Highly Regio- and Stereoselective Isomerization of Silyl Enol Ethers Catalyzed by LBA. A Remarkable Enantiomer Discrimination of Chiral LBA

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The thermodynamic equilibration of trimethylsilyl enol ethers catalyzed by a Brønsted acid such as *p*-toluenesulfonic acid was first reported by Stork and Hudrlik in 1968.[1a] Unfortunately, this type of equilibration was not established as a synthetically useful procedure for a long time, since the use of Brønsted acid was seriously complicated by the concurrent formation of substantial amounts of higher-molecular-weight materials and ketones.[1b,c] In this paper, we describe the highly regio- and stereoselective isomerization of a "kinetic" silyl enol ether to a "thermodynamic" silyl enol ether catalyzed by Lewis acid-assisted Brønsted acids (LBAs).[2,3]

In general, both protodesilylation and isomerization are able to occur in the reaction of silyl enol ethers with a Brønsted acid (Scheme 1). The greater stability of the oxygen−silicon bond in silyl enol ethers and the milder nucleophilicity of the conjugate base favors the latter process. In the previously reported enantioselective protonation of "thermodynamic" trimethylsilyl enol ethers with an optically active binaphthol (BINOL)−tin tetrachloride complex **1** in toluene, BINOL was rapidly transformed to the corresponding monosilyl ether.[2a,b] On the other hand, in the reaction with a monomethyl ether of BINOL (BINOL-Me)−tin tetrachloride complex **2** under similar conditions, chlorotrimethylsilane was generated in place of the silyl ether of BINOL-Me.[2c,4] These results reveal that the nucleophilicity of the conjugate base (aryloxy anion) of LBA **2** to the silicon atom is milder than that of LBA **1**, probably due to some steric reason. Furthermore, the silyl transfer was much slower in the case of bulky *tert*-butyldimethylsilyl (TBDMS) enol ether.

We envisioned that chiral LBA **2** and its achiral analogues would facilitate isomerization rather than protodesilylation for hydrolytically more stable "kinetic" trialkylsilyl enol ethers. This theory was confirmed by a preliminary experiment using TBDMS enol ethers **6a** and **6b** derived from 2-substituted cyclohexanone (Table 1). As expected, **6a** was isomerized to **7a** in the presence of catalytic amounts of (*R*)-**2** or **4**. LBA **5** was a more effective catalyst than **4** for the isomerization of **6b**. However, the use of the coordinated complex of tin tetrachloride with 2,2′-dihydroxy-1,1′-biphenyl (**8**) or other monoaryl alcohols predominantly afforded the corresponding ketones via protodesilylation, and the recovered silyl enol ethers were only slightly isomerized.

Scheme 1

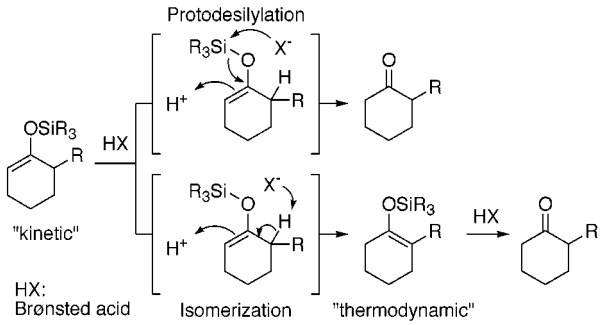
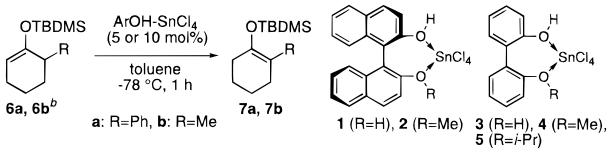


Table 1. Isomerization of TBDMS Enol Ethers[a]



	recovered silyl enol ether			
$ArOH-SnCl_4$	yield (%)	**6a**:**7a**	yield (%)	**6b**:**7b**
5			90	2:98
4	89	1:99	84	5:95
(*R*)-**2**[c]	94	2:98		
3	82	87:13		
guaiacol−$SnCl_4$			71	94:6
2,6-dimethylphenol−$SnCl_4$	91	92:8		

[a] Unless otherwise noted, the isomerization was carried out using LBA (10 mol % for **6a**, 5 mol % for **6b**). [b] Initial ratio: **6a**:**7a** = 92:8; **6b**:**7b** = 98:2. [c] 5 mol % of (*R*)-**2** was used.

