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Convenient stereoselective synthesis of (*Z*)-chalcone derivatives from 1,3-diaryl-2-propynyl silyl ethers

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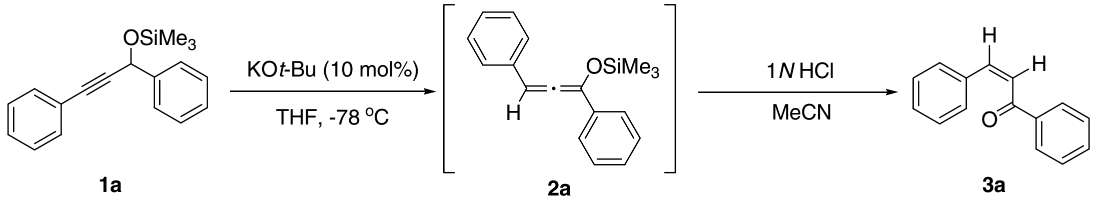
Abstract—Various (*Z*)-chalcone derivatives were easily synthesized in a stereoselective manner from 1,3-diaryl-2-propynyl silyl ethers by a catalytic reaction using potassium *tert*-butoxide under very mild conditions after acid treatment.

Chalcone derivatives are very versatile as physiologically active compounds[1a] and substrates for the evaluation of various organic reactions.[1b,c] However, most interests are concerned with the (*E*)-chalcone derivatives, which are synthesized far more easily than the (*Z*)-isomer, and there have been only a few reports concerning the synthesis of the (*Z*)-isomers.[1,2] Moreover, the general synthetic method for the (*Z*)-chalcone is only the photoisomerization of the corresponding (*E*)-isomers, and it takes time to produce the (*Z*)-chalcones.[3] We recently reported that KO-*t*-Bu catalyzed the isomerization of the 1,3-diphenyl-2-propynyl trimethylsilyl ether (**1a**) to the corresponding siloxyallene **2a** to produce the (*Z*)-chalcone (**3a**) after acid treatment in a one-pot reaction (Scheme 1).[4] This procedure is expected to become a useful approach to produce (*Z*)-chalcone derivatives and suitable for the multi-scale synthesis because special equipment is unnecessary. We now report the applications of this novel synthesis of the (*Z*)-chalcone (**3a**) to the synthesis of various (*Z*)-chalcone derivatives **3**.

The results of such applications to the various 1,3-diaryl-2-propynyl trimethylsilyl ethers **1**[5] to produce the corresponding (*Z*)-chalcone derivatives **3** are shown in Table 1. The typical procedure is as follows: To a solution of **1** (1.0 mmol) in THF (2 mL) was added 1 M KO-*t*-Bu in THF (0.1 mmol, 0.1 mL) at −78 °C under N_2. After 10 min, concd H_2SO_4 in 1,2-dimethoxyethane (2 M solution, 1 mL) was added, and the mixture was stirred at −78 °C for 10 min. Water and EtOAc were added, and the separated organic layer was washed with water then brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (hexane/EtOAc) to give the (*Z*)-chalcone derivative **3**.[6] The *Z*/*E* ratio of the product was determined by ^1H NMR in DMSO-d_6.[7]

First of all, the (*Z*)-chalcone derivatives **3** with several aryl groups were synthesized. The chalcone **3b** was produced with good stereoselectivity like the formation of the (*Z*)-chalcone (**3a**), and the (*Z*)-chalcone **3c**



Scheme 1.

Keywords: (*Z*)-Chalcone; Stereoselectivity; Siloxyallene; Isomerization.

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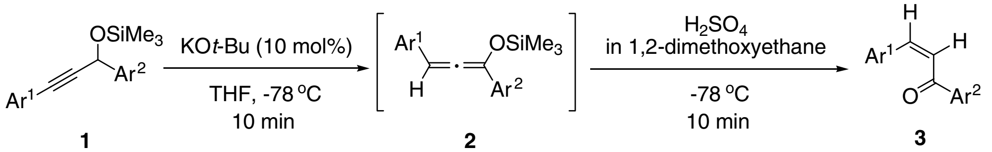
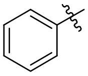
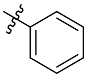
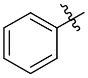
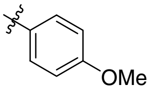
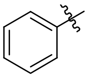
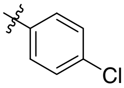
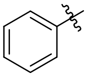
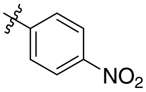
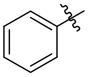
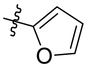
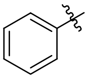
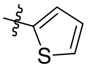
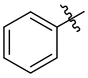
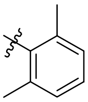
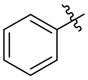
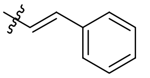
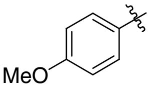
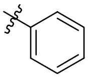
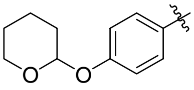
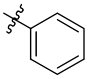
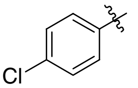
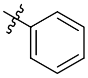
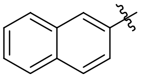
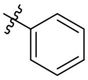
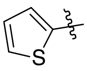
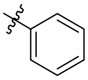
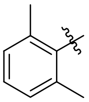
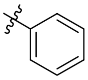
Table 1.



