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CATALYTIC VERSION OF EPOXY SILYL ETHER REARRANGEMENTS

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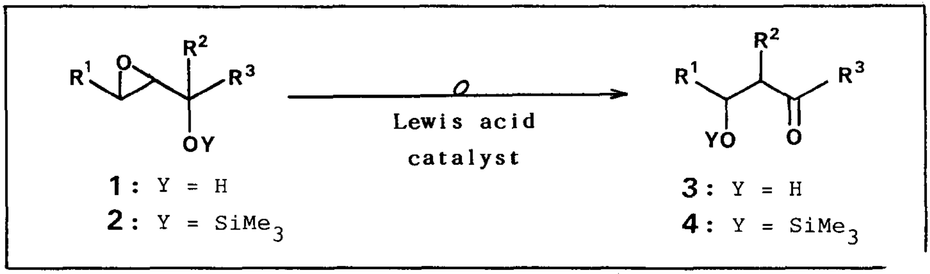
Summary: Catalytic version of epoxy silyl ether rearrangements using Me_3SiX *(X=I, OTf: 5 mol %) as the Lewis acid catalyst is reported, which leads to generally higher yields of the aldol products than stoichiometric version.*

An effective avenue to the stereo-defined aldol-type compounds has been documented in our recent reports,[1,2] which is based on the 1,2-rearrangement of epoxy alcohols or their silyl ethers under the Lewis acidic conditions. In the latter protocol, i.e. the epoxy silyl ether rearrangement, the amount of the Lewis acid is in principle reducible to catalytic if Me_3SiX is capable of promoting the rearrangement as depicted in Scheme 1. Two requirements must be fulfilled for the catalyst to be active: (1) it has sufficient Lewis acidity to promote the rearrangement, and (2) it is regenerated without being inactivated by the coordination to the product or by any other side reactions. Considering the attractiveness and the apparent merits, investigation on the catalytic rearrangement was undertaken. Herein, we describe the realization of the reaction scheme as well as the scope and limitation of the catalytic version of the epoxy silyl ether rearrangements.

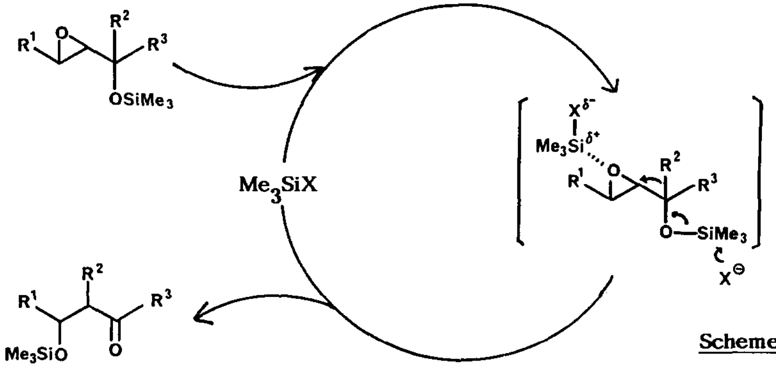


1 : Y = H

2 : Y = $SiMe_3$

3 : Y = H

4 : Y = $SiMe_3$



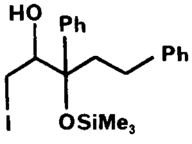
Scheme 1

To test the feasibility, rearrangements of six model compounds 2a-2f were examined under the conditions catalyzed by both of two catalysts, Me_3SiOTf[3]) and Me_3SiI.[4]) The reactions were performed by injecting the catalyst (5 mol %) to the solution of model compounds 2 in CH_2Cl_2 at -78 °C followed by gradual warming to ensure the completion of the reaction (up to -40 ~ -10 °C depending on the compounds). In Table 1 are listed the yields of the aldol products 3. In case the hydrolysis of the silyl ether 4 was incomplete by the neutral aqueous workup, the product was isolated after a brief treatment of the crude mixture with dilute HCl to convert 4 to 3.[5])

The catalytic system actually worked well to result in good to excellent yields of the aldol products 3a-3f. For the purpose of comparison, the results under the stoichiometric conditions ($TiCl_4/CH_2Cl_2$, -78 °C) are also listed in Table 1, which shows that the catalytic conditions give generally superior results. Especially clean reactions took place with the substrates having a powerful migrating group (α-trimethylsilylalkenyl group)[6]) where the yields were essentially quantitative. The rearrangements proceeded fully stereospecifically to give the aldols 3b (from 2b) and 3c (from 2c) as the sole isomer detectable in each case.[7])

On the other hand, in the rearrangements of the phenyl group, a group of weaker migratory aptitude, the efficiency of the reaction was more or less inferior to the cases cited above in light of the rates and the turnovers. Specifically, the reaction of cis-epoxide 2f using Me_3SiI resulted in the recovery of the starting material.[8]) Use of Me_3SiOTf led to 65 % of the rearranged product, however, which was contaminated by 5 % of the threo-isomer 3e, which manifests a limitation of the present method.

Several points are worthy of comment on these results. Better choice of the two catalysts differs depending on the structure of the starting material. In case the terminal epoxides are concerned such as 2a or 2d, Me_3SiOTf gave better results than Me_3SiI. This tendency is attributable to a side reaction, i.e. the ring opening of the oxirane by I^-: the reaction of 2d using Me_3SiI stopped at the very early stage, and no longer proceeded even at the higher temperature or after the prolonged reaction time. Injection of one mole equivalent of Me_3SiI led to the isolation of iodo silyl ether 5 in high yield. In the case of a terminal epoxide 2a, the high migratory aptitude of α-trimethylsilylvinyl group overrides this undesired reaction, nonetheless the slightly inferior yield with Me_3SiI may stem from this side reaction. Thus, the lesser nucleophilicity of Me_3SiOTf makes it the catalyst of choice when terminal epoxides are concerned. On the other hand, comparable or even reversed tendency were observed in the cases of the non-terminal epoxides.