To explore the generality and scope of LBA **5**-catalyzed isomerization, the reaction was examined with various structurally diverse ketones (Table 2). In most cases, the reaction proceeded cleanly, and the desirable "thermodynamic" regioisomer was obtained in high yield. Interestingly, in the case of silyl enol ethers derived from menthone, the isomerization of cis isomer **10** occurred more rapidly than that of trans isomer **9** (entries 3 vs 4). In addition, in silyl enol ethers derived from 1-decalone, the isomerization of cis isomer **12** was extremely fast, while no isomerization of trans isomer **11** occurred (entries 5−7). Catalyst **5** was useful for reacting not only cycloalkanones but also acyclic ketones. The isomerization of acyclic silyl enol ethers stereoselectively gave *Z* isomer (entries 9−12). Notably, the use of (*R*)-LBA **2** increased the *Z* selectivity (entry 9).[5]

This catalytic LBA system was applied to the enantiomer-selective isomerization of racemic **6a**. Isomerization of **6a** with (*R*)-**2** gave 42% of (*R*)-**6a** in 97% ee together with 53% of **7a**. This absolute stereopreference is consistent with that in the enantioselective protonation of **7a** with (*R*)-**1** to afford

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(1) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (c) House, H. O.; Fischer, W. F., Jr.; Gall, M.; McLaughlin, T. E. *J. Org. Chem.* **1971**, *36*, 3429. (d) Poirier, J.-M. *Org. Proc. Int.* **1998**, *20*, 317. (e) Deyine, A.; Dujardin, G.; Mammeri, M.; Poirier, J.-M. *Synth. Commun.* **1998**, *28*, 1817.

(2) For enantioselective protonation using LBA, see: (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *Croat. Chem. Acta* **1996**, *69*, 513. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (d) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411. (e) Ishihara, K.; Ishida, Y.; Nakamura, S.; Yamamoto, H. *Synlett* **1997**, 758. (f) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 6429.

(3) For recent reports of the generation of more-substituted enolates, see: (a) Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611 and references therein. (b) Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413 and references therein.

(4) The enantioselective protonation of prochiral silyl enol ethers has been realized using a catalytic amount of (*R*)-BINOL-Me in place of (*R*)-BINOL in the presence of a stoichiometric amount of 2,6-dimethylphenol as an achiral proton source in toluene.[2c]

(5) The *Z*-selectivity of the isomerization was not affected by the steric demands of the alkyl moiety in monoalkyl ethers of BINOL and **8**.

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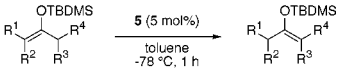
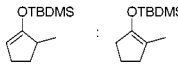
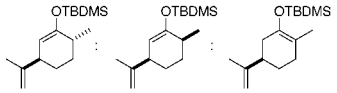
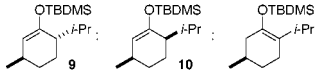
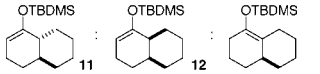
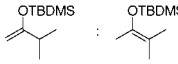
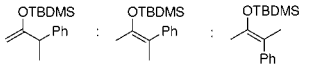
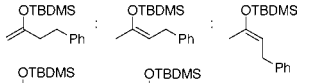
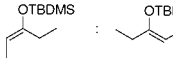
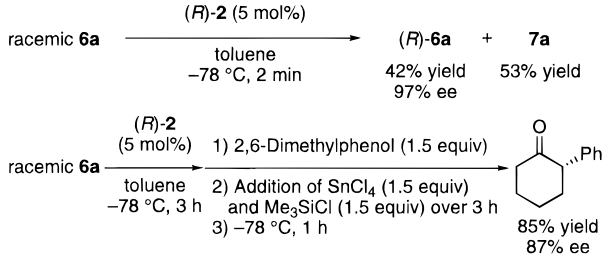
Table 2. Isomerization of TBDMS Enol Ethers[a]



Entry	Silyl enol ethers: Structure	Initial ratio	Final ratio (yield (%))
1		99 : 1	1 : 99 (80)
2[b]		64 : 15 : 21	1 : 1: 98 (87)
3		79 : 19 : 2	28 : 2 : 70 (78)
4		1 : 98 : 1	1 : 0 : 99 (83)
5		95 : 4 : 1	95 : 1 : 4 (85)
6[c]		1 : 98 : 1	0 : 2 : 98 (95)
7		1 : 98 : 1	1 : 1 : 98 (97)
8[d]		>95 : 5	1 : 99 (88)
9		99 : 1 : 0	0 : 76 : 24 (91)
10[e]		99 : 1 : 0	0 : 86 : 14 (87)
11		74 : 18 : 8	3 : 91 : 6 (84)
12[b]		65 : 35	4 : 96 (86)

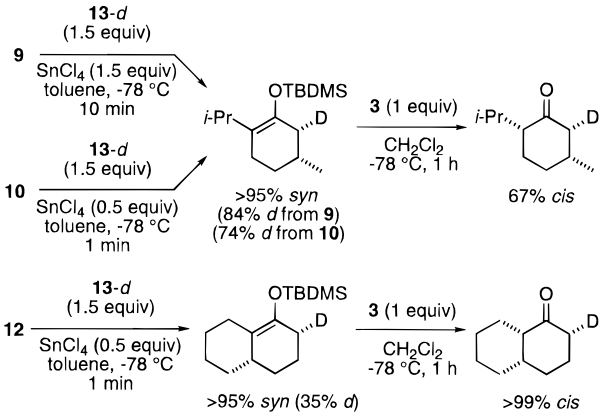
[a] Unless otherwise noted, the isomerization was carried out using LBA **5** (5 mol %). [b] Stirred for 5 h. [c] Stirred for 2 min using (*R*)-**2** (1 mol %) in place of **5**. [d] Stirred for 3 h. [e] (*R*)-**2** was used in place of **5**.

