

Stereoselective One-pot 1,4-Elimination and the [1,2]-Wittig Rearrangement of (*E*)- δ -(Arylmethoxy or 3-Silyl-2-propynyloxy)-substituted Allylic Sulfones

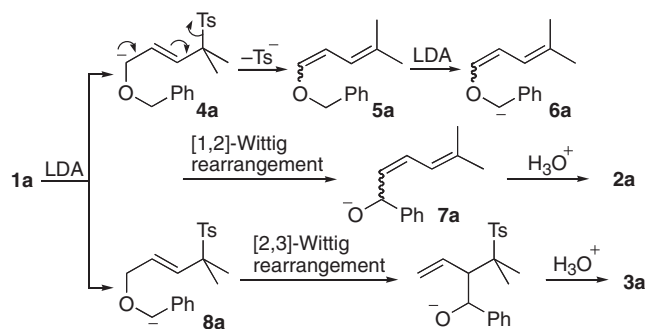
Susumu Horii, Isao Ishimaru, Yutaka Ukaji,* and Katsuhiko Inomata*
 Division of Material Sciences, Graduate School of Natural Science and Technology,
 Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192

(Received February 16, 2011; CL-110132; E-mail: inomata@se.kanazawa-u.ac.jp)

The successive treatment of (*E*)- δ -(arylmethoxy)-substituted allylic sulfones with *t*-BuOK and LDA afforded the corresponding (*Z*)-2,4-dienyl alcohols with high stereoselectivities via 1,4-elimination and the [1,2]-Wittig rearrangement. The predominant formation of (*Z*)-isomers, due to “*syn*-effect” in the elimination step, was further successfully applied to (*E*)- δ -(3-silyl-2-propynyloxy)-substituted allylic sulfones.

Stereoselective preparation of olefins is one of the most important problems in organic chemistry. In the course of studies on the preparation of allylic sulfones,¹ we investigated the stereochemistry of isomerization of α -unsubstituted (*E*)-vinylic sulfones to the corresponding allylic sulfones in the presence of a base and found that the sterically unfavorable (*Z*)-allylic sulfones were predominantly formed.² This experimental fact was rationalized by a “*syn*-effect,”³ which is primarily caused by $\sigma \rightarrow \pi^*$ interaction and/or 6π -electron homoaromaticity.^{2,4} In related studies on the “*syn*-effect,” we revealed that it works also in various kinds of isomerization reactions and elimination reactions utilizing a base.^{4,5} In particular, oxygen-substituted substrates always realized high *Z*-selectivities. During the course of the investigation of the 1,4-eliminative ring opening reaction of a benzyloxy-substituted (*E*)-vinyloxirane with LDA, the [1,2]-Wittig rearrangement⁶ was found to proceed following the initial 1,4-eliminative ring opening reaction to give an (*E,Z*)-2,4-dienyl 1,6-diol in a highly stereoselective manner.^{5g} This shows that the highest *Z*-selectivity based on the “*syn*-effect” observed for the oxygen-substituted substrates could be utilized for the successive stereoselective C–C bond formation. Herein we describe a one-pot 1,4-elimination of allylic sulfones and the subsequent [1,2]-Wittig rearrangement of (*E*)- δ -(arylmethoxy)-substituted allylic sulfones to give the corresponding (*Z*)-dienyl alcohols stereoselectively.

As described above, the “*syn*-effect” of 1,4-elimination of allylic sulfones by the treatment with a base was investigated and a δ -(benzyloxy)allylic sulfone was found to afford the corresponding (*Z*)-vinyl ether stereoselectively.^{5a} If the δ -(benzyloxy)allylic sulfone was treated with excess amounts of a base, the successive 1,4-elimination and the [1,2]-Wittig rearrangement was also anticipated to proceed. When (*E*)- δ -(benzyloxy)allylic sulfone **1a** was treated with 3.0 equiv of LDA, the desired successive reaction product **2a** was obtained in 60% yield. Stereoselectivity of the double bond in **2a** was high as expected (*E/Z* = 11/89). However, a by-product **3a** was also produced (eq 1). As shown in Scheme 1, the 1,4-elimination via



Scheme 1.