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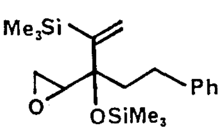
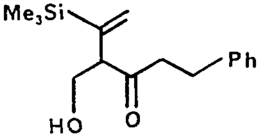
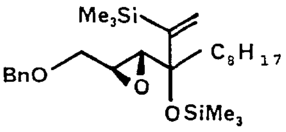
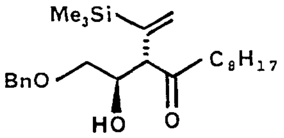
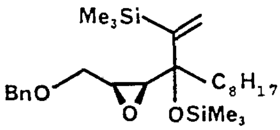
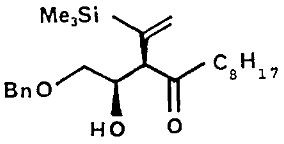
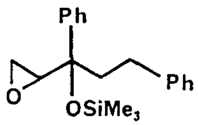
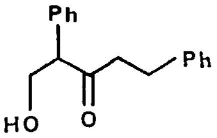
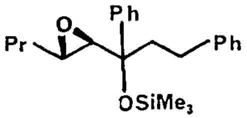
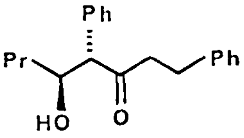
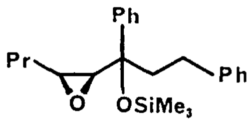
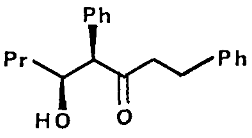
Seeking for the even milder conditions, use of some other catalysts was also attempted. Although examined for one compound 2b, Me_3SiBr was found to be a usable catalyst; treatment of 2b with Me_3SiBr (5 mol %) afforded 3b in 93

Table 1 9)

Starting Material	Product a)	Catalyst b)		
		Me_3SiOTf	Me_3SiI	$TiCl_4$ c)
 **2a**	 **3a**	99 %	91 %	79 %
 **2b**	 **3b**	92 %	100 %	90 %
 **2c**	 **3c**	82 %	98 %	91 %
 **2d**	 **3d**	72 %	12 %	44 %
 **2e**	 **3e**	76 %	62 %	100 %
 **2f**	 **3f**	65 % d)	—— e)	46 %

a) Isolated yields of purified materials are shown; b) Reactions were performed using 5 mol % of catalyst; c) 3 equiv. / CH_2Cl_2, -78 °C; d) Contained the isomer 3e (5 %)7); e) Starting material was recovered in 95 % yield.

% yield, whereas the use of Me_3SiCl led to only 17 % yield of 3b, which implies a borderline of the reactivity necessary for the catalytic activity.

In the larger-scale experiments, the amount of the catalyst can be further reduced to 2 mol % or less without any sizable decrease of the yields.

A typical procedure is described by the reaction of 2b using 2 mol % of Me_3SiI as a catalyst: Under the protection from light, Me_3SiI (12 µl, 0.084 mmol) was added to a solution of epoxy silyl ether 2b (2.0 g, 4.20 mmol) in CH_2Cl_2 (8 ml) at -78 °C. The temperature was gradually raised to -10 °C during 1 h, and the reaction was stopped by the addition of pH 7 buffer and the products were extracted with ether. Combined organic layer was concentrated in vacuo and diluted with 1,4-dioxane (4 ml), to which was added 2 N HCl (two drops) and the mixture was stirred for 10 min. After usual extractive workup, purification with silica-gel column chromatography (hexane-AcOEt=6/1) afforded aldol 3b as a colorless oil (1.66 g, 98 %).

The utility of the catalytic version is apparent in the large-scale preparation of the aldols, which can be incorporated in the synthetic scheme in the total synthesis of natural products. Threo-aldol 3b has already been utilized as a key intermediate in our recent chiral total synthesis of isoaveanaciolide.[2b] Further application of the reaction to some natural product synthesis is now in progress in our laboratory.

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References and Notes

1) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, and G. Tsuchihashi, J. Am. Chem. Soc., 108, 3827 (1986).
2) a) K. Suzuki, M. Shimazaki, and G. Tsuchihashi, Tetrahedron Lett., 27, 6233 (1986); b) K. Suzuki, M. Miyazawa, M. Shimazaki, and G. Tsuchihashi, ibid., 27, 6237 (1986); c) K. Suzuki, T. Matsumoto, K. Matsumoto, K. Tomooka, and G. Tsuchihashi, Chem. Lett., 1987, 113.
3) R. Noyori, S. Murata, and M. Suzuki, Tetrahedron, 37, 3899 (1981).
4) G. A. Olah and S. C. Narang, Tetrahedron, 38, 2225 (1982).
5) If necessary, the product is isolable as the silyl ether 4, the protected form of the aldol 3, by applying the non-aqueous workup.
6) K. Suzuki, E. Katayama, and G. Tsuchihashi, Tetrahedron Lett., 25, 1817 (1984).
7) The isomeric purities were determined by 400 MHz ^1H NMR spectroscopy.
8) Rearrangements of the cis epoxy alcohols (or silyl ethers) tend to be more problematic compared with the corresponding trans isomers both in catalytic and stoichiometric cases. Severe steric interaction of the cis-disposed substituent at the transition state may be responsible for this phenomenon.
9) All new compounds exhibited satisfactory physical properties, ^1H NMR, IR, and high-resolution MS.

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