(*S*)-2-phenylcyclohexanone via the transition-state assembly previously reported.[2a,d] Furthermore, a one-pot procedure from racemic **6a** to (*S*)-2-phenylcyclohexanone was attained by the combination of the isomerization of **6a** catalyzed by (*R*)-**2** and the subsequent enantioselective protonation of **7a** catalyzed by (*R*)-**2** in the presence of 2,6-dimethylphenol, tin tetrachloride, and chlorotrimethylsilane.[2c]

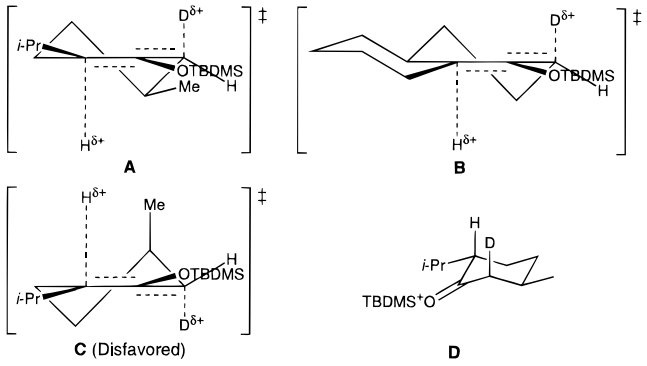


To clarify the stereochemical course of the protonation step to the vinyl carbon, silyl enol ethers **9**, **10**, and **12** were isomerized in the presence of 1.5 equiv of 2-hydroxy-2′-methyloxy-1,1′-biphenyl-*d* (**13**-*d*) and 0.5 or 1.5 equiv of tin tetrachloride (Scheme 2).[6] The ^{2}H-location in the products was determined by ^{1}H NMR analysis of the corresponding ketones following protodesilylation with LBA **3**.[7] Surprisingly, in the case of silyl enol ethers derived from menthone, only the identical syn isomer was obtained from the *trans*- and *cis*-silyl enol ethers **9** and **10** in good deuterated yield, respectively. These results show that the stereochemical course of the isomerization is dependent on the structure of substrates: the former reaction takes place via a syn S_E' mechanism, while the latter takes place via an anti S_E' mechanism. *cis*-Silyl enol ether **12**, as well as **10**, gave only the syn isomer due to an anti S_E' pathway.[8]

Scheme 2



The anti S_E' pathway for the isomerization of **10** and **12** can be explained by the product developing control via the product-like transition state assemblies **A** and **B**, respectively, if the rate-determining step is near the C−H bond-breaking (deprotonation) step rather than the protonation step to the substrates. This postulate is consistent with the experimental finding that ^{2}H was located at a pseudoaxial position of the isomerized silyl enol ether. On the other hand, the syn S_E' pathway for the isomerization of **9** can be understood in terms of the stepwise mechanism via the favored intermediate **D**. In the latter case, the anti S_E' pathway is prevented because the free energy of the product-like transition-state assembly **C** for **9** becomes relatively higher than that of **A** by pseudoaxial disposition of methyl group. The predominance of protodesilylation for trans isomer **11** can be attributed to the great conformational stability in the analogous intermediate.[9]



Supporting Information Available: Experimental procedures and analytical data for all compounds (9 pages).

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(6) Tin tetrachloride was added in a mixed solution of silyl enol ethers and **13**-*d* in toluene at −78 °C.

(7) For ^{1}H NMR (500 MHz) analysis, see the Supporting Information.

(8) The low deuterated yield observed in the isomerization of **12**, which is an extremely highly reactive silyl enol ether (see, Table 2, entry 6), may be due to the catalysis of LBA during the addition of tin tetrachloride.[6]

(9) For mechanism of protodesilylation of allylsilanes, see: (a) Fleming, I.; Marchi, D.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2518. (b) Hayashi, T.; Ito, H.; Kumada, M. *Tetrahedron Lett.* **1982**, *23*, 4605. (c) Wilson, S. R.; Price, M. F. *Tetrahedron Lett.* **1983**, *24*, 569. (d) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153. (e) Fleming, I.; Higgins, D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 206.