4a stereoselectively gave (*Z*)-vinyl ether **5a** originating from the “*syn*-effect,” which was further deprotonated at the benzylic position followed by the [1,2]-Wittig rearrangement to give **2a**. On the other hand, when deprotonation at the benzylic position initially occurred, the benzylic anion **8a** might afford **3a** by the [2,3]-Wittig rearrangement.

In order to suppress the generation of **8a**, a weaker base *t*-BuOK was first used for generation of **4a** selectively to complete the 1,4-elimination, followed by addition of LDA for further the [1,2]-Wittig transformation via **6a**. In this way, only the desired reaction proceeded to give **2a** with high *Z*-selectivity (Table 1).⁷ When 3.5 equiv of LDA was used, a by-product **9a** was also obtained (Entry 1), which might be produced via deprotonation of the rearranged intermediate **7a** and subsequent isomerization (Scheme 2).⁸ By decreasing the amount of LDA and shortening the reaction time for the [1,2]-Wittig rearrangement, the production of the by-product **9a** was rather inhibited and the stereoselectivity was further improved (Entries 2–4). By treating with 2.5 equiv of LDA for 5 min, **2a** was obtained with excellent stereoselectivity in high yield (Entry 3). Several other δ -(arylmethoxy)allylic sulfones **1b–1d** were subjected to the present one-pot 1,4-elimination reaction and the [1,2]-Wittig rearrangement, and the corresponding (*Z*)-dienyl alcohols **2b–2d** were stereoselectively obtained (Entries 5–7).

Next, propargylic ethers instead of benzylic ethers **1**, were investigated in the one-pot transformation. When (*E*)-3-phenyl-2-propynyl ether **10** was treated with *t*-BuOK, 1,4-elimination to **12** was monitored by TLC. After the addition of LDA, the reaction became messy and desired rearranged product **11** was not obtained (eq 2).⁹

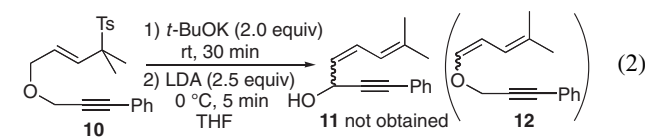
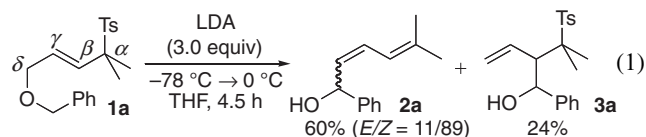
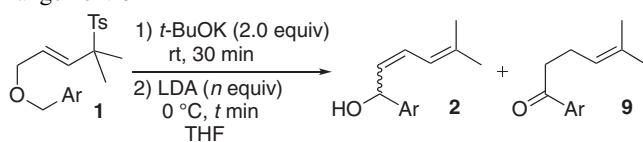
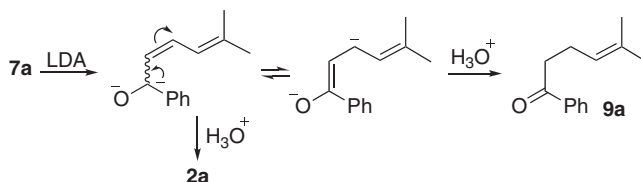
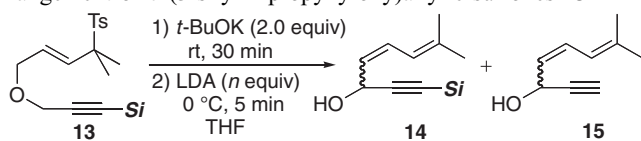


Table 1. One-pot 1,4-elimination and the [1,2]-Wittig rearrangement of **1**

Entry	Ar	1	<i>n</i> /equiv	<i>t</i> /min	Yield of 2 /%	<i>E/Z</i> ^a of 2	Yield of 9 /%
1	Ph	a	3.5	80	69	5/95	4
2			3.0	15	65	2/98	4
3			2.5	5	89 ^b	1/99	1
4			2.0	1	80 ^b	2/98	—
5	4-CH ₃ C ₆ H ₄	b	2.5	5	89	2/98	—
6	4-CH ₃ OC ₆ H ₄	c	2.5	5	85 ^c	3/97	2
7	2-Nap	d	2.5	5	89 ^c	2/98	1

^aThe ratios were determined by 400 MHz ¹H NMR spectra.

