Tandem Aldol-Reduction Reaction of Dimethylsilyl Enolates: A New Method for Stereoselective Preparation of 1,3-Diols[1]

Katsukiyo Miura, Takahiro Nakagawa, Shuntaro Suda, and Akira Hosomi*
Department of Chemistry and Graduate School of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305-8571

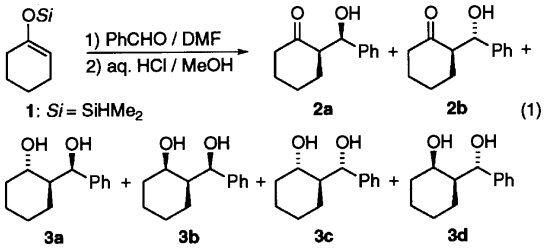
(Received November 12, 1999; CL-990971)

In the presence of a catalytic amount of TBAF (Bu_4NF), dimethylsilyl enolates derived from acyclic ketones reacted with aldehydes to give *syn,syn*-1,3-diols **7a** and **8a** with moderate to high diastereoselectivity. The stereochemical outcome can be attributed to a *syn*-selective aldol reaction and the subsequent 1,2-*syn*-selective intramolecular reduction.

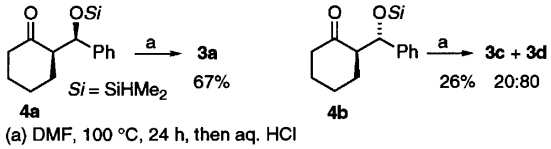
Stereoselective preparation of the 1,3-diol unit has been strongly required in synthetic organic chemistry due to its prevalence in biologically active natural products.[2-4] For this reason, the stereo-controlled reduction of β-hydroxyketones, which are readily prepared by the directed aldol reaction in regio- and stereoselective manner, has been extensively studied, and it nowadays provides an efficient and reliable method for the stereoselective synthesis of 1,3-diols.[3c,5,6] Tandem reactions, in which two or more types of processes take place in a single step, are useful for expeditious synthesis of complex molecules.[7] However, the tandem aldol-reduction reaction directly forming 1,3-diols from ketone enolates and aldehydes is largely unexplored.[8]

Previously, we have found that, in the uncatalyzed aldol reaction of dimethylsilyl (DMS) enolates with aldehydes, 1,3-diols are formed as a by-product with high diastereoselectivity.[9] This fact indicates that DMS enolates can serve as a bifunctional reagent[10] accomplishing the tandem aldol-reduction reaction. Thus, our interest focused on an efficient and stereoselective synthesis of 1,3-diols using DMS enolates. We herein report the results of the tandem reaction of DMS enolates with aldehydes.

We first examined the uncatalyzed reaction of DMS enolate **1** with benzaldehyde in DMF and attempted optimization of the reaction conditions to obtain 1,3-diols selectively (Eq. 1). As reported previously,[8] the reaction with 2 equiv. of **1** at 50 °C for 48 h followed by an acidic work-up gave aldol **2** (79%, **2a**:**2b** = 58:42) along with 1,3-diol **3** (14%, **3a**:**3c**+**3d** = 97:3). A prolonged reaction time was not so effective in improving the yield of **3** (27% after 96 h). The reaction at 100 °C gave **3** as a major product (66% after 48 h), but the diastereoselectivity was not so high (**3a**:**3c**:**3d** = 75:2:23).[11]



The formation of **3a** and **3c**,**d** should proceed *via syn*- and *anti*-isomers of β-siloxyketone, **4a** and **4b**, respectively. This was ascertained by the experiments using **4a** and **4b** prepared by silylation of **2a** and **2b** with $HN(SiHMe_2)_2$ (Scheme 1). As expected, **4a** was converted to **3a** by heating in DMF. No formation of **3b** was observed. Under the same conditions, the reaction of **4b** gave a diastereomeric mixture of **3c** and **3d** in a low yield. Accordingly, the preferred formation of **3a** to **3b**-**d** in the uncatalyzed tandem reaction would be due to fast intramolecular reduction of **4a** leading to **3a** although the rate difference between **4a** and **4b** is insufficient to promote exclusive formation of **3a** at 100 °C.



Scheme 1.

The present tandem process can realize highly stereoselective and efficient preparation of 1,3-diols when both the initial aldol reaction and the subsequent reduction efficiently proceed with high diastereoselectivity. The fluoride ion-catalyzed aldol reaction of certain silyl enolates is known to exhibit high *syn*-selectivity.[12] In addition, the fluoride ion also catalyzes carbonyl reduction with hydrosilanes.[13] Therefore, we next investigated the fluoride ion-catalyzed system.