Entry	Product	Ar^1	Ar^2	Yield[a] (%)	Z:E[b]
1	**3a**			82	93:7
2	**3b**			66	97:3
3	**3c**			73	88:12
4	**3d**			—	—
5	**3e**			83	93:7
6	**3f**			76	95:5
7	**3g**			—	—
8	**3h**			75	80:20 (84:16)
9	**3i**			76	E only (25:75)
10	**3j**			54	85:15 (89:11)
11	**3k**			71	90:10
12	**3l**			85	80:20 (95:5)
13	**3m**			82	97:3
14	**3n**			54	70:30

[a] Isolated yield.

[b] Z/E ratio was determined by ^{1}H NMR analysis. Parentheses are Z/E ratio of crude product. No parentheses depicts no isomerization during the purification step.

substituted by the 4-chlorophenyl group showed moderate selectivity. For **3d**, the isomerization from the silyl ether **1d** to siloxyallene **2d** did not proceed at even 0 °C. The reactions using heterocyclic compounds **1e** and **1f** proceeded to give the (Z)-isomers **3e** and **3f**,

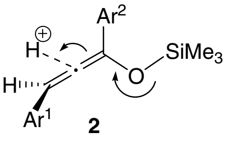
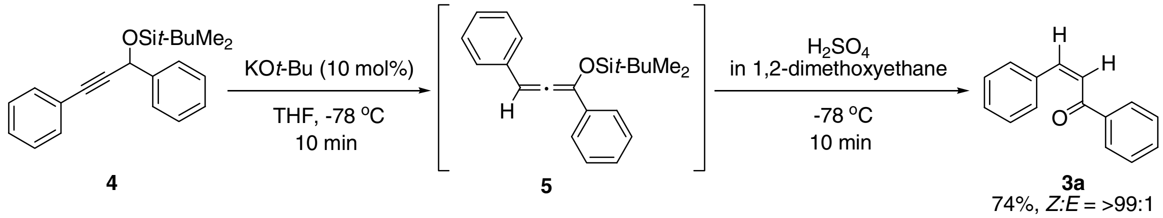


Figure 1.



Scheme 2.

respectively, with good stereoselectivity. However, the sterically hindered 2′,6′-dimethyl derivative **1g** did not yield **2g** at all. The alkyne **1h** having the (*E*)-styryl group afforded the chalcone derivative **3h** in good yield.

Next, the (*Z*)-chalcone derivatives **3** substituted by various aryl groups (Ar^1) at the vinyl position were synthesized. Although only the (*E*)-isomer **3i** was formed, the product **3i** seemed to be easily isomerized during the reaction. However, **1j** substituted with the tetrahydropyranyl group instead of the methyl group afforded the (*Z*)-isomer **3j** with moderate stereoselectivity. The reaction using **1k** and **1l** also produced the (*Z*)-chalcones **3k** and **3l**, respectively, and **3m** substituted by the thienyl group was produced with good selectivity. The 2,6-dimethyl derivative **3n** was obtained in low yield with low stereoselectivity. In this case, conversion of the silyl ether **1n** to **2n** was not complete and **1n** remained after the reaction. From the results of **3g** and **3n**, the steric factor at the 2 or 2′ position of the aryl group was revealed to significantly influence the reaction. Although some products were isomerized from the (*Z*) to (*E*)-isomer during the purification step, it is expected that the isomerization will be prevented if a suitable treatment of each compound is applied. The (*Z*)-geometry preference of the product **3** will be explained by the preferred protonation, in which the reaction exclusively occurs from the less hindered site of the siloxyallene **2** (Fig. 1).

When the *tert*-butyldimethylsilyl ether **4** was treated by a catalytic amount of KO-*t*-Bu, the siloxyallene **5** and the crude (*Z*)-chalcone (**3a**, $Z/E = 92/8$) were quantitatively obtained without decomposition as observed in the case of the trimethylsilyl ether **1a**. In addition, the nearly pure (*Z*)-chalcone (**3a**) was obtained in 74% yield by only crystallization of the crude product from *n*-hexane (Scheme 2).

In summary, we have developed the stereoselective synthesis of (*Z*)-chalcone derivatives **3** from 1,3-diaryl-2-propynyl silyl ethers **1** by a catalytic reaction using potassium *tert*-butoxide under very mild conditions after acid treatment. The method will be quite useful for the synthesis of (*Z*)-chalcone derivatives **3** since the procedure is very simple.

Acknowledgements

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References and notes

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3. (a) Lutz, R. E.; Jordan, R. H. *J. Am. Chem. Soc.* **1950**, *72*, 4090–4091; (b) Black, W. B.; Lutz, R. E. *J. Am. Chem. Soc.* **1953**, *75*, 5990–5997.
4. Yoshizawa, K.; Shioiri, T. *Tetrahedron Lett.* **2006**, *47*, 757–761.
5. The trimethylsilyl ethers **1** were synthesized as follows. Alkynes lithiated with *n*-BuLi reacted with aldehydes to afford 2-alkynyl alcohols, followed by trimethylsilylation with triethylamine and chloro trimethylsilane. Alkynes were synthesized from the corresponding aldehydes and lithium trimethylsilyldiazomethane ($TMSC(Li)N_2$). Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108.
6. The reaction was not performed under the shading conditions.
7. The main product (*Z*)-**3** readily isomerized to (*E*)-**3** upon standing in $CDC1_3$. The ratio of (*Z*)-**3** and (*E*)-**3** was determined by ^1H NMR analysis of the vinyl proton, which showed the characteristic doublet peak, $J =$ ca. 12.5 and 15.5 Hz, respectively.