h**). Type **D** intermediate (Scheme 2) was trapped by **1**. For the reaction of acyclic silyl ethers **2d**,**e**, highly *Z*-selective enyne formation (10:1) was observed in general.[10] On the other hand, diastereomeric ratios for newly generated two or three stereogenic centers turned out to be low (entries 5−9 in Table 2).[11] Although additional limitations were found,[12] the yields are very high in general. Particularly interesting are the cases of chiral enol ethers such as **1j** or **1k**[13] in which a mixture of unequal amounts of diastereo-

Table 2. Synthesis of Acyclic Conjugated Enynes[a]

entry	substrate	product[b]		yield/%[c] (isomer ratio)
1	**1a** + **2e**		**5a**	92 ($Z:E$ = 10 : 1)
2	**1b** + **2d**		**5b**	89 ($Z:E$ = 10 : 1)
3	**1c** + **2d**		**5c**	97 ($Z:E$ = 10 : 1)
4[d]	**1d** + **2d**		**5d**	98 ($Z:E$ = 10 : 1.2) (dr 4 : 3)
5[e]	**1e**,**f** + **2d** (**1e** : **1f** = 1 : 2)		**5e**	55 [78][f] (dr 4:3)
6	**1g** + **2d**		**5f**	72 ($Z:E$ = 10 : 1) (dr 6 : 5)
7[e]	**1h**,**i** + **2d** (**1h** : **1i** = 1 : 4)		**5g**	22 [78][f] (dr 1.1 : 1)
8	**1j** + **2d**		**5h**	92 (dr 6 : 1.5 : 1)[g]
9	**1k** + **2d**		**5i**	91 (many isomers)

[a] Conducted with **1** (1.2 equiv) and 10 mol % $BF_3{\cdot}OEt_2$ based on **2**. [b] Structures were determined by NMR, HRMS, IR, and elemental analysis. [c] Yields for isolated products; dr (diastereomer ratio) for (*Z*)-isomers. Relative configuration was not determined. [d] Data for TMSOTf. [e] Carried out with 1.4 equiv of **1**. [f] Yields in square brackets for consumed **2**. [g] (*Z*)-Isomer as a major product.

Table 3. Synthesis of Cyclic Conjugated Enynes[a]

entry	substrate	product[b]		yield/%[c] (isomer ratio)
1	**1b** + **2f**		**6b**	77
2	**1c** + **2f**		**6c**	93
3	**1a** + **2g** (Z= CO_2Et)	 **6d**  **[7a]**		28 [55][d]
4	**1a** + **2h** (Z= TMS)	 **6e**  **[7b]**		46 [29][d]
5[e]	**1e**,**f** + **2f** (**1e**:**1f** =1:2)		**6f**	72 (dr 1 : 1)
6	**1g** + **2f**		**6g**	69 (dr 3 : 1)
7[e]	**1h**,**i** + **2f** (**1h**:**1i**=1:4)		**6h**	72 (dr 1.1 : 1)
8	**1j** + **2f**		**6i**	74 (dr 5 : 3)

[a] Conducted with **1** (1.2 equiv) and 10 mol % $BF_3{\cdot}OEt_2$ based on **2**. [b] Structures were determined by NMR, MS, IR, and elemental analysis. [c] Yields for isolated products; dr (diastereomer ratio) was determined by NMR analysis. Relative configuration was not determined. [d] Yields in square brackets are for byproducts (**7a** or **7b**). [e] Conducted with 1.5 equiv of **1e**,**f** or **1h**,**i**.

---

(4) Enol silyl ethers except for **1j** and **1k** were prepared from ketones by means of TBDMSOTf (1.2 equiv) and Et_3N (2 equiv) using CH_2Cl_2 (5 mL/1 mmol of ketone) as a solvent at 0 °C for 1.5 h.

(5) Prepared from ketones for **2a**−**c** or enones for **2d**−**h** with corresponding acetylide anions followed by O-silylation; see ref 3.

(6) (a) Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072−9073. (b) Matsuda, I.; Wakamatsu, S.; Komori, K.; Makino, T.; Itoh, K. *Tetrahedron Lett.* **2002**, *43*, 1043−1046.