^bVinyl ether **5a** was obtained in 7% (Entry 3) and 10% (Entry 4) yields, respectively. ^cVinyl ethers **5c** and **5d** were obtained in 7% (Entry 6) and 6% (Entry 7) yields, respectively.

**Scheme 2.****Table 2.** One-pot 1,4-elimination and the [1,2]-Wittig rearrangement of δ -(3-silyl-2-propynyloxy)allylic sulfones **13**

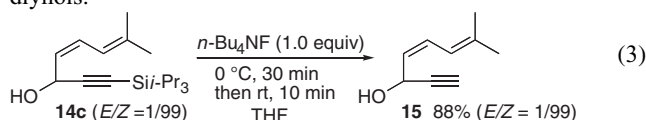
Entry	Si	13	<i>n</i> /equiv	Products	Yield/%	<i>E/Z</i> ^a
1	Me ₃ Si	a	2.5	15	45	12/88
2	<i>t</i> -BuPh ₂ Si	b	2.5	14b	29	3/97
3 ^b	<i>i</i> -Pr ₃ Si	c	2.5	14c	70 ^c	1/99
4 ^b			2.2	14c	74 ^c	1/99

^aThe ratios were determined by 400 MHz ¹H NMR spectra.

^bOn step 1, **13c** was treated with *t*-BuOK at 0 °C for 20 min. ^cA by-product, 7-methyl-1-(triisopropylsilyl)-6-octen-1-yn-3-one, produced via deprotonation of the rearranged intermediate followed by isomerization, was obtained in 14% (Entry 3) and 15% (Entry 4) yields, respectively.

When (*E*)- δ -(3-silyl-2-propynyloxy)allylic sulfones **13** were used as substrates, the desired [1,2]-Wittig rearrangement was found to proceed (Table 2). In the case of trimethylsilyl-substituted substrate **13a**, the rearranged desilylated product **15** was obtained (Entry 1). In order to prevent the desilylation, bulky silyl groups were introduced (Entries 2–4). γ -(Triisopropylsilyl)propargylic ether was a substrate of choice to give the desired product **14c** with excellent *Z*-selectivity (Entries 3 and 4). The desilylation of **14c** was readily carried out by treating with tetrabutylammonium fluoride to afford **15** (eq 3),¹⁰ which

could not be prepared by the conventional Lindlar reduction of diynols.



As described above, the one-pot transformation of (*E*)- δ -(arylmethoxy)- or (3-silyl-2-propynyloxy)-substituted allylic sulfones into (*Z*)-2,4-dienyl alcohols via 1,4-elimination and the [1,2]-Wittig rearrangement were developed,¹¹ which demonstrates a smart application of the “*syn*-effect” to stereoselective C–C bond formation.

The present work was financially supported in part by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (JSPS).