In the presence of TBAF (6 mol%), the reaction of DMS enolate **1** (1.1 equiv.) with benzaldehyde at -78 °C for 15 h gave a diastereomeric mixture of **3** (**3a**:**3b**:**3c**:**3d** = 27:6:53:14) in 75% yield. The low stereoselectivity is reasonable in view of the unsuccessful stereochemical result in the fluoride ion-catalyzed aldol reaction of TMS enolate of cyclohexanone.[12] In contrast, the use of DMS enolate **5** (1.2 equiv.) achieved high yield and stereoselectivity (91%, **7a**:**7b** = 97:3, Eq. 2). In this case, *syn,syn*-1,3-diol **7a** was formed exclusively, and no aldol adduct **6** was detected.[14] Lowering the reaction temperature to -98 °C improved the selectivity (**7a**:**7b** = >99:1) although the yield decreased to 51% due to a considerable formation of aldol adduct **6** (30%). Other examples of the tandem aldol-reduction reaction are summarized in Table 1. The reactions of **5** with aromatic aldehydes gave good results in both yield and stereoselectivity. 3-Phenylpropanal was less reactive to **5**. DMS enolates of aliphatic ketones also reacted with benzaldehyde to afford the corresponding *syn,syn*-1,3-diols **8a** predominantly.

The exclusive formation of *syn,syn*-1,3-diol **7a** indicates that the aldol reaction of **5** with benzaldehyde proceeds with high *syn*-selectivity. This is consistent with the previously reported results with TMS enolate of propiophenone.[12a] The formation of **7a** also suggests that the subsequent carbonyl

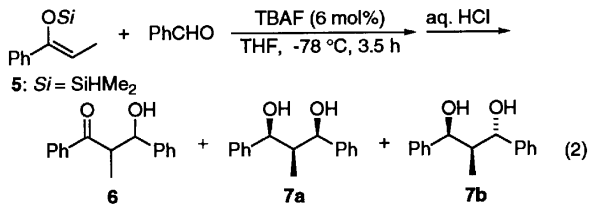
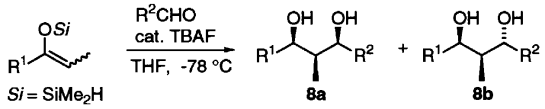


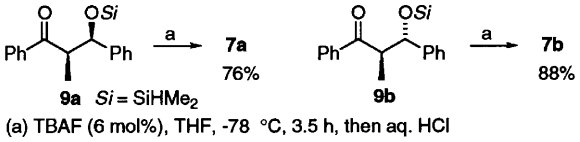
Table 1. Reaction of DMS Enolates with Aldehydes[a]



Enolate		Aldehyde	Yield / %	8a:8b
R^1	Z:E	R^2		
Ph	>98:2	*p*-MeC_6H_4	87	96:4
		p-$MeOC_6H_4$	74	94:6
		p-$O_2NC_6H_4$	84	85:15
		2-furyl	73	91:9
		$Ph(CH_2)_2$	43	82:18
Et	74:26	Ph	64[b]	68:32[c]
i-Pr	75:25	Ph	64	88:12[c]
t-Bu	>98:2	Ph	65	99:1

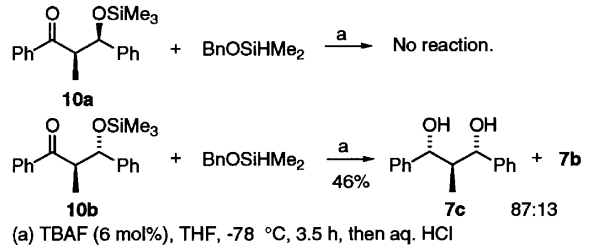
[a]All reactions were carried out with silyl enolate (0.6 mmol), aldehyde (0.5 mmol), and TBAF (0.03 mmol) in THF (1 mL) at -78 °C for 3.5 h unless otherwise noted. [b]TBAF (0.06 mmol). [c]The ratio of **8a** to other diastereomers including **8b**.

reduction is highly 1,2-*syn*-selective.[15] Indeed, the fluoride ion-catalyzed reduction of **9a** and **9b** derived from *syn*- and *anti*-isomers of **6** proceeded with high levels of 1,2-*syn*-selectivity to give **7a** and **7b**, respectively, without another possible isomer (Scheme 2).



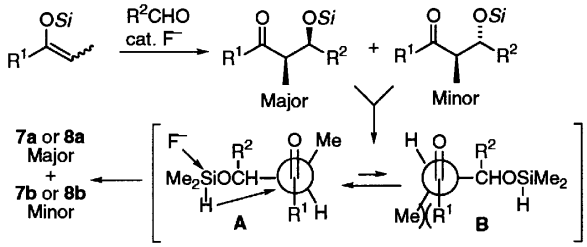
Scheme 2.