(7) Selectivity of this class is difficult to explain only on the basis of the steric effect, and clarification of the other factors, if any, must await future studies.

(8) Similar trends were reported in alkoxide-promoted Michael addition reactions using simple ketones; for example, see: (a) House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646−655. (b) Ishikawa, T.; Kadoya, R.; Arai, M.; Takahashi, H.; Kaisi, Y.; Mizuta, T.; Yoshikai, K.; Saito, S. *J. Org. Chem.* **2001**, *66*, 8000−8009.

isomers was obtained, indicative of asymmetric induction by means of carbocations (entries 8 and 9 in Table 2). When a mixture of **1f** and **1e** (**1e**,**f**) was treated with **2d** under the given conditions, **1f** (more hindered than **1e**) led to the coupled product **5e**. Similarly, **1h**,**i** (a mixture of **1h** and **1i**) afforded **5g** in which **1i** (more hindered than **1h)** was embedded (entries 5 and 7 in Table 2).

Table 3 summarizes the reactions of cyclic substrates **2f−h**, and again the same regioselectivity as that for the acyclic versions was observed without fail. Most striking in this series is that the ring-to-ring coupling reactions could be achieved so easily that functionalized ring-assemblies such as **6f−h** (entries 5−7, Table 3) were obtained in a rapid and simple manner: the construction of complex molecules of this class should be highly beneficial to organic synthesis and are otherwise difficult to access.

Entries 5 and 7 in Table 3 show that the same events as those in entry 2 in Table 1 or entries 5 and 7 in Table 2 occurred again. Thus, the more substituted sp^2-carbon of enol silyl ethers has higher reactivity toward the cationic species in general. These cases efficiently provide quaternary carbon centers. Clarification of the exact reason responsible for the unique chemoselectivity[8] of this class must await future theoretical and/or experimental studies.

In conclusion, we have demonstrated highly effective coupling reactions between enol silyl ethers and carbocation species that deserve consideration as a practical method for carbon−carbon bond formation. Substrates **2a−c** or **2d−h** can easily be prepared from ketones or enones, respectively, with corresponding acetylide anions followed by O-silylation.[5] This requires no special skill, conditions, or reagents. Also, enol silyl ethers **1a−k** were available through traditional protocol uneventfully.[4] Thus, the present method is highly convenient and useful for the introduction of allenic or enyne functionalities to the α-position of substituted ketones. Further explorations of this chemistry, including complex natural product syntheses, are under investigation.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and spectroscopic data for coupling products **3−6** and copies of ^{1}H and ^{13}C NMR spectra for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0271537

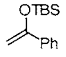
---

(9) General procedure: to a solution of **1** (0.5 mmol) and **2** (0.6 mmol) in CH$_2$Cl$_2$ (5 mL) was added Lewis acid (0.05 mmol) at −30 °C. The reaction was stirred at −30 °C until the disappearance of **1** was indicated by TLC. To the mixture was added water (20 mL), and the resulting mixture was extracted several times with 1:3 ethyl acetate−hexane. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated to give a crude residue, which was purified by column chromatography on silica gel using ethyl acetate−hexane to afford **4**, **5**, or **6**. For the reaction of **1a** with **2a**, TMSOTf afforded 60% yield of **3a** (Scheme 1) and BF$_3$·OEt$_2$ afforded 80% yield (Table 1). Therefore, in this work, BF$_3$·OEt$_2$ was used as the Lewis acid except for the case of entry 4 in Table 2, where TMSOTf was used.

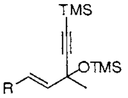
(10) The reason for the preferential formation of (*Z*)-enynes was already discussed; see ref 3.

(11) Structures and isomer ratios for the products were determined by careful analysis of NMR spectra, although the relative configurations of major isomers were not determined yet; see also Supporting Information.

(12) Reactions of **1l** with **2a**,**d**, **2i** with **1a**, and **2j** with **1a**,**d** did not take place under the given reaction conditions.



1l



2i: R = Me
2j: R = c-Hex

(13) Denmark, S. E.; Pham, S. M. *Org. Lett.* **2001**, *3*, 2201−2204.