References and Notes

- N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, **1993**, pp. 40–50.
- T. Hirata, Y. Sasada, T. Ohtani, T. Asada, H. Kinoshita, H. Senda, K. Inomata, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75.
- The “*syn*-effect” is herein defined as an effect which stabilizes the *syn*-conformation against the steric hindrance at the transition state.
- K. Inomata, *J. Synth. Org. Chem., Jpn.* **1992**, *50*, 326; K. Inomata, *J. Synth. Org. Chem., Jpn.* **2009**, *67*, 1172.
- Related studies on the “*syn*-effect.” a) A. Shibayama, T. Nakamura, T. Asada, T. Shintani, Y. Ukaji, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 381. b) T. Nakamura, S. K. Guha, Y. Ohta, D. Abe, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2031. c) S. K. Guha, A. Shibayama, D. Abe, Y. Ukaji, K. Inomata, *Chem. Lett.* **2003**, *32*, 778. d) S. K. Guha, Y. Ukaji, K. Inomata, *Chem. Lett.* **2003**, *32*, 1158. e) S. K. Guha, A. Shibayama, D. Abe, M. Sakaguchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2147. f) H. Takenaka, Y. Ukaji, K. Inomata, *Chem. Lett.* **2005**, *34*, 256. g) N. Takeda, T. Chayama, H. Takenaka, Y. Ukaji, K. Inomata, *Chem. Lett.* **2005**, *34*, 1140. h) M. Yamazaki, S. K. Guha, Y. Ukaji, K. Inomata, *Chem. Lett.* **2006**, *35*, 514. i) M. Yamazaki, S. K. Guha, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 740.
- U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763; J. A. Marshall, in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon Press, Oxford, **1991**, Vol. 3, pp. 979–981; K. Tomooka, *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 322; N. C. Giampietro, J. W. Kampf, J. P. Wolfe, *J. Am. Chem. Soc.* **2009**, *131*, 12556; N. C. Giampietro, J. P. Wolfe, *Angew. Chem., Int. Ed.* **2010**, *49*, 2922.
- Vinyl migration in the [1,2]-Wittig rearrangement is known to proceed with retention of geometry: V. Rautenstrauch, G. Büchi, H. Wüest, *J. Am. Chem. Soc.* **1974**, *96*, 2576; K. Tomooka, T. Inoue, T. Nakai, *Chem. Lett.* **2000**, 418. It was also confirmed **2a** was generated via **5a** while retaining stereochemistry: The treatment of **5a** (*E/Z* = 3/97) with LDA (1.5 equiv) in THF at 0 °C for 5 min afforded **2a** (*E/Z* = 2/98) in 46% yield and 34% of **5a** (*E/Z* = 3/97) was recovered.

- 8 The formation of **9a** was not observed by the treatment of **2a** with LDA (2.5 equiv) in THF at 0 °C for 80 min. However, after 1 d at rt, **9a** was confirmed to be produced in ca. 4% yield based on the analysis of a ¹H NMR spectrum of the crude products. Furthermore, isomerization was also observed (*E/Z* of **2a**; from 5/95 to 14/86).
- 9 Delocalization of the generated propargylic anion into the benzene ring through the triple bond might retard the [1,2]-Wittig rearrangement.
- 10 J. A. Marshall, S. L. Crooks, B. S. DeHoff, *J. Org. Chem.* **1988**, *53*, 1616.
- 11 A representative procedure for the one-pot 1,4-elimination and the [1,2]-Wittig rearrangement of **1a** (Table 1, Entry 3): To a suspension of *t*-BuOK (125 mg, 1.12 mmol) in THF (1.1 mL), a THF (4.5 mL) solution of **1a** (193 mg, 0.56 mmol) was added under a N₂ atmosphere and the mixture was stirred for 30 min at rt. After the mixture was cooled to

0 °C, LDA·THF (0.934 mL, 1.40 mmol, 1.5 M in cyclohexane) was added and the reaction mixture was stirred for 5 min at 0 °C. The reaction was quenched by the addition of saturated aqueous solution of NH₄Cl, and the organic substances were extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over Na₂SO₄, and condensed in vacuo. The residue was separated by flash column chromatography (SiO₂, hexane/AcOEt = 30/1–15/1, v/v) to give **2a** (94 mg, 89%, *E/Z* = 1/99) and a mixture of **5a** (7%) and **9a** (1%) (total 8 mg). ¹H NMR (400 MHz, CDCl₃): (*Z*)-**2a**; δ 1.78 (3H, s), 1.85 (3H, s), 1.87 (1H, br s), 5.50 (1H, dd, *J* = 10.7, 8.8 Hz), 5.71 (1H, d, *J* = 8.8 Hz), 6.26 (1H, d, *J* = 11.7 Hz), 6.34 (1H, dd, *J* = 11.7, 10.7 Hz), 7.24–7.42 (5H, m). (*E*)-**2a**; δ 1.78 (6H, s), 1.91 (1H, br s), 5.26 (1H, d, *J* = 7.0 Hz), 5.73 (1H, dd, *J* = 15.0, 7.0 Hz), 5.83 (1H, d, *J* = 11.0 Hz), 6.53 (1H, dd, *J* = 15.0, 11.0 Hz), 7.24–7.42 (5H, m).