In order to prove that the reduction of **9** proceeds intramolecularly, the fluoride ion-catalyzed reactions of TMS ethers **10a** and **10b** with (benzyloxy)dimethylsilane were performed (Scheme 3). As a result, no reduction of **10a** was observed under the same conditions as those shown in Scheme 2. On the other hand, the reaction of **10b** gave *anti,anti*-1,3-diol **7c** as a major product in a moderate yield. The slow reaction rate and the reversed stereoselectivity in this intermolecular system strongly support that the reduction of **9** is an intramolecular process.



Scheme 3.

In the tandem reaction of acyclic DMS enolates, the *syn*-selectivity of the initial aldol reaction can be rationalized by consideration of the antiperiplanar transition state as proposed by Noyori et al.[12a] The reason for the 1,2-*syn*-selectivity of the carbonyl reduction is probably that the intramolecular hydride transfer proceeds *via* conformation **A** rather than the unfavorable conformation **B** including the steric repulsion between the methyl and R^1 groups (Scheme 4). In the transition state of the hydride transfer, the repulsive interaction would be enhanced by a torsional effect. It may also work against the reduction *via* **B**.



Scheme 4.

In conclusion, the fluoride-ion catalyzed reaction of DMS enolates with aldehydes provides a convenient method for the stereoselective synthesis of certain 1,3-diols.

References and Notes

1 Studies on Organosilicon Chemistry. No. 150.
2 Reviews on 1,3-diol synthesis: T. Oishi and T. Nakata, *Synthesis*, **1990**, 635; C. Schneider, *Angew. Chem., Int. Ed. Engl.*, **37**, 1375 (1998).
3 Recent papers on 1,3-diol synthesis: a) N. A. Powell and S. D. Rychnovsky, *J. Org. Chem.*, **64**, 2026 (1999). b) Y. Q. Tu, L. D. Sun, and P. Z. Wang, *J. Org. Chem.*, **64**, 629 (1999). c) D. Blanc, V. Ratovelomanana-Vidal, A. Marinetti, and J.-P. Genêt, *Synlett*, **1999**, 480.
4 Natural products including 1,3-diol unit: S. D. Rychnovsky, *Chem. Rev.*, **95**, 2021 (1995); R. D. Norcross and I. Paterson, *Chem. Rev.*, **95**, 2041 (1995); R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **26**, 489 (1987).
5 N. Greeves, in "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 8, Chap. 1.1, p. 1.
6 S. Anwar, G. Bradley, and A. P. Davis, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1383 and references cited therein.
7 L. F. Tietze, *Chem. Rev.*, **96**, 115 (1996); G. A. Molander and C. R. Harris, *Chem. Rev.*, **96**, 307 (1996).
8 R. Mahrwald and B. Gundogan, *Chem. Commun.*, **1998**, 2273; P. M. Bodnar, J. T. Shaw, and K. A. Woerpel, *J. Org. Chem.*, **62**, 5674 (1997); R. Mahrwald and B. Costisella, *Synthesis*, **1996**, 1087.
9 K. Miura, H. Sato, K. Tamaki, H. Ito, and A. Hosomi, *Tetrahedron Lett.*, **39**, 2585 (1998).
10 L. M. Frost, J. D. Smith, and D. J. Berrisford, *Tetrahedron Lett.*, **40**, 2183 (1999).
11 We also attempted the uncatalyzed reaction of **5** with benzaldehyde. However, it hardly afforded 1,3-diol **7** even at 100 °C.
12 a) R. Noyori, I. Nishida, and J. Sakata, *J. Am. Chem. Soc.*, **105**, 1598 (1983). b) E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama, and R. Noyori, *J. Org. Chem.*, **48**, 932 (1983).
13 M. Fujita and T. Hiyama, *J. Org. Chem.*, **53**, 5405 (1988).
14 The Lewis acid ($SnCl_4$, $TiCl_4$, and $BF_3{\cdot}Et_2O$)-mediated reaction of **5** with benzaldehyde gave only **6** without **7**, although it was known that a Lewis acid induced the intramolecular hydrosilylation of ketones. S. Anwar and A. P. Davis, *J. Chem. Soc., Chem. Commun.*, **1986**, 831. See also Ref. 6.
15 Fujita and Hiyama have reported that the fluoride ion-catalyzed intramolecular reduction of a β-(dimethylsilyloxy)ketone proceeds with moderate 1,3-*anti*-selectivity. See Ref. 13.